



Health Evidence Review Commission's Value-based Benefits Subcommittee

August 14, 2014
8:30 AM

**Meridian Park Hospital
Community Health Education Center, Room 117
19300 SW 65th Avenue, Tualatin, OR 97062**

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE

August 14, 2014

8:30am - 1:00pm

Meridian Park Room 117B&C

Community Health Education Center

Tualatin, OR 97062

A working lunch will be served at approximately 12:00 PM

All times are approximate

I.	Call to Order, Roll Call, Approval of Minutes – Kevin Olson	8:30 AM
II.	Staff report – Ariel Smits, Cat Livingston, Darren Coffman	8:35 AM
III.	Straightforward/Consent Agenda – Ariel Smits A. Straightforward table	8:40 AM
IV.	New discussion items – Ariel Smits, Cat Livingston A. Nerve blocks B. Diabetic retinopathy codes C. Tympanostomy tube removal D. Spinal manipulation for treatment of migraine and tension headaches E. Wearable cardiac defibrillators F. Fibromyalgia related diagnoses A. General conditions B. Chronic fatigue syndrome	8:45 AM
V.	Coverage Guidances for review – staff A. Hyperbaric oxygen B. Percutaneous intervention for cervical spine	10:00 AM
VI.	Guidelines – Ariel Smits, Cat Livingston A. GN 37 B. Rehabilitation guideline C. Lymphedema guideline D. Denture guideline E. Adenoidectomy – revisions to the obstructive sleep apnea guideline and sinusitis surgery guideline F. RSV guideline	10:40 AM
VII.	Previous Discussion Items – Ariel Smits, Cat Livingston A. Botulinum toxin B. Gender dysphoria C. Hepatitis C D. The new “non-covered” section of the Prioritized List	11:45 PM

- E. Applied behavior analysis for the treatment of non-autistic self-injurious behavior
- F. Standardized assessment tools for evaluating progress in the treatment of autism spectrum disorder

VIII. Public comment 12:55 PM

IX. Adjournment – Kevin Olson 1:00 PM

Value-based Benefits Subcommittee Recommendations Summary For Presentation to: Health Evidence Review Commission in June, 2014

For specific coding recommendations and guideline wording, please see the text of the 06/12/14 VbBS minutes.

CODE MOVEMENT

- Procedure codes for placement and removal of audient bone conductors were removed from two covered lines
- Physical therapy procedure codes were added to two covered gynecological lines for pelvic physical therapy
- Electroconvulsive therapy (ECT) procedure codes were added to the schizophrenia line
- Procedure codes for applied behavioral analysis for autism were added to the autism line

GUIDELINE CHANGES

- A new guideline regarding bone anchored hearing aids was adopted
- The guideline on treatment resistant depression was modified to remove reference to ECT and to change the title to reflect that the guideline only concerned repetitive transcranial stimulation
- A new guideline regarding use of ECT was adopted
- The bariatric surgery guideline was modified to clarify intent and update references to accrediting organizations
- The guideline for treatment of autism spectrum disorder was replaced with a new guideline on applied behavioral analysis

BIENNIAL REVIEW

- The audient bone conductor line (line 570) was deleted
- The autism spectrum disorder line was rescored from line 313 to approximately 199

VALUE-BASED BENEFITS SUBCOMMITTEE
Meridian Park Health
Community Health Education Center, Room 117B&C
Tualatin, OR
June 12, 2004
8:30 AM – 1:00 PM

Members Present: Lisa Dodson, MD, Chair; James Tyack, DMD; Susan Williams, MD; Mark Gibson; David Pollack, MD (via phone, left at 11:50 PM); Irene Croswell, RPh

Members Absent: Kevin Olson, MD, Vice-chair; Laura Ocker, LAc

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Dorothy Allen-Peck; Denise Taray, RN.

Also Attending: Jesse Little, OHA Actuarial Services Unit; Wally Shaffer, MD, DMAP; Brian Neiubuur, OHA; Holly Jo Hodges, MD, Trillium Health; Henry Milzcuk MD, OHSU ENT (via phone); Jennifer Ratigan, Pacific University Audiology (via phone); Megan Bird, MD, Legacy; Maura Roche, Aubrey Harrison, and Danielle Askini, Basic Rights Oregon; Atif Zaman MD, OHSU Hepatology; Jose Cruz, RN; Andrew Wolfe; Karynn Fish, OHA; Cheryl Fletcher, Abbvie; Stephanie Heburn, PT; Stephanie Peters and Becca Reish, Oregon Physical Therapy Association; John Peterson and Michelle Bece, Gilliad; Shane Jackson and Tobi Rates, Autism Society of Oregon; Eric Larsson, Lovaas Institute; Becky Straus, ACLU of Oregon; Tom Culhane, Atrio Healthplan; Larren Sandt, Caring Ambassadors; Anne Murray, Bristol-Myers Squibb; Ashlen Strong, HealthShare of Oregon; Jenny Fischer, ORABA; Dianna Matthews, Johnson and Johnson; Black Wilson and Shane Gelcher, BMS; David Robertson, Providence Health Plan; Shelley Kailey, Central Drugs; BJ Cavnor, 1-in-Four and Cascadia Project.

➤ **Roll Call/Minutes Approval/Staff Report**

The meeting was called to order at 8:40 am and roll was called. Minutes from the May, 2014 VbBS meeting were reviewed and approved with no corrections or changes.

ACTION: HERC staff will post the approved minutes on the website as soon as possible.

Smits introduced Holly Jo Hodges, MD, who is a new VbBS member pending approval at the HERC's afternoon meeting. Dr. Hodges is a family physician who is the medical director of Trillium Healthcare in Eugene. She would be serving on the VbBS as the CCO/Medical Director member. Smits also noted that today is the last meeting for Lisa Dodson, MD. Her guidance as VbBS Chair has been exceptional and will be sorely missed.

Coffman noted that ICD-10 implementation is delayed until October 1, 2015; therefore there is no need to publish the biennial list in October 2014 anymore. The biennial list will instead be published January 1, 2015 to coincide with the CCO contract periods.

➤ **Topic: Audiant bone conductor biennial review**

Discussion: Smits reviewed the summary document regarding deletion of the audient bone conductor line. Smits noted that there remains a line below the funding line for sensory conditions with no treatment necessary for any ENT/hearing technology which requires placement on a non-funded line. There was minimal discussion.

MOTION: To approve the proposed List changes as presented. CARRIES 6-0.

Actions:

- 1) Delete line 570 CONDUCTIVE HEARING LOSS Treatment: AUDIANT BONE CONDUCTORS from the Prioritized List
- 2) Remove CPT 69710 (Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone) from line 427 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
- 3) Remove CPT 69711 (Removal or repair of electromagnetic bone conduction hearing device in temporal bone) from line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
- 4) Add an entry regarding audient bone conductors to the new list of items reviewed by not placed on the Prioritized List. This new list will be reviewed at the August, 2014 VbBS meeting.

➤ **Topic: Unilateral hearing loss**

Discussion: Smits reviewed the summary document regarding the coverage of unilateral vs. bilateral hearing loss. The subcommittee was comfortable with the evidence for treatment of unilateral hearing loss in children (language development improvement, school success improvement, etc.), but felt that the evidence for treatment in adults needed further review. Henry Milzcuk, MD, OHSU Pediatric Audiology, testified that adults with unilateral hearing loss have significant disability. They have problems with following conversations or speech in loud environments. He testified that treatment of unilateral hearing loss in children should be higher priority than treatment in adults, but that treatment in adults was also important. Gibson requested further information on the utilization of unilateral hearing loss treatment in adults—number of requests for treatment, treatment costs, etc. Jennifer Ratigan, audiologist from Pacific University, testified that the impact of treatment of unilateral hearing loss in adults depends on whether the hearing loss was long standing/congenital vs. sudden hearing loss in adulthood. Sudden unilateral hearing loss has impact on balance,

functionality, etc. The decision was to cover unilateral hearing loss in children, and to have staff further investigate coverage of unilateral hearing loss in adults.

Actions:

- 1) HERC staff will review the evidence of effectiveness of treatment of unilateral hearing loss in adults, both for adults with long term hearing loss and with sudden loss. Staff will work with the OHP health plans to determine the level of utilization of treatment of unilateral hearing loss in adults, and cost of such treatment. Staff will mock up possible lines with scoring for treatment of unilateral hearing loss in children and in adults, and compare this line scoring with current lines 317 and 450 (hearing loss medical treatment lines). This information will be brought back to the August VbBS meeting.

➤ **Topic: Bone anchored hearing aids**

Discussion: Smits reviewed the summary document regarding the coverage of bone anchored hearing aids (BAHA). Smits specified that the proposed new guideline does not address the treatment of children younger than age 5, or the use of technology such as SoftBand. Such treatment is still covered on the hearing loss lines. There was minimal discussion.

MOTION: To approve the new guideline as presented. CARRIES 6-0.

Actions:

- 1) A new guideline regarding BAHA was adopted as shown in Appendix A.

➤ **Topic: Physical therapy (PT) for urinary incontinence**

Discussion: Smits reviewed the summary document regarding the addition of PT procedure codes to two gynecology lines. Testimony was heard from two physical therapists, Stephanie Heburn and Becca Reisch from the Oregon Physical Therapy Association, who were present to answer questions. There was discussion about whether the guidelines in question should specify PT training type. The experts testified that PT providers need specialized training to provide pelvic PT; however, while certification of training in pelvic PT is available, such certification is not standardized or widely used. There was additional discussion about adding "pelvic" to the physical therapy requirement in the referenced guidelines, but the examples already in these guidelines were felt to be sufficient.

MOTION: To approve the staff recommendations as presented. CARRIES 6-0.

Actions:

- 1) Add the following PT services to line 471 UTERINE PROLAPSE;
CYSTOCELE

- a. 97001 Physical therapy evaluation
 - b. 97002 Physical therapy re-evaluation
 - c. 97110 Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
 - d. 97140 Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
 - e. 97530 Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes
- 2) Add CPT 97140 and 97530 to line 459 URINARY INCONTINENCE
 - 3) Add reference to line 471 to the Rehabilitation Guideline

➤ **Topic: Electroconvulsive therapy**

Discussion: Smits reviewed the summary document regarding the coverage of electroconvulsive therapy (ECT). There was discussion about the proposed addition of a clause stating that vagal nerve stimulation was not covered for treatment of depression. The committee felt that this clause would be better put in the new “excluded” list. Pollack requested that the new ECT guideline reference the DSM-V condition names (e.g. major depressive disorder rather than major depression).

MOTION: To approve the staff recommendations as amended. CARRIES 6-0.

Actions:

- 1) Modify GN 102 as shown in Appendix B
- 2) Add reference to vagal nerve stimulation (CPT 64568) to the new list of technology reviewed but not included on the Prioritized List
- 3) Add CPT 90870 (electroconvulsive therapy) to line 26 SCHIZOPHRENIC DISORDERS
- 4) Adopt a new guideline for ECT as shown in Appendix A

➤ **Topic: Applied behavior analysis for autism spectrum disorders**

Discussion: Livingston presented an issue summary discussing the process the evaluation of evidence has taken, from the direction of SB365, the Evidence-based Guidelines Subcommittee deliberations, and staff amendments regarding specific intensity and duration limits. Staff recommended being more description of the evidence base to help guide medical appropriateness and being less proscriptive about specific limits.

Dr. Eric Larsson, Director of the Lovaas Institute, presented for invited expert testimony. He stated the Association of Professional Behavior Analysts dispute some specific conclusions of the evaluation of evidence, and think studies are

misrepresented. They recommend that the evaluation of an individual's responsiveness to treatment is the best way to maximize value and that treatment intervals of 6 months allow establishment of baselines and progress. With the challenges of the parity rules, they feel that socially significant behavioral objectives should be evaluated and providers should be evaluated on their ability to improve outcomes with appropriate treatment planning.

There was a discussion about standardization of assessments. Larsson responded that standards of different providers are influenced by the level of funding that is available to them. Use of objective assessments does help, but there are many of them. Subcommittee members discussed that it would be very helpful for there to be a single assessment tool for all CCOs to use. Other states may be able to offer guidance about this. There is the challenge of identifying optimal tools amongst the many standardized tools. This may end up being a best practices consensus-type exercise rather than a current evidence-based pathway approach.

Public testimony was received from Jenny Fisher, representing the Oregon Association for Behavior Analysts. She recommends using existing codes in addition to adding temporary codes as they become available and to not delay the addition of ABA treatment for children and adolescents who need it. Additional public testimony was received by Tobi Rates, Executive Director of Autism Society of Oregon, who is also the parent of 2 children with ASD. She also requested ABA therapy be offered to autism spectrum disorder individuals as quickly as possible and is most concerned that children would potentially have to wait 6 months to get this therapy when early intervention is very important. They appreciate removal of duration and intensity limits. Rates expressed ongoing concern about the rating of evidence, particularly with regard to older patients.

With regard to the coding concerns, Coffman responded that current codes on the line would be inappropriate, as they refer to medication management and other non-related services. Nonspecific codes would have to be added to the line to comply with the request and the commission does not do that when more specific codes are available. The implementation delay specified in SB 365 was based on ICD-10 implementation, but because of the ICD-10 implementation delay, coding changes could be made to any upcoming List. The final decision on the go live date is up to OHA leadership.

Staff had presented a proposed rescoring of the autism line. Additionally, Coffman discussed Paul Terdal's submitted testimony on scoring changes. Coffman affirmed that the healthy life score of 5 was appropriate with precedent given that it is the highest score possible for a nonfatal condition. In terms of population effects, there can be dangerous or societal behaviors, and so the decision was to change this score from a 1 to a 2. The cost of this therapy was discussed, and while public testimony suggests it has a high offset to societal

costs, the medical costs continue to be significantly increased and the decision was made to change this from a 3 to a 1. Members affirmed that examining medical costs is consistent with the score of costs of other services on the Prioritized List. The new scoring would place the autism spectrum disorder line at approximately Line 199.

Actions:

- 1) Change treatment description of line: ~~CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION~~ MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIOR ANALYSIS
- 2) Replace Guideline Note 75 with a new guideline as shown in Appendix B
- 3) Add CPT 0359T-0374T (adaptive behavior assessments and treatments) to line 313 AUTISM SPECTRUM DISORDERS
- 4) Recommend that EbGS review and revise their summary conclusions as time and meetings allows
- 5) Staff is directed to identify a pathway to determine the best standardized tools for assessment of ABA
- 6) Staff will bring the issue of a guideline for self-injurious behavior in non-autistic children back to a future meeting
- 7) Rescore the Autism Spectrum Disorders Line as follows (previous scoring in parenthesis):
 - Category: 3 (3)
 - HL: 5 (5)
 - Suffering: 4 (4)
 - Population effects: 2 (1)**
 - Vulnerable population: 0 (0)
 - Tertiary prevention: N/A
 - Effectiveness: 3 (2)**
 - Need for service: 0.7 (0.7)
 - Net cost: 1 (3)**
 - Approximate new line placement: 199 (313)**

➤ **Topic: Gender dysphoria**

Discussion: Smits introduced a summary of the evidence for the effectiveness of treatment of gender dysphoria in reducing depression, anxiety, suicide attempts, IV drug use and other high risk behavior. She reviewed expected numbers of patients who would request treatments for gender dysphoria in OHP, and the expected costs for such treatment. She reviewed staff recommendations to add cross-sex hormone therapy and sex reassignment surgery to the current gender dysphoria line, rather than creating a new surgical treatment line.

There was discussion about the evidence of effectiveness of treatments for gender dysphoria. There was discussion about whether outcomes were self-

reported. Smits noted that most older studies relied on self-reported outcomes, whereas most newer studies used validated tools to measure anxiety and depression symptoms.

Maura Roche, from Basic Rights Oregon, testified about her organization's concerns about proposed guideline wording which restricts sex reassignment surgery to patients 18 years and older. This concern was echoed by Danielle Askini from Basic Rights Oregon and Megan Bird, MD from Legacy Health Systems. There was discussion about committee member concerns about performing irreversible surgery on teens who are still undergoing brain development. Roche pointed out that the age of consent for medical procedures in Oregon is 15. Askini testified that teens are at higher risk for suicidality, and therefore should not have surgical treatments withheld if appropriate. The decision was to remove the age 18 requirement for surgery and replace with wording about patients must "have the capacity to make a fully informed decision and to give consent for treatment."

Roche, Askini, and Bird also expressed concern with the requirement to have "real life" experience living as the desired gender. Some persons who may not be able to easily physically pass as their desired gender face increased risk of discrimination, harassment, and violence. The experts felt that the requirement for 12 months of hormone therapy prior to surgery should provide an adequate waiting period. The experts suggested adding wording allowing a waiver of this requirement for certain patients. Committee members expressed concern with removing this requirement, given the irreversible nature of surgical therapies. Experts noted that very few patients expressed regrets about having surgical treatments (~1%), particularly when compared to the incidence of suicide attempts. Staff proposed adding a clause to this requirement stating that patients must live as their desired gender "unless a medical and a mental health professional both determine that this requirement is not safe for the patient." This was considered acceptable by the experts and committee members.

The scoring of the new line was briefly discussed. Askini expressed support for moving gender dysphoria to category 6, given the high risk of suicide and suicide attempts in this population, which are considerably higher than in major depression. Staff noted that they have received a comment that the Healthy Life score should be increased from 3 to 6, due to changing the category from 7 to 6. Completion of the re-scoring of the new gender dysphoria line with cross-sex hormone therapy and sex reassignment surgery was tabled until August.

There was extensive discussion of the proposed guideline for gender dysphoria, including the suggested changes to the requirements for an age limit and a requirement for "real life" experience prior to surgery. There was considerable discussion about the mental health assessment required prior to surgery. Pollack requested the addition of wording that the assessment be done by mental health professionals "with experience in working with patients with gender

dysphoria.” There was also discussion about requiring this assessment to address the relevance and urgency of the requested procedure(s). Bird noted that pages 26 and 27 of the WPATH guideline outline what should be done in the mental health assessment. Askini stated that she felt that adding such wording to the guideline was too detailed and redundant to WPATH requirements, which are followed by most professionals in the field. Committee members expressed concern that such major surgery should be authorized without specifying what the mental health evaluation should provide.

General consensus was reached that cross-sex hormone therapy and sex reassignment surgery should be added to the gender dysphoria line. The surgical codes required to be added to this line were not discussed. The scoring of the line was tabled. Staff will work on refining the gender dysphoria guideline, and will send out to committee members for comments and input prior to the packet being sent out.

Actions:

- 1) HERC staff will work with experts to revise the proposed guideline regarding gender dysphoria. This guideline will be sent to the VbBS members via email prior to the next meeting for feedback.
- 2) Discussion of adding cross-sex hormone therapy and sex reassignment surgery to the gender dysphoria line and rescoring this line was tabled to the August VbBS meeting

➤ **Topic: Bariatric surgery guideline clarification**

Discussion: Smits introduced a summary of suggested modifications to clarify the bariatric surgery guideline. There was some discussion about eliminating the requirement for Centers of Excellence, as CMS has removed this requirement. The group decided to continue to require COE at this time.

MOTION: To approve the modified guideline as presented. CARRIES 5-0.

Actions:

- 1) The bariatric surgery guideline was modified as shown in Appendix B

➤ **Topic: Rehabilitation guideline clarifications**

Discussion: Smits summarized concerns that have been brought to HERC staff by the OHP Medical Directors regarding proposed changes to the rehabilitation guideline approved in May, 2014. Holly Jo Hodges testified that the medical directors are requesting guidance on the number of PT/OT visits that should be approved for a given condition and how to monitor whether the patient is improving with therapy. Staff noted that it was beyond the capability of the HERC

and HERC staff to determine the number of visits that should be authorized for various individual conditions, given the vast amount of literature that would need to be reviewed. Additionally, there is very poor evidence for the effectiveness of PT/OT for most conditions. Staff noted that the cost of PT/OT with the current guideline restriction in place (unlimited care for 3 months, then 2 visits a year for adults) was approximately \$2 PMPM.

HERC staff was directed to propose guideline revisions that include a total number of visits allowed per year (for all conditions), such as 30 visits per year, with additional visits allowed in case of significant change in status, such as surgery, new major diagnosis, or major developmental change. Staff was directed to send this proposed guideline to the medical directors for comment at their July meeting.

Actions:

- 1) Tabled for further discussion in August, 2014

➤ **Topic: Lymphedema guideline**

Discussion: Smits briefly introduced a summary of suggested changes to the lymphedema guideline. The recommended changes referenced the rehabilitation guideline, which are still being discussed. Staff requested that this topic be brought back in August to be discussed after the rehabilitation guideline.

Actions:

- 1) Tabled for further discussion in August, 2014

➤ **Topic: Treatment of hepatitis C**

Discussion: Livingston presented an issue summary. Dr. Atif Zaman, a hepatologist at OHSU provided expert input. He testified that due to the side effects of interferon, none of his patients are interested in interferon treatment. He argued that the focus should be on who needs treatment now versus who can wait. He is having meetings with CareOregon and other payors to try to come up with appropriate limitations. As the new treatments emerge, ongoing decisions will have to be made about prioritizing appropriate candidates for treatment.

He answered questions about the progression of the disease and encouraged coverage of patients with stage 3 or stage 4 fibrosis. However, by the time someone reaches stage 4, they will need monitoring for liver cancer every 6 months. It was reiterated that most patients will never progress to cirrhosis.

Advocates argued that treating would result in fewer liver transplants and thus be cost-saving. However, it was clarified the limiting factor of liver transplantation is

the waitlist for available donor organs. Therefore if liver transplants due to complications of hepatitis C, those organs will still be used to treat other patients, which will not result in a true cost savings to the system, but will provide additional health benefits to the population

Public testimony was received from Larren Sandt representing Caring Ambassadors. A conflict of interest of unrestricted funding grants from pharmaceutical companies was disclosed. She recommended coverage. There are active studies being done about real world outcomes. Next, BJ Cavanaugh, Cascade AIDS project testified. He also disclosed a conflict of interest that his organization receives unrestricted funding from pharmaceutical companies. He argued it was important to treat, especially those with HIV, because of their higher rate of comorbidities and poorer health outcomes.

Subcommittee members discussed the problem that the budget is a zero sum game. Paying for hepatitis C drugs will take away from other health care services, or if more money is allocated, then either taxes would need to go up or cuts would be made to such areas as education or public safety. The concern was stated that as long as health plans keep paying for it, the drug companies are going to continue charging these increasingly high prices.

It was agreed that the prioritized list gives Oregon a unique opportunity to base coverage on value. Several members suggested that Oregon attempt to negotiate with manufacturers based on the value to the state.

Testimony was received by Ashlen Strong, JD, MPH of Health Share of Oregon. She stated if they treated hepatitis C with the newer drugs, it would cost them 68 million dollars compared to a 72 million dollar total drug budget. It would entirely wipe out the pharmaceutical budget for their CCO. They also have 60,000 new members since January.

Health Share offered a consensus recommendation to convene 2 panels:

- 1) The first to include clinical experts (including hepatology, infectious disease) to develop prescribing criteria to ensure patients who need the drug right now can get it
- 2) The second comprised of health economists to determine the price at which Sovaldi is sustainable and value-based for OHP

She stated that health care organizations have been charged with the goal of improving the proposition of health care. It was stated it is time to ask pharmaceutical companies to step up the plate.

The question was asked by subcommittee members why CCOs can't negotiate price. The answer was, without competition, the company doesn't have to negotiate the price.

Health Share has calculated that the total cost to fly someone to Egypt, cover their stay and physician visits and the cost of the drug is about \$3,000, compared to \$84,000 for the drug treatment alone in the U.S.

Subcommittee members expressed interest in knowing more about the net costs of treatment and a possibility of a health economic analysis.

Actions:

- 1) Staff will bring back this issue to the August meeting for more discussion
- 2) Staff will obtain information about a proposal for a health economic analysis
- 3) Staff will confer with the P&T Committee about community standard discussions

➤ **Public Comment:**

No additional public comment was received

➤ **Issues for next meeting:**

- 1) Unilateral vs bilateral hearing loss coverage in adults
- 2) Gender dysphoria
- 3) Hepatitis C treatments
- 4) Self-injurious behavior guideline
- 5) Standardized tools for ABA assessment
- 6) Rehabilitation guideline
- 7) Lymphedema guideline
- 8) Botulinum toxin therapy for various indications
- 9) Electronic tumor treatment fields
- 10) New list of items reviewed but not included in the Prioritized List

➤ **Next meeting:**

Meridian Park Health Education Center, Tualatin, OR Room 117B&C

➤ **Adjournment:**

The meeting was adjourned at 1:20 PM.

Appendix A

New Guideline for implementation on 10/1/14

GUIDELINE NOTE XXX, BONE ANCHORED HEARING AIDS

Lines 317, 450

Bone anchored hearing aids (BAHA, CPT 69714, 69715) are included on these lines when the following criteria are met:

- 1) The patient is age 5 years or older
- 2) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing
- 3) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective.
- 4) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered.

GUIDELINE NOTE XXX, ELECTROCONVULSIVE THERAPY (ECT)

Line 7,26,29

Electroconvulsive therapy (ECT; CPT 90870) is included on these lines for the treatment of major depressive disorder, bipolar disorder, schizophrenic disorder, or schizoaffective disorder when one or more of the following conditions are present:

- 1) Acute suicidality with high risk of acting out suicidal thoughts
- 2) Psychotic features
- 3) Rapidly deteriorating physical status due to complications from the depression, such as poor oral intake
- 4) Catatonia
- 5) History of poor response to multiple adequate trials of medications and/or combination treatments, or the patient is unable or unwilling to comply with or tolerate side effects of available medications, or has a co-morbid medical condition that prevents the use of available medications
- 6) History of good response to ECT during an earlier episode of the illness
- 7) The patient is pregnant and has severe mania or depression, and the risks of providing no treatment outweigh the risks of providing ECT

The frequency and number of treatments need to be determined by the severity of illness and by the relative benefits and risks of ECT treatment. During the course of ECT, it is important to monitor therapeutic responses and adverse effects of treatment. Continuation treatment of patients who have responded to ECT consists of treatment with antidepressant medications and/or a tapering schedule of ECT treatments. Continuation treatment reduces the risk of relapse and should be offered to all patients who respond to ECT. Continuation ECT treatments should be tapered and discontinued as the patient's clinical condition allows. Maintenance treatment with ECT is indicated to prevent recurrence of depression in patients whose remission of symptoms cannot be maintained with pharmacologic antidepressant treatment.

Appendix B

Modified guidelines

For implementation on 10/1/14

GUIDELINE NOTE 102, ~~NON-PHARMACOLOGIC INTERVENTIONS FOR TREATMENT-RESISTANT DEPRESSION~~ REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Line 7

Repetitive transcranial magnetic stimulation (CPT 90867-90868) ~~and electroconvulsive therapy (CPT 90870) are~~ is covered only after failure of at least two antidepressants.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,594

Bariatric surgery ~~for obesity~~ is included ~~on Line 30 TYPE II DIABETES MELLITUS, and Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)~~ under the following criteria:

- A) Age ≥ 18
- B) The patient has
 - 1) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE II DIABETES MELLITUS; OR
 - 2) BMI ≥ 35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI ≥ 40 without a significant co-morbidity for inclusion on Line 594 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)

~~For inclusion on Line 30: BMI ≥ 35 with co-morbid type II diabetes. For inclusion on Line 594: BMI ≥ 35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI ≥ 40 without a significant co-morbidity.~~
- C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
- D) Participate in the following four evaluations and meet criteria as described.
 - 1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
 - a) Evaluation to assess potential compliance with post-operative requirements.
 - b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
 - c) No mental or behavioral disorder that may interfere with postoperative outcomes¹.

Appendix B

- d) Patient with previous psychiatric illness must be stable for at least 6 months.
- 2) Medical evaluation: (Conducted by OHP primary care provider)
 - a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
 - b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
 - c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
- 3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program²)
 - a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
 - b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure³ and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
- 4) Dietician evaluation: (Conducted by licensed dietician)
 - a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
 - b) Counseling in dietary lifestyle changes
- E) Participate in additional evaluations:
 - 1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

¹ Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

² All surgical services must be provided by a program with current certification by the ~~American College of Surgeons (ACS) or the American Society for Metabolic and Bariatric Surgery (ASMBS)~~, [Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program \(MBSAQIP\)](#) or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365; appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing [MBSAQIP ACS or ASMBS](#) certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

³ Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

⁴ ~~The patient must meet criteria #1, #2, and #3, and be referred by the OHP primary care provider as a medically appropriate candidate, to be approved for evaluation at a qualified bariatric surgery program.~~

Appendix B

Implementation date to be determined by OHA Leadership

GUIDELINE NOTE 75, APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER

Line 313

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 0359T-0374T, is included on line 313 for the treatment of autism spectrum disorders.

ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in guideline note 6, REHABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.

Individuals ages 1-12

Intensive interventions

Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Appendix B

Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. The quality of evidence is insufficient to support these interventions in this population. However, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.

Section 2.0

Staff Report

Section 3.0

Consent Agenda-

Straightforward Items

Straightforward Issues—August, 2014

Code	Code Description	Line(s) Involved (October 2014 list/Jan. 1 list)	Issue	Recommendation(s)
40530	Resection of lip, more than 1/4, without reconstruction	292/279 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA	DMAP requests 40530 pair with 173.02 (Squamous cell carcinoma of skin of lip). 40530 appears on lines 168, 292, 636, 326.	Add 40530 to line 292/279
77418 77421	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session Stereoscopic X-ray guidance for localization of target volume for the delivery of radiation therapy	252/242 CANCER OF OVARY 459/439 CANCER OF GALLBLADDER AND OTHER BILIARY	DMAP requests 77418 and 77421 pair with malignant neoplasms of the ovary (ICD-9 183.0) and gallbladder (ICD-9 156.0). 77418 and 77421 are currently on more than 35 lines.	Add 77418 and 77421 to lines 252/242 and 459/439
35606	Bypass graft, with other than vein; carotid-subclavian	440/419 TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION	DMAP requests 35606 pair with 435.2 (Subclavian steal syndrome). 35606 is currently on lines 239, 289, 290, 310, 330, 352, 452.	Add 35606 to line 440/419
35452	Transluminal balloon angioplasty, open; aortic	472/452 ATHEROSCLEROSIS, AORTIC AND RENAL	DMAP requests 35452 pair with 440.0 Atherosclerosis of aorta. 35452 is currently on lines 48,74,110,227,239,352. Other balloon angioplasty codes are on line 452.	Add 35452 to line 472/452

Straightforward Issues—August, 2014

Code	Code Description	Line(s) Involved (October 2014 list/Jan. 1 list)	Issue	Recommendation(s)
15120 15121	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof	448/427 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP requests that 15120 pair with 998.83 (Non-healing surgical wound). 15120 is on 14 lines. 15121 is also missing from line 427. Similar skin graft codes appear on line 427.	Add 15120 and 15121 to line 448/427
14040	Adjacent tissue transfer or rearrangement, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; defect 10 sq cm or less	459/438 HYPOSPADIAS AND EPISPADIAS	DMAP requests that 14040 pair with 752.61 (Hypospadias). 14040 is on multiple lines. This pairing concern doing a “Dartos tissue transfer” with a hypospadias repair. Dr. Steven Skoog from OHSU states that this Dartos procedure has decreased the rate if urethrocutaneous fistula formation. He states this tissue transfer is not part to the hypospadias repair as defined in the CPT manual.	Add 14040 to line 459/438

Straightforward Issues—August, 2014

Code	Code Description	Line(s) Involved (October 2014 list/Jan. 1 list)	Issue	Recommendation(s)
62311	Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; lumbar or sacral	78/75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 318/297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	DMAP requests that 62311 pair with 343.9 (Unspecified infantile cerebral palsy). 62311 was Ancillary until January, 2013 when it was moved to line 400 only as part of the review for percutaneous interventions for low back pain. This code appears to be used for baclofen trails before pump insertion. 62310 (cervical or thoracic level injections) remains Ancillary.	Add 62311 to lines 78/75 and 318/297
90670	Pneumococcal conjugate vaccine, 13 valent	For October 1 PL: 3 PREVENTIVE SERVICES, BIRTH TO 10 YEARS OF AGE 4 PREVENTIVE SERVICES, OVER AGE OF 10 For January 1 PL: 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	90670 is currently Excluded. It should be on the prevention lines as this is the standard pneumococcal vaccine for children. When reviewed in 2009, this vaccine was not FDA approved. HSC staff was charged with adding this code to the appropriate line once FDA approval was received; however, this was not done.	Add 90670 to line 3,4/3 Advise DMAP to remove 90670 from the Excluded List.

Section 4.0

New Discussion Items

Nerve Blocks

Question: Should we modify the nerve block guideline to include CPT codes? Should we remove nerve blocks from various lines?

Question source: HERC staff

Issue: The nerve block CPT codes were placed on the Ancillary list in 2004, with the intent that DMAP treat them as ancillary services to be covered for funded diagnoses. In January 2009 the HSC reaffirmed the recommendation that DMAP place codes 64400-64550 in the Ancillary file and further specified that these nerve blocks should be provided according to the following guideline (Guideline Note 76). These CPT codes are still listed as Ancillary for the October 1, 2014 Prioritized List. However, they appear on 359 lines on the January 1, 2015 List, many of which are inappropriate. The current nerve block guideline does not specify the CPT codes for these procedures.

HERC staff recommendation:

- 1) Option 1: Put all nerve block CPT codes (64400-64550) back on the Ancillary List and making the guideline an Ancillary Guideline again (with codes added to guideline), effective with the January 1, 2015 Prioritized List.
- 2) Option 2: Remove CPT codes 64400-64550 from the following lines (left on all lines with surgical treatments) for the January 1, 2015 Prioritized List.
 - 1) 9 ASTHMA
 - 2) 11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN
 - 3) 20 HYDROCEPHALUS AND BENIGN INTRACRANIAL HYPERTENSION
 - 4) 24 CYSTIC FIBROSIS
 - 5) 52 CHRONIC RESPIRATORY DISEASE ARISING IN THE NEONATAL PERIOD
 - 6) 54 PULMONARY TUBERCULOSIS
 - 7) 63 END STAGE RENAL DISEASE
 - 8) 72 ACUTE BACTERIAL MENINGITIS
 - 9) 83 PHLEBITIS AND THROMBOPHLEBITIS, DEEP
 - 10) 97 CHILDHOOD LEUKEMIAS
 - 11) 102 HEART FAILURE
 - 12) 107 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS
 - 13) 115 CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART
 - 14) 119 CHRONIC MYELOID LEUKEMIA
 - 15) 125 ABUSE AND NEGLECT
 - 16) 131 ACUTE KIDNEY INJURY
 - 17) 139 HODGKIN'S DISEASE
 - 18) 141 OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED HOSTS;
CANDIDIASIS OF STOMA; PERSONS RECEIVING CONTINUOUS ANTIBIOTIC
THERAPY
 - 19) 148 HYPOTHERMIA
 - 20) 156 NON-PULMONARY TUBERCULOSIS
 - 21) 160 ACROMEGALY AND GIGANTISM

Nerve Blocks

- 22) 162 NON-HODGKIN'S LYMPHOMAS
- 23) 167 NON-HODGKIN'S LYMPHOMAS
- 24) 169 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS
- 25) 173 NON-DIABETIC HYPOGLYCEMIC COMA
- 26) 174 ACUTE MASTOIDITIS
- 27) 175 AMEBIASIS
- 28) 183 ACUTE LEUKEMIA, MYELOYDYSPLASTIC SYNDROME
- 29) 186 SEPTICEMIA
- 30) 197 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN
- 31) 198 ACUTE PANCREATITIS
- 32) 208 PNEUMOCOCCAL PNEUMONIA, OTHER BACTERIAL PNEUMONIA, BRONCHOPNEUMONIA
- 33) 216 BULLOUS DERMATOSES OF THE SKIN
- 34) 221 TESTICULAR CANCER
- 35) 225 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE
- 36) 226 OCCUPATIONAL LUNG DISEASES
- 37) 235 MYCOBACTERIA, FUNGAL INFECTIONS, TOXOPLASMOSIS, AND OTHER OPPORTUNISTIC INFECTIONS
- 38) 237 ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS
- 39) 238 ACUTE LYMPHOCYTIC LEUKEMIAS (ADULT) AND MULTIPLE MYELOMA
- 40) 241 ACUTE PROMYELOCYTIC LEUKEMIA
- 41) 253 PARKINSON'S DISEASE
- 42) 254 CHRONIC PANCREATITIS
- 43) 255 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM
- 44) 264 MULTIPLE MYELOMA
- 45) 269 ACUTE, SUBACUTE, CHRONIC AND OTHER TYPES OF IRIDOCYCLITIS
- 46) 273 ADVANCED DEGENERATIVE DISORDERS AND CONDITIONS OF GLOBE
- 47) 278 UROLOGIC INFECTIONS
- 48) 293 OSTEOPETROSIS
- 49) 300 APLASTIC ANEMIAS
- 50) 306 GOUT
- 51) 309 VIRAL PNEUMONIA
- 52) 314 CHRONIC INFLAMMATORY DISORDER OF ORBIT
- 53) 317 HEARING LOSS - AGE 5 OR UNDER
- 54) 322 STROKE
- 55) 334 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME
- 56) 335 ACUTE PROMYELOCYTIC LEUKEMIA
- 57) 338 ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER
- 58) 339 SCLERITIS
- 59) 343 CHRONIC KIDNEY DISEASE
- 60) 346 RHEUMATIC FEVER
- 61) 349 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS

Nerve Blocks

- 62) 350 CARDIAC ARRHYTHMIAS
 - 63) 364 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS
 - 64) 368 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS
 - 65) 381 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION
 - 66) 386 LATE SYPHILIS
 - 67) 392 ANOGENITAL VIRAL WARTS
 - 68) 397 CROUP SYNDROME, EPIGLOTTITIS, ACUTE LARYNGOTRACHEITIS
 - 69) 401 ACUTE MYELOID LEUKEMIA
 - 70) 402 MYELOID DISORDERS
 - 71) 404 CHRONIC MYELOID LEUKEMIA
 - 72) 410 EPIDERMOLYSIS BULLOSA
 - 73) 419 TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION
 - 74) 424 CHRONIC LEUKEMIAS WITH POOR PROGNOSIS
 - 75) 431 NON-MALIGNANT OTITIS EXTERNA
 - 76) 432 VAGINITIS AND CERVICITIS
 - 77) 440 PRECANCEROUS VULVAR CONDITIONS
 - 78) 450 HEARING LOSS - OVER AGE OF FIVE
 - 79) 464 ACUTE BRONCHITIS AND BRONCHIOLITIS
 - 80) 468 OSTEOARTHRITIS AND ALLIED DISORDERS
 - 81) 469 ATELECTASIS (COLLAPSE OF LUNG
 - 82) 472 BRACHIAL PLEXUS LESIONS
 - 83) 496 CLOSED FRACTURES OF RIBS, STERNUM AND COCCYX
 - 84) 504 CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD) AND HYDROXYAPETITE DEPOSITION DISEASE
 - 85) 519 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
 - 86) 526 FOREIGN BODY IN GASTROINTESTINAL TRACT WITHOUT RISK OF PERFORATION OR OBSTRUCTION
 - 87) 527 PANNICULITIS
 - 88) 630 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS
- 3) Both options: Add the CPT codes for the nerve blocks to GN 76, as shown below

Nerve Blocks

GUIDELINE NOTE 76, NERVE BLOCKS

Lines 1,3,6,8,9,11,20,24,25,28,30,32,37-41,46-55,59-63,65,67,68,70-76,81-100,102-105,107,109-112,115-121,123-125,129-132,134-145,147,148,154,156-164,166-170,172-175,178,180,183-195,197-201,203,204,206,208,209,211-214,216-221,223,225-228,230,232-239,241-251,253-255,257-267,269,273-275,277-280,283-286,289-294,297-306,308-312,314-317,319-324,327,328,330-335,337-341,343,344,346,349,350,352,354-360,362-370,372,374-376,378-384,386,389,391,392,394,397-402,404-408,410,412,417,419-424,426-428,430-436,438-441,443-447,450,452,453,456,458,459,464-466,468-472,474,476,477,480-484,486,487,496,504,519,526,527,532,535,549,568,630

The Health Evidence Review Commission intends that single injection and continuous nerve blocks ([64400-64550](#)) should be covered services if they are required for successful completion of perioperative pain control for, or post-operative recovery from a covered operative procedure when the diagnosis requiring the operative procedure is also covered. Additionally, nerve blocks, are covered services for patients hospitalized with trauma, cancer, or intractable pain conditions, if the underlying condition is a covered diagnosis.

Diabetic Retinopathy Codes

Question: Should placement of the diabetic retinopathy ICD-9 and 10 codes be clarified?

Question source: Allergan, HERC staff

Issue: The ICD-9 codes for diabetic retinopathy (367.0x) are currently Excluded. Coding convention has these codes placed as secondary codes after the diabetes with ophthalmologic complications code (250.5x). However, the 367.0x codes are required for use of Ozurdex (dexamethasone intravitreal implant) and similar treatments. Diabetic retinopathy appears on line 106/100 DIABETIC AND OTHER RETINOPATHY.

The majority of ICD-10 codes for diabetic retinopathy (E10.311, E11.3xx) are on line 106/100. However, E10.319 (Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema) is on lines 10/8 TYPE 1 DIABETES MELLITUS and 273 ADVANCED DEGENERATIVE DISORDERS AND CONDITIONS OF GLOBE only. The other codes in the E10.3xx series (Type 1 diabetes mellitus with ophthalmic complications) are on lines 10/8 and 273 only. The E11.3xx family (Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema) is not on the type 2 diabetes line.

Additionally, other types of diabetes mellitus (due to underlying condition/drug or chemical induced diabetes mellitus/other specified diabetes mellitus) with retinopathy (E08.3xx, E09.3xx, E13.3xx) are not all on the type 2 diabetes line 33/30 TYPE 2 DIABETES MELLITUS.

HERC staff recommendations (October 1, 2014 List/January 1, 2015 List):

- 1) Add the 367.0x codes (diabetic retinopathy, mild/moderate/severe, with or without proliferative retinopathy, and diabetic macular edema) to line 106/100 DIABETIC AND OTHER RETINOPATHY
 - a. Advise DMAP to remove the 367.0x codes from the Excluded List
- 2) Add all codes in the E10.3xx family (Type 1 diabetes mellitus with ophthalmologic complications) to line 106/100 DIABETIC AND OTHER RETINOPATHY
- 3) Add all codes in the E08.3xx family (diabetes due to underlying condition with retinopathy), E09.3xx family (drug or chemical induced diabetes with retinopathy), E11.3xx family (Type 2 diabetes mellitus with ophthalmologic complications), and E13.3xx family (other specified diabetes with retinopathy) to line 33/30 TYPE 2 DIABETES MELLITUS.

Tympanostomy tubes and tympanic membrane perforation

Question: Should tympanic membrane perforation be reprioritized and should a guideline be added regarding tympanostomy tubes?

Question source: Medical Directors from CCOs

Issue: Multiple medical directors from CCOs have raised questions about placement and coverage intent about perforated tympanic membranes and retained tympanostomy tubes.

From Holly Jo Hodges:

Tympanostomy tubes often get coded as ICD-9: 384.20-PERFORAT TYMPAN MEMB UNSPEC, on non-funded line 502.

However it makes perfect sense to me that they are retained foreign bodies in the tympanic membrane, 385.83-FOREIGN BODY MIDDLE EAR, and V90.2-Retained plastic fragments,

Which is funded on line 405 and pairs with CPT=69620.

I just had a conversation with one of our local ENT's, Dr. Susan Urben, and I agree with her statement, "DMAP pays to put them in, they should pay to take them out."

What about perforated TM after prolonged PE tubes that we (OHP) paid to put in??

Seems like those should be covered as well??

Clinical background:

From emedicine

Presentation

Perforation symptoms may include audible whistling sounds during sneezing and nose blowing, decreased hearing, and a tendency to infection during colds and when water enters the ear canal. Copious purulent drainage, which may be sanguineous in both acute and chronic perforation, confirms both perforation and infection. Ear canal infections also can cause purulent drainage, but usually in lesser amounts. Perforations uncomplicated by infection or cholesteatoma are never painful. Presence of pain should alert the physician to a concurrent disease process. Perforations accompanied by otorrhea or cholesteatoma are usually not painful.

Indications for repair

Many persons live their lives with tympanic membrane perforations that are entirely without symptoms. Repair of such lesions is usually not indicated. Perforations may be associated with recurrent infection when exposed to water. In swimmers, divers, and other water sports enthusiasts, repair may be indicated as a quality-of-life issue. Hearing loss may be present, especially with larger perforations, and may be a reason for repair.^[7] Because a risk to residual hearing exists with every operation on the ear drum, a risk-benefit analysis in which the patient participates is mandatory.^[8] For example, question whether the person may be helped just as much with use of a [hearing aid](#).

Tympanostomy tubes and tympanic membrane perforation

Current Prioritized List Status

Line: 383
Condition: HEARING LOSS - AGE 5 OR UNDER (See Guideline Notes 51,64,65,76)
Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS
ICD-9: 388.00,388.02-388.2,388.40-388.5,388.8,389.00-389.9,V53.2
CPT: 69210,69424-69436,69714,69715,92590-92595,92597,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Line: 405
Condition: CHOLESTEATOMA; INFECTIONS OF THE PINNA (See Guideline Notes 64,65,76)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-9: 380.00-380.03,380.11,380.21,383.30-383.89,384.1,384.81-384.82,385.00-385.9
CPT: 21235,69220,69420-69540,69601-69646,69662,69670,69700,69905,69910,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Pertinent codes

385.83	Retained foreign body of middle ear

Line: 418
Condition: ACUTE OTITIS MEDIA (See Guideline Notes 29,64,65,76)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-9: 381.00-381.06,381.51,381.81-381.9,382.00-382.02,382.4-382.9,384.00-384.09,993.0
CPT: 69210,69420-69436,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Line: 502
Condition: CHRONIC OTITIS MEDIA (See Guideline Notes 51,64,65,76)
Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY
ICD-9: 380.50-380.53,381.10-381.89,382.1-382.3,382.9,383.1,383.20-383.31,383.9,384.20-384.9
CPT: 42830-42836,69210-69222,69310,69400-69511,69601-69650,69700,69801,69905,69910,69979,92562-92565,92571-92577,92590,92591,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

69610
myringoplasty

Pertinent codes

Code	Description
384.20	Perforation of tympanic membrane, unspecified
384.21	Central perforation of tympanic membrane
384.22	Attic perforation of tympanic membrane
384.23	Other marginal perforation of tympanic membrane
384.24	Multiple perforations of tympanic membrane
384.25	Total perforation of tympanic membrane
384.9	Unspecified disorder of tympanic membrane

Tympanostomy tubes and tympanic membrane perforation

Line: 505
Condition: FOREIGN BODY IN EAR AND NOSE (See Guideline Notes 64,65,76)
Treatment: REMOVAL OF FOREIGN BODY
ICD-9: 931-932,V90.01-V90.9
CPT: 30300-30320,69200,69205,98966-98969,99051,99060,99070,99078,99201-99239,99281-99360,99366,99374,99375,99379-99412,99429-99449,99471-99476,99487-99496,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Cpt code 69424 Ventilating tube removal requiring general anesthesia is located on the following lines

Line	Condition	Treatment
178	ACUTE MASTOIDITIS	MASTOIDECTOMY, MEDICAL THERAPY
308	COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	MEDICAL AND SURGICAL TREATMENT
383	HEARING LOSS - AGE 5 OR UNDER	MEDICAL THERAPY INCLUDING HEARING AIDS
405	CHOLESTEATOMA; INFECTIONS OF THE PINNA	MEDICAL AND SURGICAL TREATMENT
418	ACUTE OTITIS MEDIA	MEDICAL AND SURGICAL TREATMENT
502	CHRONIC OTITIS MEDIA	PE TUBES/ADENOIDECTOMY/TYM PANOPLASTY, MEDICAL THERAPY

GUIDELINE NOTE 29, TYMPANOSTOMY TUBES IN ACUTE OTITIS MEDIA

Line 418

Tympanostomy tubes (CPT 69436) are only included on this line as treatment for

1. recurrent acute otitis media (three or more well-documented and separate episodes in the past 12 months with at least one episode in the past six months) in patients who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, or
2. patients with complicating conditions (immunocompromised host, meningitis by lumbar puncture, acute mastoiditis, sigmoid sinus/jugular vein thrombosis by CT/MRI/MRA, cranial nerve paralysis, sudden onset dizziness/vertigo, need for middle ear culture, labyrinthitis, or brain abscess).

Patients with craniofacial anomalies, Down's syndrome, cleft palate, permanent hearing loss of 25dB or greater independent of otitis media with effusion, and patients with speech and language delay may be considered for tympanostomy if unresponsive to appropriate medical treatment or having recurring infections (without needing to meet the strict "recurrent" definition above).

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 383,502

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 383. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 502.

For coverage to be considered on either Line 383 or Line 502, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay (should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected).

Tympanostomy tubes and tympanic membrane perforation

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children over 3 years who are having their second set of tubes.

Coding guidance

From the American Academy of Otolaryngology – Head and Neck Surgery

Q: How Do I code for PE tube removal?

A: In January 2003, the American Medical Association (AMA) CPT Editorial Panel revised the coding for removal of tympanostomy (PE) tubes. Prior to the revision in January 2003, CPT code 69424 described: "ventilating tube removal when originally inserted by another physician." Post revision, the code descriptor for 69424 indicates ventilating tube removal requiring general anesthesia."

Physicians should bill CPT code 69424 for tube removal in the operating room only. If the physician removes PE tubes in the office, he or she should use an appropriate E/M CPT code. For any additional procedures performed simultaneously with this removal, submit appropriate modifiers, CPT, and ICD 9 CM codes.

NOTE: Removal of tympanostomy tubes in the office setting does not meet the criteria of a foreign body removal. If you remove a tube on the same date of service from the same ear for which a repair is performed (e.g. CPT code 69610- Tympanic membrane repair, with or without site preparation of perforation for closure, with or without patch), report only the repair code. This is because removal of the tube is part of the repair service; this is reflected in the higher value of the repair.

HERC Staff Assessment

Removal of tympanostomy tubes (under general anesthesia) is already present on multiple lines. Usually, removal of tubes can be done in the office and would be billed as an E&M code. However, if a patient has a diagnosis on Line 502 only, coverage of tube removal is not clearly covered.

Tympanic membrane perforation appears to be self-resolving or minimally symptomatic. If significant health issues are arising from persistent perforation, another diagnosis would emerge and treatment would pair on the more appropriate line.

HERC Staff Recommendations:

- 1) Make no change to placement of tympanic membrane perforation codes (Line 502).
- 2) Add a new guideline

Guideline Note XXX Retained tympanostomy tubes

Lines 178, 308, 405, 418, 502

Removal of retained tympanostomy tubes under anesthesia, if indicated (cpt code 69424 *Ventilating tube removal requiring general anesthesia*) or as part of an office visit, are intended to be covered for Line 502 diagnoses with the Line 405 icd-9 code 383.83 *Retained foreign body of middle ear*.

Osteopathic/Chiropractic Manipulation for Migraine and Tension Headache

Question: should osteopathic manipulation (OMT, CPT 98926- 98929) and chiropractic manipulation (CMT, CPT 98940-98943) continue to be included as treatments for migraine headache and for tension headache?

Question source: Lyle Jackson, MD, OHP Medical Director

Issue: Both migraine and tension headache have been paired with OMT and CMT since a taskforce recommended coverage in 1997. Migraine is on line 414 MIGRAINE HEADACHES and tension headache is on line 546 TENSION HEADACHES. Cervicogenic headache is located on line 546 and is represented by the generic ICD-9 code 784.0 (headache)

1997 Taskforce Report on Migraine and Non-migraine Headaches

- 1) Chiropractic referral could be considered if the patient has a history of neck trauma, palpation of the cervical spine area reproduces the headache or neck movement or sustained neck posture aggravate the headache. Migraine and tensions headaches that have a “cervicogenic” component may also benefit from treatment.
 - a. This recommendation is based on
 - i. 1 review (Hurwitz 1996) which included 3 RCTs, found short term benefit (up to 4 weeks)
 - ii. 2 RCTs (N=141 patients)--found reduced medication use and improved symptoms (Nilsson 1997); equivalent response between CMT and PT (Parker 1978)

Evidence

Migraine headache

- 1) **Posadzki 2011**, systematic review
 - a. N=3 RCTs of poor methodological quality
 - b. Two RCTs suggested no effect of spinal manipulations in terms of Headache Index or migraine duration and disability compared with drug therapy, spinal manipulation plus drug therapy, or mobilization.
 - c. One RCT showed significant improvements in migraine frequency, intensity, duration and disability associated with migraine compared with detuned interferential therapy. The most rigorous RCT demonstrated no effect of chiropractic spinal manipulation compared with mobilization or spinal manipulation by medical practitioner or physiotherapist on migraine duration or disability.
 - d. Conclusions: Current evidence does not support the use of spinal manipulations for the treatment for migraine headaches.
- 2) **Chialbi 2011**, systematic review
 - a. N=3 RCTs (N=430), 2 considered good quality and 1 considered poor quality

- i. One study compared CMT done by physician vs chiropractor vs PT (i.e. all patients received CMT)
- ii. One study compared CMT to amitriptyline (N=77 vs 70)
 1. No significant differences found in mean frequency or mean intensity of headache between groups
- iii. One study compared CMT (N=83) to control of detuned interferential therapy (n=40)
 1. The average response was statistically significantly better in the CSMT than the control group regarding migraine frequency ($p<0.005$), duration ($p<0.01$), disability ($p<0.05$), and reduction in medication use ($p<0.001$) The frequency and duration was reduced from baseline to follow-up by 35 and 40% in the CSMT group, and 17 and 20% in the control group
- iv. Conclusions: Current RCTs suggest that massage therapy, physiotherapy, relaxation and chiropractic spinal manipulative therapy might be equally efficient as propranolol and topiramate in the prophylactic management of migraine. However, a firm conclusion requires, in future, well-conducted RCTs without the many methodological shortcomings of the evaluated RCTs on manual therapies.

Tension headache

1) **Fernandez-de-las-Penas 2006**, systematic review

- a. N=5 RCTs (321 patients), studies compared spinal manipulation to other physical modalities (soft tissue or connective tissue manipulation) or amitriptyline (1 study), 4-14 week follow up
- b. Analysis of the quality and the outcomes of all trials did not provide rigorous evidence that manual therapies have a positive effect in reducing pain from TTH: spinal manipulative therapy showed inconclusive evidence of effectiveness (level 4), whereas soft tissue techniques showed limited evidence (level 3).
- c. Conclusions: The authors found no rigorous evidence that manual therapies have a positive effect in the evolution of TTH.

Cervicogenic headache

1) **Posadzki 2011**, systematic review

- a. 9 RCTs (407 patients), of mostly poor methodological quality
- b. Six RCTs suggested that spinal manipulation is more effective than physical therapy, gentle massage, drug therapy, or no intervention.
- c. Three RCTs showed no differences in pain, duration, and frequency of headaches compared to placebo, manipulation, physical therapy, massage, or wait list controls.
- d. Adequate control for placebo effect was achieved in 1 RCT only, and this trial showed no benefit of spinal manipulations beyond a placebo effect.
- e. Conclusions: there are few rigorous RCTs testing the effectiveness of spinal manipulations for treating cervicogenic headaches. The results are

mixed and the only trial accounting for placebo effects fails to be positive. Therefore, the therapeutic value of this approach remains uncertain.

Multiple headache types

1) **NICE 2012**

a. Tension headache

- i. Bronfort 2009 Cochrane review was excluded as it included quasi-randomised studies in addition to randomised controlled trials and reported outcomes at four weeks post treatment
- ii. Manual therapies vs placebo
 1. One study with 75 people with tension type headache suggested that there is no difference between spinal manipulation with soft tissue therapy and placebo at reducing headache intensity at 3 months follow-up, but there is some uncertainty. [Low quality].
 2. One study of with 75 people with tension type headache suggested that there is no difference between spinal manipulation with soft tissue therapy and placebo at reducing the use of acute pharmacological treatments at 3 months follow-up, but there is some uncertainty. [Low quality].
 3. No studies reported outcome data for change in patient reported headache days or frequency, responder rate, functional health status or quality of life, resource use or incidence of serious adverse events.

iii. Manual therapies vs usual care

1. One study with 82 people with chronic tension type headache showed that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction is more clinically effective than usual care at reducing number of headache days at 26 weeks.[Low quality].
2. One study with 82 people with chronic tension type headache suggested that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction may be more clinically effective than usual care at reducing headache intensity at 26 weeks, but there is some uncertainty. [Very low quality].
3. One study with 82 people with chronic tension type headache suggested that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction may be more clinically effective than usual care at improving headache specific quality of life scores (HIT-6) at 26 weeks, but there is some uncertainty. [Very low quality].

4. One study with 82 people with chronic tension type headache showed that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction is more clinically effective than usual care at increasing responder rate at 26 weeks. [Low quality].
5. One study with 82 people with chronic tension type headache suggested that there is no difference between manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction, and usual care in reducing the use of additional medical specialists at 26 weeks, but there is some uncertainty. [Very low quality].
6. One study with 82 people with chronic tension type headache suggested that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction, and usual care may be similarly effective in reducing the use of additional resources at 26 weeks, but there is some uncertainty. [Very low quality].

b. Migraine

i. Manual therapies vs placebo

1. One study with 127 people with migraine suggested that spinal manipulative therapy may be more clinically effective than placebo at reducing number of migraine days at 3 months follow-up, but there is some uncertainty. [Low quality].
2. One study with 127 people with migraine suggested that placebo may be more clinically effective than spinal manipulative therapy at reducing migraine intensity at 3 months follow-up, but there is some uncertainty. [Low quality].
3. One study with 127 people with migraine suggested that spinal manipulative therapy may be more clinically effective than placebo at reducing the average number of acute pharmacological treatments used per month at 3 months follow-up, but there is some uncertainty. [Low quality].

ii. Manual therapies vs pharmacological treatment

- a. One study with 147 people with migraine suggested that there is no difference between spinal manipulative therapy and amitriptyline at reducing number of migraine days at 3 months follow-up, but there is some uncertainty. [Very low quality].
- b. One study with 147 people with migraine showed that there is no difference between spinal manipulative therapy and amitriptyline at reducing migraine intensity at 3 months follow-up. [Low quality].
- c. One study with 147 people with migraine suggested that there is no difference between spinal manipulative therapy

and amitriptyline at modifying functional health status at 3 months follow-up, but there is some uncertainty. [Very low quality].

- d. One study with 147 people with migraine showed that there is no difference between spinal manipulative therapy and amitriptyline

c) Overall recommendation

- ii. The evidence reviewed was low to very low quality.
- iii. **There was not enough evidence to form a recommendation for or against manual therapies for prophylaxis of tension type headache or migraine from the evidence reviewed.**

2) SIGN 2008

- a. Evaluation of manual therapy including spinal manipulation therapy (SMT) and spinal mobilisation.

b. **Cervicogenic headache**

- i. In a Cochrane systematic review five studies of spinal manipulation therapy for cervicogenic headache were described. SMT was compared with placebo, mobilisation, NSAIDs, exercise and massage plus placebo laser. Although the studies were too dissimilar for results to be pooled, there was moderate evidence that SMT is superior to no treatment in reducing headache pain and frequency one week and 12 months following six weeks of treatment and superior to placebo SMT for pain, disability and number of headache sites three weeks after treatment. A comparison with massage plus placebo laser found SMT produced a significantly greater decrease in pain intensity (effect size 0.6; 95% CI 0.1-1.1)
- ii. Recommendation: **Spinal manipulation therapy should be considered in patients with cervicogenic headache.**

c. **Migraine**

- i. A Cochrane systematic review (Bronfort 2004, updated 2009) identified three studies of effectiveness of spinal manipulation in migraine compared with amitriptyline, spinal mobilisation and placebo electrotherapy. The studies were too dissimilar for results to be pooled and the evidence of effectiveness is too limited to lead to recommendation.

d. **Tension-type headache**

- i. Two studies of SMT in patients with chronic tension-type headache were included in a Cochrane systematic review. In one study SMT was inferior to amitriptyline for effect on pain intensity during six weeks of treatment, although this was reversed at four weeks post-treatment. The second study examined the immediate effects of a single treatment and found more pain reduction in the SMT group than in a no-treatment control group. A systematic review of a range of manual therapies for pain reduction in tension-type headache found no rigorous positive effect of manual therapies.

- ii. A small single blind RCT (n=26) found that three osteopathic treatments, one each week for three weeks, plus relaxation exercises, increased the number of headache free days per week in patients with TTH compared with relaxation exercises alone (0.21 days to 1.79 days, $p=0.016$).
- iii. An RCT in a mixed group of patients with episodic and chronic TTH compared a craniocervical training programme combined with physiotherapy with physiotherapy alone. There was a positive and clinically relevant effect on headache frequency at six months following a six week programme. 85% of patients in the treatment group (n=39) experienced a reduction of $\geq 50\%$ in their headache frequency at six months compared to 35% in the control group.
- iv. No recommendation made

3) **Bronfort 2009**, Cochrane review of spinal manipulation on headache

- a. N=22 studies (2628 patients)
- b. Five types of headache were studied: migraine, tension-type, cervicogenic, a mix of migraine and tension-type, and post-traumatic headache.
- c. Ten studies had methodological quality scores of 50 or more (out of a possible 100 points), but many limitations were identified.
- d. For the prophylactic treatment of migraine headache, there is evidence that spinal manipulation may be an effective treatment option with a short-term effect similar to that of a commonly used, effective drug (amitriptyline).
- e. For the prophylactic treatment of chronic tension-type headache, amitriptyline is more effective than spinal manipulation during treatment. However, spinal manipulation is superior in the short term after cessation of both treatments.
- f. For episodic tension-type headache, there is evidence that adding spinal manipulation to massage is not effective.
- g. For the prophylactic treatment of cervicogenic headache, there is evidence that both neck exercise (low-intensity endurance training) and spinal manipulation are effective in the short and long term when compared to no treatment. There is also evidence that spinal manipulation is effective in the short term when compared to massage or placebo spinal manipulation, and weaker evidence when compared to spinal mobilization. There is weaker evidence that spinal mobilization is more effective in the short term than cold packs in the treatment of post-traumatic headache.
- h. **Authors' conclusions** A few non-invasive physical treatments may be effective as prophylactic treatments for chronic/recurrent headaches. Based on trial results, these treatments appear to be associated with little risk of serious adverse effects. The clinical effectiveness and cost-effectiveness of non-invasive physical treatments require further research using scientifically rigorous methods.

4) **Bryans 2011**, evidence based review

- a. N=21 articles, moderate of low quality of evidence

- b. For migraine, spinal manipulation and multimodal multidisciplinary interventions including massage are recommended for management of patients with episodic or chronic migraine.
- c. For tension-type headache, spinal manipulation cannot be recommended for the management of episodic tension-type headache. A recommendation cannot be made for or against the use of spinal manipulation for patients with chronic tension-type headache
- d. For cervicogenic headache, spinal manipulation is recommended.
- e. Adverse events were not addressed in most clinical trials; and if they were, there were none or they were minor.
- f. Conclusions: Evidence suggests that chiropractic care, including spinal manipulation, improves migraine and cervicogenic headaches. Evidence for the use of spinal manipulation as an isolated intervention for patients with tension-type headache remains equivocal.

Summary: There is conflicting conclusions about the evidence of effectiveness in the literature for OMT/CMT as treatment for migraine and tension headaches, but the majority of reviews found no evidence of effectiveness or insufficient evidence to make a recommendation. Studies were generally of low to very low quality. Trusted sources (SIGN, Cochrane) conclude that when these headaches have a cervicogenic component, OMT/CMT can have short term benefit with little risk of adverse effects.

Expert input: Dr. Vern Saboe, DC

The supposed systematic reviews by Posadzki (2011) and Nice (2012) have issues not the least of which are to completely ignore the Nelson (1998 citation below) study which explicitly demonstrated CMT is as effective as amitriptyline but with fewer side effects and CMT was shown to retard reoccurrence of migraine compared to amitriptyline after the treatment period ended. Though Bronfort's (2009) review acknowledges this trial he conveniently states that the RCTs combined at that time are too few and dissimilar to come to a definitive conclusion.

Our HERC and the Center for Evidence-based Policy need to consider the shortcomings of systematic reviews and meta-analyses which often omit observational studies and always disregard basic science reports. I have attached a couple articles written in this regard by my colleague and friend Tony Rosner and something I believe the Center staff and Commission members should consider in the future, this is probably not the proper venue by which to bring this up and you are probably not going to "go there".....

Utilization

Second 6 months of 2013, FFS and CCOs

Migraine (primary or secondary diagnosis): 84 claims (approximately \$900)

Tension or cervicogenic: 216 claims (approximately \$2332)

HERC staff recommendation (October 1, 2014 List/January 1, 2015 List):

- 1) Option 1:
 - a. Remove osteopathic and chiropractic manipulation (CPT 98926- 98929, 98940-98943) from line 435/414 MIGRAINE HEADACHES and restrict on line 563/546 TENSION HEADACHES to only cervicogenic headache with the coding specification shown below
 - i. Little or no evidence of effectiveness
 - ii. Coding specification for line 563/546
 1. "OMT and CMT (CPT 98926- 98929, 98940-98943) pair on this line only with cervicogenic headache (R51)."
- 2) Option 2
 - a. Keep OMT/CMP on lines 435/414 MIGRAINE HEADACHES and 563/546 TENSION HEADACHES
 - b. Add a new guideline to the migraine and tension headache lines specifying the OMT/CMT is only covered when there is a cervicogenic component to the headache

GUIDELINE NOTE XXX SPINAL MANIPULATION FOR HEADACHES

Lines 435,563 (October 1, 2014 List)

Lines 414,546 (January 1, 2015 List)

Osteopathic and chiropractic manipulation (CPT 98926- 98929, 98940-98943) are only included on these lines for treatment of migraine headache (ICD-9 346.xx/ICD-10 G43.xx), tension headache (ICD-9 307.81, 339.1x/ICD-10 G44.2xx), and cervicogenic headache (ICD-9 784.0/ICD-10 R51) when one of the following is present:

- 1) the patient has a history of neck trauma
- 2) palpation of the cervical spine area reproduces the headache or
- 3) neck movement or sustained neck posture aggravate the headache.

Task Forces

Migraine and Non-Migraine
Headache Referral Guideline

December 11, 1997

MIGRAINE AND NON-MIGRAINE HEADACHE

The Health Services Commission (HSC) convened a multidisciplinary Task Force (including representatives from Internal Medicine, Family Practice, Neurology, Psychiatry, Psychology, Chiropractic, Naturopathic and Acupuncture) that reviewed the literature on conventional drug therapy, the use of effective non-pharmacological treatments, and appropriate referrals for complicated headaches. The Task Force recommended and the HSC concurred that all headache diagnoses would reside on line 462 as a covered service. Most headache patients can be effectively managed with medications as summarized in the "Guidelines for the Diagnosis and Management of Migraine in Clinical Practice."¹

The Canadian Medical Association is in the process of developing a companion paper comparing traditional and non-traditional therapy for headaches. In the meantime, the Task force collected the best evidence based studies from each discipline on headaches that support the recommendations. Each discipline was compared for its ability to effectively treat migraine, cluster, tension, and cervicogenic headache. Each representative of that discipline gave their best estimate of the number of visits necessary to improve the patient.

REFERRAL GUIDELINE

The following subset of patients with non-responsive, severe, or complicated headaches may benefit from referral:

1. Emergency room visits for headache > 2 over 6 months, over-utilization of primary care, or demand for inappropriate referrals or testing.
2. Analgesic rebound headache², addiction, or over-utilization of medications.
3. Significant disability or absenteeism from work or school due to chronic headaches.
4. Symptoms that are progressive and uncontrolled with pharmacological therapy.
5. Co-morbid psychiatric diagnoses of anxiety, depression, or addictive personality.
6. Drastic change in headache pattern or onset of neurological localizing signs or seizures.
7. History of head and neck trauma or musculoskeletal signs or symptoms aggravated by neck movement.

Referral Strategy

Suggested Number of Visits*

1. Referral to a psychologist or stress management program to learn coping strategies and identification of trigger factors. Therapy for analgesic rebound daily headaches.	6-8
2. Psychiatric referral for depression or dual diagnosis of headache with depression, anxiety, or addictive personality.	4-6
3. Neurology referral for suspected neuropathology, management of severe migraine, or analgesic rebound headache.	2-4
4. Acupuncture referral for tension, migraine or cervicogenic headaches.	6-8
5. Biofeedback referral for migraine, tension or cervicogenic headaches.	6-8
6. Chiropractic referral for cervicogenic, tension, or mixed migraine headaches.	6-8

References:

1. Pryse-Phillips, Wm. et al., "Guidelines for the Diagnosis and Management of Migraine in Clinical Practice." *Canadian Medical Association Journal*, 156:1273-87 1997.
2. Walker, Jerome, MD et al, "Analgesic Rebound Headache," *Seminars in Headache Management*, Vol. 2, Number 3, September 1997.

* The appropriate number of visits has not been established in the literature. Both referral to and continued use of a treatment modality should be determined by medical effectiveness.

ATTACHMENT OF SUPPORTING LITERATURE

NEUROLOGIST

Neurological consultation should be considered if a patient has any of the following:

- 1) Onset of headache after age 50
- 2) Worst headache ever experienced
- 3) Onset of headache with exertion, sexual activity, coughing or sneezing
- 4) Headache with new neurological signs:
 - a. Change in mental status
 - b. Weakness, numbness, pupil asymmetry, ataxia, nuchal rigidity.
 - c. Fever, weight loss, hypertension.

Reference:

1. *Standards of Care for Headache Diagnosis and Treatment*, by National Headache Foundation 1996 p. 5

Comment: Excellent timely relevant monograph that is a comprehensive guideline addressing diagnosis, pharmacological, non-pharmacological, and referral management of all types of headaches.

BEHAVIORAL MEDICINE

Behavioral medicine may include psychosocial assessment, cognitive therapy, biofeedback, physical therapy, and muscle training. Also educational programs³ that promote patient involvement in their treatment program are valuable adjunctive treatment for all types of headaches.

References:

1. Holroyd, KA and Penzien, DB "Pharmacological Versus Non-pharmacological Prophylaxis of Recurrent Migraine Headache: A Meta-analytic Review of Clinical Trials," *J. of Consulting and Clinical Psychology* 59:387-393 1991

Comment: Propranolol (25 clinical trials) is compared to relaxation/biofeedback-training (35 clinical trials) with a total of 2445 patients using meta-analysis technique. Both therapies were equivalent in reducing headache frequency and intensity; 43% by patient evaluation and 60% by therapist/physician evaluation

2. Blanchard, EB et al, "Placebo-controlled Evaluation of Abbreviated Progressive Muscle Relaxation and of Relaxation Combined with Cognitive Therapy in the Treatment of Tension Headache," *J. of Consulting and Clinical Psychology* 58:210-215 1990.

Comment: This random controlled double-blinded study compared progressive muscle relaxation with and without cognitive therapy to control patients with no therapy or pseudomeditation in 66 patients. Muscle relaxation with or without cognitive therapy resulted in significant improvement in headache scores and reduction and analgesic use.

C-2

3. PHIP (Personal Health Improvement Program), Behavioral Health Connections, Sisters of Providence, Brian Liebrecht, MD, Medical Director.

Comment: PHIP is a multi-disciplinary treatment program developed by Harvard Managed Care Plan for patients with somatic symptoms that significantly decreases physical discomfort, reduces Primary Care Services 50%, reduces ER visits by 90%, and yet has an 83% satisfaction rating of patients at a cost of \$300/ for 6 two hour educational sessions. Patients gain awareness of their reactions to daily life and insights into how these reactions can adversely impact their life. Follow up 2 years later shows persistence of these favorable markers.

ACUPUNCTURE

Acupuncture has been used for the treatment of chronic pain, substance abuse, anesthesia, and other miscellaneous conditions. Headaches, which are responsive to treatment, include migraine, tension, cervicogenic, and analgesic rebound headache.

References:

1. Vincent, C.A., "A Controlled Trial of the Treatment of Migraine by Acupuncture," *The Clinical Journal of Pain* 5:305-312, 1989

Comment: A randomized controlled true vs. sham acupuncture, single blinded study with 30 patients. The credibility of the true and sham treatment procedures was also assessed. Post-treatment reductions in pain scores and reduction in medication was 43 and 38% and maintained at both a 4 month and 1 year follow-up.

2. Carlsson J. et al, "Muscle Tenderness in Tension Headache Treated with Acupuncture or Physiotherapy," *Cephalalgia* 10:131-141. 1990

Comment: 62 patients randomized study comparing acupuncture 4-10 sessions to physiotherapy 10 treatment. Both groups had significant reduction in muscle tenderness, and acupuncture was as least as cost-effective as physiotherapy for tension headaches.

3. Hesses J. et al, "Acupuncture vs. Metoprolol in Migraine Prophylaxis" - *J. Internal Medicine* 235:451-456, 1994.

Comment: Acupuncture plus placebo medication was compared to active medication plus placebo needling for treatment of chronic migraine headaches. 77 patients randomized for 17 weeks of treatment keeping diaries of symptoms and consumption of analgesics. No significant difference in improvement, however there were considerably fewer side effects reported in the acupuncture treated group. Thus acupuncture was at least as effective as metoprol in reducing frequency and duration, but not severity of attacks and was superior in terms of negative side effects.

4. Baischer, W "Acupuncture in Migraine: Long-term outcome and Predicting Factors" *Headache* 35(8): 472-4, September 1995

Comment: 26 patients with chronic migraine according to IHS criteria kept headache diary and use of analgesics. They were studied immediately after, 5 weeks and 3 years later. Improvement was 69% post-treatment and 58% at 3-year follow-up. Treatment outcome was associated with personality traits, but not severity of migraines.

C-3

CHIROPRACTIC

Chiropractic referral could be considered if a patient has history of neck trauma, palpation of the cervical spine area reproduces the headache or neck movement or sustained neck posture aggravates the headache. Migraine and tension headaches that have "cervicogenic" component may also benefit from treatment.

References:

1. Hurwitz EL, et al, "Manipulation and Mobilization of the Cervical Spine," *Spine* 21:1746-1760 1996

Comment: Review that includes 3 randomized controlled studies on muscle-contraction headaches. Although chiropractic treated patients had significant improvement the patients were only followed for 4 weeks. Thus the claim is only for short-term benefit to post traumatic headaches. One study on migraine headaches showed decreased frequency and intensity of pain after two months.

2. NILSSON, n. ET AL, "The Effect of Spinal Manipulation in the Treatment of Cervicogenic Headaches," *J. Manipulative Physiological Therapy* 20:326-30, 1997

Comment: Randomized prospective study of 28 headache sufferers in each arm: Chiropractic manipulation vs. Massage and low level laser. The manipulative arm had 36% decreased medication use, 60% decrease in hours of headache per day, and a 36% decrease in headache intensity.

3. Parker, GB et al, "A Controlled Trial of Cervical Manipulation for Migraine," *Austr. N.Z. J. Medicine* 8:589-593 1978

Comment: Randomized old prospective study with 85 migraine patients serving as their own control for a 2 month before the study. Three arms: chiropractic manipulation; physician or PT manipulation; and physician or PT mobilization. No statistically significant difference between chiropractic vs. the other modalities, although "the therapists enthusiasm for the therapy effectiveness and potential for continued treatments to improve the patient was greatest in the chiropractors."

4. Basicher, W "Acupuncture in Migraine: Long-term Outcome and Predicting Factors," *Headache* 35 (8):472-4 September 1995.

Comment: 26 patients with chronic migraine according to HIS criteria kept a headache diary and record of analgesic use. The patients were studied immediately after acupuncture treatment, 5 weeks, and 3 years later. Improvement was 69% post-treatment and 58% at the 3-year follow-up. Treatment outcome was associated with personality traits, but not severity of migraines.

C-4

Line: 462

Condition: MIGRAINE AND NONMIGRAINE HEADACHES
Treatment: MEDICAL THERAPY

CPT Codes:

90780 IV INFUSION THERAPY, 1 HOUR
90781 IV INFUSION, ADDITIONAL HOUR
90782 INJECTION (SC)/(IM)
90784 INJECTION (IV)
90799 THERAPEUTIC/DIAG INJECTION
90801 PSYCHIATRIC INTERVIEW
90901 BIOFEEDBACK TRAINING
92599 ENT PROCEDURE/SERVICE (S?)
95115 IMMUNOTHERAPY, ONE INJECTION
95117 IMMUNOTHERAPY INJECTIONS
95120 IMMUNOTHERAPY, ONE INJECTION
95125 IMMUNOTHERAPY, MANY ANTIGENS
97010 HOT OR COLD PACKS THERAPY
97012 MECHANICAL TRACTION THERAPY
97014 ELECTRIC STIMULATION THERAPY
97024 DIATHERMY TREATMENT (S)
97032 ELECTRICAL STIMULATION
97033 ELECTRIC CURRENT THERAPY
97035 ULTRASOUND THERAPY
97039 PHYSICAL THERAPY TREATMENT
97112 NEUROMUSCULAR REEDUCATION
97122 MANUAL TRACTION THERAPY
97124 MASSAGE THERAPY
97250 MYOFASCIAL RELEASE
97265 JOINT MOBILIZATION
98925 OSTEOPATHIC MANIPULATION, 1-2 BODY REGIONS
98926 OSTEOPATHIC MANIPULATION, 3-4 BODY REGIONS
98940 CHIROPRACTIC MANIPULATION, 1-2 SPINAL REGIONS
98941 CHIROPRACTIC MANIPULATION, 3-4 SPINAL REGIONS
98943 CHIROPRACTIC MANIPULATION, NONSPINAL
99058 OFFICE EMERGENCY CARE
99201-
99205 OFFICE/OUTPATIENT VISIT, NEW
99211-
99215 OFFICE/OUTPATIENT VISIT, EST
99217 OBSERVATION CARE DISCHARGE
99218-
99220 OBSERVATION CARE
99221-
99223 INITIAL HOSPITAL CARE
99231-
99233 SUBSEQUENT HOSPITAL CARE
99238-
99239 HOSPITAL DISCHARGE DAY
99241-
99245 OFFICE CONSULTATION
99251-
99255 INITIAL INPATIENT CONSULT

C-5

Line: 462 MIGRAINE AND NONMIGRAINE HEADACHES(CONT'D)

99261-
99263 FOLLOW-UP INPATIENT CONSULT
99271-
99275 CONFIRMATORY CONSULTATION
99281-
99285 EMERGENCY DEPT VISIT
99401-
99404 PREVENTIVE COUNSELING, INDIV
BA008 PSYCHIATRIC ASSESSMENT <21
BA009 PSYCHOLOGICAL ASSESSMENT <21
BA010 MENTAL HEALTH ASSESSMENT <21
BA011 INDIVIDUAL THERAPY <21
BA013 FAMILY THERAPY <21
BA019 MEDICATION MANAGEMENT <21
BA026 PHYSICIAN MEDICATION MGMT <21
BA108 ADULT PSYCHIATRIC ASSESSMENT
BA109 ADULT PSYCHOLOGICAL ASSESSMENT
BA110 MENTAL HEALTH ASSESSMENT >=21
BA111 INDIV THERAPY - PR#1 >=21
BA112 INDIV THERAPY - PR#2 & 3 >=21
BA113 FAMILY THERAPY - PR#1 >=21
BA114 FAMILY THERAPY - PR#2 & 3 >=21
BA117 CONSULTATION PR#1 >=21
BA118 CONSULTATION PR#2 & 3 >=21
BA119 MEDICATION MANAGEMENT >=21
BA126 PHYS MED MANAGEMENT PR#1 >=21
G0071 OP INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 20-30 MIN
G0072 OP INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 20-30 MIN, W/E&M
G0073 OP INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 45-50 MIN
G0074 OP INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 45-50 MIN, W/E&M
G0083 IP/RCF INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 20-30 MIN
G0084 IP/RCF INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 20-30 MIN, W/
G0085 IP/RCF INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 45-50 MIN
G0086 IP/RCF INSIGHT ORIENTED/BEHAVIOR MOD PSYCHOTHERAPY, 45-50 MIN, W/
ACP01 ACUPUNCTURE

ICD-9 Codes:

Special symptoms or syndromes, not elsewhere classified

307.81 Tension headache

346 Migraine

346.0 Classical migraine

Migraine preceded or accompanied by transient focal neurological phenomena

Migraine with aura

346.00 Without mention of intractable migraine

346.01 With intractable migraine, so stated

346.1 Common migraine

Atypical migraine

Sick headache

346.10 Without mention of intractable migraine

346.11 With intractable migraine, so stated

C-6

Line: 462 MIGRAINE AND NONMIGRAINE HEADACHES(CONT'D)

- 346.2 Variants of migraine
- | | |
|---------------------------|----------------------------|
| <i>Cluster headache</i> | <i>Histamine cephalgia</i> |
| <i>Horton's neuralgia</i> | <i>Migraine:</i> |
| <i>Neuralgia:</i> | <i>Abdominal</i> |
| <i>Ciliary</i> | <i>Basilar</i> |
| <i>Migrainous</i> | <i>Lower half</i> |
| | <i>Retinal</i> |
- 346.20 Without mention of intractable migraine
- 346.21 With intractable migraine, so stated
- 346.8 Other forms of migraine
- | | |
|-------------------|------------------------|
| <i>Hemiplegic</i> | <i>Ophthalmoplegic</i> |
|-------------------|------------------------|
- 346.80 Without mention of intractable migraine
- 346.81 With intractable migraine, so stated
- 346.9 Migraine, unspecified
- 346.90 Without mention of intractable migraine
- 346.91 With intractable migraine, so stated

Symptoms involving head and neck

- 784.0 Headache

C-7

Spinal manipulations for the treatment of migraine: A systematic review of randomized clinical trials

Cephalalgia

31(8) 964–970

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**P Posadzki and E Ernst**

Abstract

Aims: The objective of this systematic review was to assess the effectiveness of spinal manipulations as a treatment for migraine headaches.

Method: Seven databases were searched from inception to November 2010. All randomized clinical trials (RCTs) investigating spinal manipulations performed by any type of healthcare professional for treating migraine headaches in human subjects were considered. The selection of studies, data extraction and validation were performed independently by two reviewers.

Results: Three RCTs met the inclusion criteria. Their methodological quality was mostly poor and ranged between 1 and 3 on the Jadad scale. Two RCTs suggested no effect of spinal manipulations in terms of Headache Index or migraine duration and disability compared with drug therapy, spinal manipulation plus drug therapy, or mobilization. One RCT showed significant improvements in migraine frequency, intensity, duration and disability associated with migraine compared with detuned interferential therapy. The most rigorous RCT demonstrated no effect of chiropractic spinal manipulation compared with mobilization or spinal manipulation by medical practitioner or physiotherapist on migraine duration or disability.

Conclusions: Current evidence does not support the use of spinal manipulations for the treatment for migraine headaches.

Keywords

Spinal manipulation, migraine headache, effectiveness, systematic review, alternative medicine

Date received: 11 February 2011; revised: 1 March 2011; accepted: 5 March 2011

Introduction

Migraine headache (MH) is a common episodic neurobiological disorder, typically presenting with recurrent attacks of severe headache and autonomic dysfunction (1). The pathophysiology of MH is complex and may involve activation of sub-cortical structures such as the midbrain and the pons (2,3) as well as the trigemino-vascular system (4). Recent research has also established the first genetic risk factor for MH (1). The prevalence of MH is high, affecting more than 10% of the general population (4). MH is associated with a high burden of personal suffering and considerable socioeconomic costs (5,6). The World Health Organization (WHO) ranked MH as number 19 among all diseases causing disability (7).

Most chiropractors feel that spinal manipulative therapy (SMT) is an effective treatment for MH. For instance, a 2004 survey of the UK General Chiropractic

Council showed that 91% of all UK chiropractors believe that migraine ‘can be treated or managed by chiropractors’ (8). However, SMT has repeatedly been found to be a concept of debatable plausibility (9,10), which renders it an unlikely candidate for an effective therapy of MH. In addition, SMT is neither inexpensive nor entirely free of risks (11–13). Several hundred severe complications after upper spinal manipulations have been reported (e.g. (14,15)). However, the estimates as to the incidence of these complications vary

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Manual therapies for migraine: a systematic review

Aleksander Chaibi · Peter J. Tuchin ·
Michael Bjørn Russell

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Abstract Migraine occurs in about 15% of the general population. Migraine is usually managed by medication, but some patients do not tolerate migraine medication due to side effects or prefer to avoid medication for other reasons. Non-pharmacological management is an alternative treatment option. We systematically reviewed randomized clinical trials (RCTs) on manual therapies for migraine. The RCTs suggest that massage therapy, physiotherapy, relaxation and chiropractic spinal manipulative therapy might be equally effective as propranolol and topiramate in the prophylactic management of migraine. However, the evaluated RCTs had many methodological shortcomings. Therefore, any firm conclusion will require future, well-conducted RCTs on manual therapies for migraine.

Keywords Manual therapies · Massage · Physiotherapy · Chiropractic · Migraine · Treatment

Introduction

Migraine is usually managed by medication, but some patients do not tolerate acute and/or prophylactic medicine

due to side effects, or contraindications due to co-morbidity of myocardial disorders or asthma among others. Some patients wish to avoid medication for other reasons. Thus, non-pharmacological management such as massage, physiotherapy and chiropractic may be an alternative treatment option. Massage therapy in Western cultures uses classic massage, trigger points, myofascial release and other passive muscle stretching among other treatment techniques which are applied to abnormal muscle tissue. Modern physiotherapy focuses on rehabilitation and exercise, while manual treatment emphasis postural corrections, soft tissue work, stretching, active and passive mobilization and manipulation techniques. Mobilization is commonly defined as movement of joints within the physiological range of motion [1]. The two most common chiropractic techniques are the diversified and Gonstead, which are used by 91 and 59% of chiropractors [2]. Chiropractic spinal manipulation (SM) is a passive-controlled maneuver which uses a directional high-velocity, low-amplitude thrusts directed at a specific joint past the physiological range of motion, without exceeding the anatomical limit [1]. The application and duration of the different manual treatments varies among those who perform it. Thus, manual treatment is not necessarily as uniform as, for instance, specific treatment with a drug in a certain dose.

This paper systematically review randomized controlled trials (RCTs) assessing the efficacy of manual therapies on migraine, i.e., massage, physiotherapy and chiropractic.

Method

The literature search was done on CINAHL, Cochrane, Medline, Ovid and PubMed. Search words were migraine

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Are Manual Therapies Effective in Reducing Pain From Tension-Type Headache?

A Systematic Review

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Objectives: A systematic review was performed to establish whether manual therapies have specific efficacy in reducing pain from tension-type headache (TTH).

Methods: Computerized literature searches were performed in MEDLINE, EMBASE, AMED, MANTIS, CINAHL, PEDro, and Cochrane databases. Papers were included if they described clinical (open noncontrolled studies) or randomized controlled trials in which any form of manual therapy was used for TTH, and if they were published after 1994 in the English language. The methodologic quality of the trials was assessed using the PEDro scale. Levels of scientific evidence, based on the quality and the outcomes of the studies, were established for each manual therapy: strong, moderate, limited, and inconclusive evidence.

Results: Only six studies met the inclusion criteria. These trials evaluated different manual therapy modalities: spinal manipulation (three trials), classic massage (one trial), connective tissue manipulation (two trials), soft tissue massage (one trial), Dr. Cyriax's vertebral mobilization (one trial), manual traction (one trial), and CV-4 craniosacral technique (one trial). Methodologic PEDro quality scores ranged from 2 to 8 points out of a theoretical maximum of 10 points (mean = 5.8 ± 2.1). Analysis of the quality and the outcomes of all trials did not provide rigorous evidence that manual therapies have a positive effect in reducing pain from TTH: spinal manipulative therapy showed inconclusive evidence of effectiveness (level 4), whereas soft tissue techniques showed limited evidence (level 3).

Conclusions: The authors found no rigorous evidence that manual therapies have a positive effect in the evolution of TTH. The most urgent need for further research is to establish the

efficacy beyond placebo of the different manual therapies currently applied in patients with TTH.

Key Words: tension-type headache, manual therapy, soft tissue techniques, spinal manipulation

(*Clin J Pain* 2006;22:278–285)

Headaches are one of the most common problems seen in medical practice. Among the many types of headache disorders, tension-type headache (TTH) is the most prevalent in adults. Population-based studies suggest 1-year prevalence rates of 38.3% for episodic TTH and 2.2% for chronic TTH.¹ Recently, the second edition of the *Classification of Headache Disorders* of the International Headache Society (IHS) has kept the clinical criteria for the diagnosis of TTH^{2,3} but has withdrawn EMG or pressure algometry from the diagnostic features for subdivision, as only tenderness on manual palpation has proved useful to distinguish the different subtypes of TTH.³ Accordingly, the following subtypes of TTH are now considered: infrequent episodic TTH associated/not associated with pericranial tenderness; frequent episodic TTH associated/not associated with pericranial tenderness; chronic TTH associated/not associated with pericranial tenderness; and probable TTH (infrequent, frequent, or chronic TTH).

Despite its scientific interest, the pathophysiology of TTH is not clearly understood. Bendtsen reported that both peripheral mechanisms (ie, myofascial tenderness of pericranial structures) and central mechanisms (ie, sensitization of supraspinal neurons and decreased antinociceptive activity from supraspinal structures) might explain some of the symptoms of TTH.⁴

There are many therapeutic approaches aimed at treating benign chronic and recurrent headaches such as TTH, including pharmacotherapy, cognitive therapy, relaxation therapy, biofeedback, and physical therapy.⁵ Headache sufferers are also frequent users of complementary techniques such as manual therapies and chiropractic care.⁶ Vernon and McDermaid reported that upper cervical manipulation, soft tissue therapy, and myofascial trigger point treatment were the techniques

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Review Articles

Spinal Manipulations for Cervicogenic Headaches: A Systematic Review of Randomized Clinical Trials

Paul Posadzki, PhD, MSc, BSc; Edzard Ernst, MD, PhD, FMedSci, FSB, FRCP, FRCPEd

The objective of this systematic review was to assess the effectiveness of spinal manipulations as a treatment option for cervicogenic headaches. Seven databases were searched from their inception to February 2011. All randomized trials which investigated spinal manipulations performed by any type of healthcare professional for treating cervicogenic headaches in human subjects were considered. The selection of studies, data extraction, and validation were performed independently by 2 reviewers. Nine randomized clinical trials (RCTs) met the inclusion criteria. Their methodological quality was mostly poor. Six RCTs suggested that spinal manipulation is more effective than physical therapy, gentle massage, drug therapy, or no intervention. Three RCTs showed no differences in pain, duration, and frequency of headaches compared to placebo, manipulation, physical therapy, massage, or wait list controls. Adequate control for placebo effect was achieved in 1 RCT only, and this trial showed no benefit of spinal manipulations beyond a placebo effect. The majority of RCTs failed to provide details of adverse effects. There are few rigorous RCTs testing the effectiveness of spinal manipulations for treating cervicogenic headaches. The results are mixed and the only trial accounting for placebo effects fails to be positive. Therefore, the therapeutic value of this approach remains uncertain.

Key words: spinal manipulation, cervicogenic headache, effectiveness, systematic review, complementary and alternative medicine

(*Headache* 2011;51:1132-1139)

INTRODUCTION

Cervicogenic headache (CGH) is associated with a high burden of suffering and considerable socioeconomic costs. The clinical classifications and definitions of CGH are ambiguous.¹ The International Headache Society classified CGH as “pain, referred from a source in the neck and perceived in one or more regions of the head and/or face” and stressed the importance of clinical evidence of a disorder or

lesion within the cervical spine or soft tissues of the neck as a valid cause of headache.²

Spinal manipulation (SM) is a manual technique often practiced by chiropractors, osteopaths, physiotherapists, and some doctors to correct misalignments of the spinal joints.³ Chiropractors suggest that SM is an effective treatment for CGH.⁴ However, SM has repeatedly been criticized for not being biologically plausible.^{5,6} The effectiveness, safety, and cost-effectiveness of SM have also been questioned.⁷⁻¹⁰ Thus, it seems crucial to be certain about its benefits for patients suffering from CGH.

This systematic review is aimed at critically evaluating the evidence for or against the notion that SM is effective in treating CGH.

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Conflict of Interest: None

Headaches

Diagnosis and management of headaches in young people and adults

Clinical Guideline 150

Methods, evidence and recommendations

September 2012

*Commissioned by the National Institute for
Health and Clinical Excellence*

3 Guideline summary

3.1 Algorithms

Algorithm to be developed as part of NICE pathways.

3.2 Key priorities for implementation

From the full set of recommendations, the GDG selected ten key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual¹⁸¹. The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter. The recommendations are listed in the order they appear in the NICE guideline, and accordingly.

Diagnosis

Tension-type headache, migraine and cluster headache

- Diagnose tension-type headache, migraine or cluster headache according to the headache features in the table. [1.2.1]

Medication overuse headache

- Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:
 - o triptans, opioids, ergots or combination analgesic medications on 10 days per month or more
 - or
 - o paracetamol, aspirin or an NSAID, either alone or any combination, on 15 days per month or more. [1.2.7]

Management

All headache disorders

- Do not refer people diagnosed with tension-type headache, migraine, cluster headache or medication overuse headache for neuroimaging solely for reassurance. [1.3.3]

Information and support for people with headache disorders

- Include the following in discussions with the person with a headache disorder:
 - o a positive diagnosis, including an explanation of the diagnosis and reassurance that other pathology has been excluded **and**
 - o the options for management **and**
 - o recognition that headache is a valid medical disorder that can have a significant impact on the person and their family or carers. [1.3.4]

Migraine with or without aura

Acute treatment

- Offer combination therapy with an oral triptan^a and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan. [1.3.10]
- For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:
 - o offer a non-oral preparation of metoclopramide, or prochlorperazine^b **and**
 - o consider adding a non-oral NSAID or triptan if these have not been tried. [1.3.15]

Prophylactic treatment

- Offer topiramate^c or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception. [1.3.17]

Cluster headache

Acute treatment

- Offer oxygen and/or a subcutaneous^d or nasal triptan^e for the acute treatment of cluster headache. [1.3.27]

^a At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

^b At the time of publication (September 2012), prochlorperazine (except for a buccal preparation) did not have a UK marketing authorisation for this indication but is licensed for the relief of nausea and vomiting. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

^c At the time of publication (September 2012), topiramate did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

^d At the time of publication (September 2012), subcutaneous triptans did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

^e At the time of publication (September 2012), nasal triptans did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the

- When using oxygen for the acute treatment of cluster headache:
 - o use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag **and**
 - o arrange provision of home and ambulatory oxygen. [1.3.28]
- When using a subcutaneous^f or nasal triptan^g, ensure the person is offered an adequate supply of triptans calculated according to their history of cluster bouts, based on the manufacturer's maximum daily dose. [1.3.29]

Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

^f At the time of publication (September 2012), subcutaneous triptans did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

^g At the time of publication (September 2012), nasal triptans did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

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Diagnosis and management of headache in adults

A national clinical guideline



November 2008

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- ☒ Recommended best practice based on the clinical experience of the guideline development group.

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity. This guideline has been assessed for its likely impact on the six equality groups defined by age, disability, gender, race, religion/belief, and sexual orientation.

For the full equality and diversity impact assessment report please see the “published guidelines” section of the SIGN website at www.sign.ac.uk/guidelines/published/numlist.html. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

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Scottish Intercollegiate Guidelines Network

Diagnosis and management of headache in adults

A national clinical guideline



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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Headache is common, with a lifetime prevalence of over 90% of the general population in the United Kingdom (UK).¹ It accounts for 4.4% of consultations in primary care² and 30% of neurology outpatient consultations.^{3,4}

Headache disorders are generally classified as either primary or secondary, and these classifications are further divided into specific headache types. Primary headache disorders are not associated with an underlying pathology and include migraine, tension-type, and cluster headache. Secondary headache disorders are attributed to an underlying pathological condition and include any head pain of infectious, neoplastic, vascular, or drug-induced origin.⁵

Migraine is the most common severe form of primary headache affecting about six million people in the UK in the age range 16-65, and can cause significant disability.⁶ The World Health Organisation (WHO) ranks migraine in its top 20 disabling conditions for women aged 15 to 44.⁷ It is estimated that migraine costs the UK almost £2 billion a year in direct and indirect costs,⁸ with over 100,000 people absent from work or school because of migraine every working day.⁹ Tension-type headache affects over 40% of the population at any one time. Although less of a burden to the individual sufferer than migraine, its higher prevalence results in a greater societal burden, with as many lost days from work as with migraine.¹⁰ Chronic headache, defined as headache on 15 or more days per month, affects three per cent of people worldwide.¹⁰

Healthcare professionals often find the diagnosis of headache difficult and both healthcare professionals and patients worry about serious rare causes of headaches such as brain tumours.^{2,11} General practitioners (GPs) are often uncertain about when to refer patients to secondary care.² GPs refer 2-3% of patients consulting for headaches to neurological clinics.² This may allow the exclusion of secondary headache but often does not provide a headache management service. Most primary headache can be managed in primary care and investigations are rarely needed.¹²

There are effective therapies for many of the primary headaches^{11,13} but treatments can cause headache themselves.¹¹ Despite this many patients are inappropriately prescribed analgesics and many patients with headache never consult their doctor because of poor expectations of what doctors can offer.^{14,15}

1.2 REMIT OF THE GUIDELINE

This guideline provides recommendations based on evidence for best practice in the diagnosis and management of headache in adults. The International Classification of Headache Disorders lists over 200 headache types and a comprehensive review of all headaches is beyond the scope of these guidelines.¹⁶ This guideline focuses on the more common primary headaches such as migraine and tension-type headache, and addresses some of the rarer primary headaches which have recognisable features with specific treatments. Secondary headache due to medication overuse is addressed, as the overuse of headache medication can compromise the management of primary headache. "Red flags" for secondary headache are highlighted. A guide to the main investigations used in headache is provided.

Disorders that primarily cause facial pain, such as trigeminal neuralgia, are outwith the remit of this guideline, as is treatment of meningitis.

This guideline will be of interest to healthcare professionals in primary and secondary care, including general practitioners, community pharmacists, opticians and dental practitioners, and patients with headache.

1.3 DEFINITIONS

The guideline uses the definitions given in the International Headache Society International Classification of Headache Disorders, 2nd edition (see *Annex 2*).¹⁶

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4.1 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in section 16.3.

1.4.2 DRUG LICENSING STATUS

The majority of headache treatments commonly used do not have a specific licence for this indication in the UK. In this guideline, recommendations which include the use of licensed drugs outwith the terms of their licence reflect the evidence base reviewed. More details on licensing status are given in *Annex 6*.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as being clinically very important. They are the key clinical recommendations that should be prioritised for implementation. The clinical importance of these recommendations is not dependent on the strength of the supporting evidence.

2.1 SYMPTOMS AND SIGNS

C Patients who present with a pattern of recurrent episodes of severe disabling headache associated with nausea and sensitivity to light, and who have a normal neurological examination, should be considered to have migraine.

Migraine has specific treatment options. It is often underdiagnosed with up to 50% of patients misdiagnosed with another headache type.¹⁷⁻²⁰ Better recognition allows more effective treatment.

D Patients who present with headache and red flag features for potential secondary headache should be referred to a specialist appropriate to their symptoms for further assessment.

Most patients have primary headache and do not require further investigation.^{12,20} Red flag warning features highlight which patients require further investigation for potential secondary headache.

D Patients with a first presentation of thunderclap headache should be referred immediately to hospital for same day specialist assessment.

Thunderclap headache is a medical emergency as it may be caused by subarachnoid haemorrhage.

D Giant cell arteritis should be considered in any patient over the age of 50 presenting with a new headache or change in headache.

Giant cell arteritis is a medical emergency because of the possibility of neurological and visual complications and availability of effective treatment.

2.2 ASSESSMENT TOOLS

D Practitioners should consider using headache diaries and appropriate assessment questionnaires to support the diagnosis and management of headache.

The use of diaries and questionnaires can aid diagnosis and prompt discussion of symptoms and the impact of the headaches on quality of life. This can help guide treatment and ensure appropriate follow up.

2.3 INVESTIGATIONS

D Neuroimaging is not indicated in patients with a clear history of migraine, without red flag features for potential secondary headache, and a normal neurological examination.

Magnetic resonance imaging (MRI) and computerised tomography (CT) can identify neurological abnormalities incidental to the patient's presenting complaint, which may result in heightened patient anxiety and clinician uncertainty.^{21,22} Further investigation and treatment of incidental abnormalities can cause both morbidity and mortality and investigation should generally be reserved for patients with "red flag features".

D In patients with thunderclap headache, unenhanced CT of the brain should be performed as soon as possible and preferably within 12 hours of onset.

C Patients with thunderclap headache and a normal CT should have a lumbar puncture.

Subarachnoid blood degrades rapidly. Performing CT brain imaging as soon as possible maximises the chance of accurate diagnosis. Even timely CT brain imaging may not pick up subarachnoid blood, so lumbar puncture is also required. Lumbar puncture should be delayed till 12 hours after headache onset.

2.4 MIGRAINE

A Oral triptans are recommended for acute treatment in patients with all severities of migraine if previous attacks have not been controlled using simple analgesics.

Migraine is associated with significant disability and is often under-treated. A stepped approach for acute treatment of migraine is recommended, starting with aspirin or an NSAID. If this is not effective a triptan should be used.

D Opioid analgesics should not be routinely used for the treatment of patients with acute migraine due to the potential for development of medication overuse headache.

Opioids and opioid-containing analgesics are associated with medication overuse headache and their use can result in dependence. They have no role in the treatment of migraine.

B Women with migraine with aura should not use a combined oral contraceptive pill.

Migraine with aura and the combined oral contraceptive pill are both independent risk factors for ischaemic stroke. Although the absolute increased risk of stroke is small, this increased risk is unacceptable when equally effective alternative methods of contraception are available.

2.5 TRIGEMINAL AUTONOMIC CEPHALALGIAS

A Subcutaneous injection of 6 mg sumatriptan is recommended as the first choice treatment for the relief of acute attacks of cluster headache.

Individual attacks of cluster headache are very severe and build up rapidly. The onset of action of oral triptans is too long and subcutaneous or nasal triptans are required.

2.6 MEDICATION OVERUSE HEADACHE

D Medication overuse headache must be excluded in all patients with chronic daily headache (*headache ≥ 15 days / month for > 3 months*).

D Clinicians should be aware that patients using any acute or symptomatic headache treatment are at risk of medication overuse headache. Patients with migraine, frequent headache and those using opioid-containing medications or overusing triptans are at most risk.

Medication overuse results in the development of chronic daily headache. Stopping the overused medication usually results in improvement in headache frequency and severity. The risks of medication overuse headache should be discussed with all patients when initiating acute treatment for migraine.

3 Symptoms and signs

3.1 INTRODUCTION

Most patients with headache who present in primary care have primary headache.²⁰ Patients may have more than one type of primary headache (eg migraine without aura and tension-type headache) and each headache type should be dealt with separately.¹⁶ Presentation with secondary headache is rare. In primary headache, findings on neurological examination are usually normal and investigations are not helpful for diagnosis.^{12,23}

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The individual patient's history is of prime importance in the evaluation of headache.^{11,23} The aim of the history is to classify the headache type(s) and screen for secondary headache using "red flag" features (see section 3.3). An inadequate history is the probable cause of most misdiagnosis of the headache type.¹¹ The British Association for the Study of Headache has produced a list of questions to help with taking a patient's headache history (see Annex 4). Diaries and tools to aid diagnosis are discussed in section 4.

4

The evidence base regarding signs and symptoms is limited to observational studies and the recommendations are based mainly on case series and expert opinion.

3.2 PRIMARY HEADACHE

3.2.1 MIGRAINE

Migraine is the most common severe primary headache disorder.^{6,10} The global lifetime prevalence is 10% in men and 22% in women.¹⁰

A migraine headache is characteristically:

- unilateral
- pulsating
- builds up over minutes to hours
- moderate to severe in intensity
- associated with nausea and/or vomiting and/or sensitivity to light and/or sensitivity to sound
- disabling
- aggravated by routine physical activity.¹⁶

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Migraine is classified by the presence or absence of aura.¹⁶ A typical aura comprises fully reversible visual and/or sensory and/or dysphasic speech symptoms. Symptoms may be positive (eg flickering lights, spots, zig zag lines, tingling) and negative (eg visual loss, numbness). Symptoms characteristically evolve over ≥ 5 minutes and resolve within 60 minutes.¹⁶ Different aura symptoms may occur in succession. A transient ischaemic attack should be considered if the aura has a very rapid onset, there is simultaneous rather than sequential occurrence of different aura symptoms, the aura is purely negative or is very short.^{24,25} Prolonged aura should raise the possibility of a secondary cause (see section 3.3).^{24,25} Aura may occur without headache.

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Recurrent attacks lasting four to 72 hours, occur as infrequently as one per year or as often as daily. The median frequency is one to two per month.²⁶ Chronic migraine is classified as migraine occurring on 15 or more days per month for more than three months.^{16,27} In chronic migraine the headache may have features more typical of tension-type headache (see Annex 2).

4

Fifty per cent of patients with migraine are misdiagnosed with another headache type.¹⁷⁻²⁰ Often the wrong diagnosis of episodic tension-type headache is given. When prospective diaries were reviewed for headaches diagnosed as episodic tension-type headache, in the Landmark study, 82% of the physician diagnoses were changed to migraine or probable migraine.²⁰

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As many as 75% of patients with migraine describe neck pain associated with migraine attacks. Patients may present with more than one headache type. Any single International Classification of Headache Disorders (ICHD-II) criterion will be missing in up to 40% of patients; 40% of patients report bilateral pain, 50% describe the pain as non-pulsating, and vomiting occurs in less than 33%.²⁴

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Given the difficulty in differentiating between migraine without aura and infrequent episodic tension-type headache the ICHD-II criteria require five attacks before a diagnosis of migraine without aura can be made. Two attacks are required for the diagnosis of migraine with aura.¹⁶ In patients with more than one type of headache the International Headache Society (IHS) suggests a hierarchical diagnostic strategy with the diagnosis based on the most severe headache.

4

Cohort studies and case studies have highlighted the features of a history that help to differentiate migraine from other headache. Not all have to be present to make the diagnosis:

- episodic severe headache that causes disability^{13,28,29}
- nausea^{23,28}
- sensitivity to light during headache^{23,28}
- sensitivity to light between attacks³⁰
- sensitivity to noise²³
- typical aura (in 15–33% of patients with migraine)^{23,24}
- exacerbation by physical activity²³
- positive family history of migraine.^{23,31}

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When combined with assessment of functional impairment, the features which give the greatest sensitivity and specificity for the diagnosis of migraine are nausea and sensitivity to light.²⁸

3

C Patients who present with a pattern of recurrent episodes of severe disabling headache associated with nausea and sensitivity to light, and who have a normal neurological examination, should be considered to have migraine.

3.2.2 TENSION-TYPE HEADACHE

Tension-type headache (TTH) is the most common primary headache disorder.¹⁰ It has a global lifetime prevalence of 42% in men and 49% in women. The pain is generally not as severe as in migraine.¹⁰

The pain is typically bilateral, characteristically pressing or tightening in quality and mild to moderate in intensity. Nausea is not present and the headache is not aggravated by physical activity. There may be associated pericranial tenderness, sensitivity to light or sensitivity to noise. Episodic tension-type headache (ETTH) occurs in episodes of variable duration and frequency. Chronic tension-type headache (CTTH) occurs on more than 15 days per month for more than three months.¹⁶

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Disabling ETTH is rare. Most patients with ETTH do not consult a primary care clinician.^{19,20} Migraine is often mistaken for ETTH in the initial diagnosis (see section 3.2.1).²⁰

2+

C A diagnosis of tension-type headache should be considered in a patient presenting with bilateral headache that is non-disabling where there is a normal neurological examination.

3.2.3 TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal autonomic cephalalgias (TACs) are rare and are characterised by attacks of severe unilateral pain in a trigeminal distribution.^{16,32} They are associated with prominent ipsilateral cranial autonomic features. Cluster headache (CH) is the most common TAC (estimated prevalence 1 in 1,000). Paroxysmal hemicrania (PH) is probably under-recognised (estimated prevalence 1 in 50,000).³² Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) are very rare.

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Cluster headache attacks cause severe, strictly unilateral pain. The pain is located in one or a combination of orbital, supraorbital, or temporal regions. The ICHD-II classification requires ipsilateral autonomic features to occur with an attack (see *Annex 2*). Each attack starts and ceases abruptly, lasting 15 minutes to three hours and the patient is restless during an attack. The frequency of attacks varies from one every other day to eight per day. There may be a continuous background headache between attacks and migrainous features may be present (see *section 3.2.1*). There is often a striking circadian rhythm; attacks often occur at the same time each day and clusters occur at the same time each year.³² Eighty to 90% of patients have episodic cluster headache where attacks “cluster” into periods lasting weeks to months, separated by periods of headache freedom. The remaining 10-20% have chronic cluster headache (no remission within one year or remissions last less than one month).¹⁶

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Paroxysmal hemicrania has similar characteristics to cluster headache, but attacks are shorter (2-45 minutes), more frequent (up to 40 per day) and it is more common in women. The majority of patients have the chronic rather than episodic form. Most attacks are spontaneous but 10% can be precipitated mechanically by bending or rotating the head. Diagnosis using ICHD-II criteria consists of the presence of a complete response to indometacin and ipsilateral autonomic features during an attack (see *Annex 2*).^{16,32}

4

SUNCT has similar characteristics to cluster headache and paroxysmal hemicrania. Attacks are shorter (2-250 seconds) and more frequent (up to 30 per hour). They occur as single stabs, groups of stabs or in an overlapping fashion (“sawtooth”). Bouts may last one to three hours at a time. Conjunctival injection and/or tearing are a requirement for the diagnosis. Attacks may be spontaneous or triggered by trigeminal (eg touching face) or extra-trigeminal (eg exercise) manoeuvres. Relapses and remissions are erratic.^{16,32,33} SUNA is a proposed classification for patients with the headache characteristics of SUNCT, but with other cranial autonomic features.

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Secondary mimics are common and need to be excluded before a diagnosis of cluster headache, PH, SUNCT or SUNA can be made. For example, symptomatic cluster headache has been described after infections and with vascular and neoplastic lesions. In the case of PH a good response to indometacin does not exclude a secondary cause.³²

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Features differentiating TACs from migraine are listed in Table 1. Features which differentiate trigeminal autonomic cephalalgias from each other and from trigeminal neuralgia, are listed in Annex 3.

Table 1: Features distinguishing TACs from migraine. ^{23,32,33}

	Headache type			
	SUNCT	PH	CH	Migraine
Duration	2-250 secs	2-45 mins	15 mins–3 hrs	4-72 hrs
Onset	rapid	rapid	rapid	gradual
Frequency	1/day-30/hr	1-40/day	1 every other day-8 /day	< 1/year-1/day (median 1-2/ month)
Restlessness during an attack	50%	50%	100%	0%
Ipsilateral autonomic features	prominent	prominent	prominent	occasional

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D When a patient presents with frequent, brief, unilateral headaches with autonomic features a trigeminal autonomic cephalgia should be considered.

D Patients with a new suspected trigeminal autonomic cephalgia should be referred for specialist assessment.

3.2.4 HEMICRANIA CONTINUA

Hemicrania continua is a continuous strictly unilateral headache that waxes and wanes in intensity without disappearing completely.^{16,32} Brief stabbing pain may be superimposed on the continuous headache and may be accompanied by ipsilateral autonomic features. While it is rare, it is an important diagnosis to consider as there is an absolute response to indometacin.³²

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Secondary mimics are common and need to be excluded before a diagnosis of primary hemicrania continua can be made. A good response to indometacin does not exclude a secondary cause.³²

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D When a patient presents with chronic daily headache which is strictly unilateral, hemicrania continua should be considered.

D Patients with a new suspected hemicrania continua should be referred for specialist assessment.

3.2.5 NEW DAILY PERSISTENT HEADACHE

Headache that is daily and unremitting from onset is classified as new daily persistent headache.¹⁶ It is essential to consider secondary headache and allow three months to elapse before a diagnosis of primary new daily persistent headache can be made. New daily persistent headache can have any phenotype. Secondary headaches to consider are subarachnoid haemorrhage (SAH), meningitis, raised intracranial pressure, low cerebrospinal fluid (CSF) pressure, giant cell arteritis and post-traumatic headache.³⁴

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☒ In patients with new daily persistent headache, referral for specialist assessment should be considered.

3.3 SECONDARY HEADACHE

Secondary headache (ie headache caused by another condition) should be considered in patients presenting with new onset headache or headache that differs from their usual headache. Observational studies have highlighted the following warning signs or red flags for potential secondary headache which requires further investigation:

Red flag features:

- new onset or change in headache in patients who are aged over 50^{12,35-37}
- thunderclap: rapid time to peak headache intensity (seconds to 5 mins)^{35,36,38-41}
- focal neurological symptoms (eg limb weakness, aura < 5 min or > 1 hr)^{24,25,37,39,42,43}
- non-focal neurological symptoms (eg cognitive disturbance)^{38,42}
- change in headache frequency, characteristics or associated symptoms^{12,24,37,38}
- abnormal neurological examination^{12,36,38,43}
- headache that changes with posture^{44,45}
- headache wakening the patient up (NB migraine is the most frequent cause of morning headache)^{12,45}
- headache precipitated by physical exertion or valsalva manoeuvre (eg coughing, laughing, straining)^{12,45}
- patients with risk factors for cerebral venous sinus thrombosis^{42,46,47}
- jaw claudication or visual disturbance^{23,48}
- neck stiffness^{35,49}
- fever⁴⁹
- new onset headache in a patient with a history of human immunodeficiency virus (HIV) infection³⁸
- new onset headache in a patient with a history of cancer.¹¹

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D Patients who present with headache and red flag features of potential secondary headache should be referred to an appropriate specialist for further assessment.

In patients with a stable pattern of headache, neurological examination is normal other than occasional ptosis during and persisting after an attack of cluster headache.^{12,23} The presence of focal or non-focal symptoms and/or abnormal neurological signs significantly increases the chance of there being an abnormality.^{12,23,36,38} An appropriate clinical examination, a neurological examination including fundoscopy, and blood pressure measurement are essential when patients first present.¹¹

3

D Patients presenting with headache for the first time or with headache that differs from their usual headache should have a clinical examination, a neurological examination including fundoscopy, and blood pressure measurement.

- ☒ Neurological examination in patients first presenting with headache should include:
- fundoscopy
 - cranial nerve assessment, especially pupils, visual fields, eye movements, facial power and sensation and bulbar function (soft palate, tongue movement)
 - assessment of tone, power, reflexes and coordination in all four limbs
 - plantar responses
 - assessment of gait, including heel-toe walking.

There should be more detailed assessment if prompted by the history. The examination should be tailored to include any focal neurological symptoms.

3.3.1 THUNDERCLAP HEADACHE

Thunderclap headache may be primary or secondary. It is defined by the ICHD-II as a high-intensity headache of rapid onset mimicking an SAH from a ruptured aneurysm with maximum intensity being reached in less than a minute.¹⁶ In most patients thunderclap headache peaks instantaneously. In a small case series 19% of patients with SAH had headache that reached maximum severity more gradually (up to 5 minutes).⁴¹ Sudden severe headache may also occur during sexual activity or exercise.¹⁶

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Other causes of sudden severe headache include: intracerebral haemorrhage, cerebral venous sinus thrombosis, arterial dissection and pituitary apoplexy.¹⁶

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There are no reliable features to differentiate between primary and secondary thunderclap headache and SAH can present with milder sudden onset headache.³⁵ A significant minority of thunderclap headache is secondary. In one case series 11% of patients with thunderclap headache had SAH.³⁵ When a patient presents for the first time with a sudden severe headache they should be referred immediately for consideration of a secondary cause, particularly SAH (this includes delayed presentation).^{35,36,38}

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If negative results are obtained from both brain computerised tomography and lumbar puncture with cerebrospinal fluid analysis (see section 5.2) within two weeks of onset of thunderclap headache, subarachnoid haemorrhage can be excluded from diagnosis.^{35,38,50}

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D Patients with a first presentation of thunderclap headache should be referred immediately to hospital for same day specialist assessment.

3.3.2 MEDICATION OVERUSE HEADACHE

Overuse of all acute headache treatments including simple and combination analgesics can cause medication overuse headache (see section 9).¹⁶

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3.3.3 CERVICOGENIC HEADACHE

The contribution of cervical spine disorders to migraine and tension-type headache is poorly understood. Fourteen to 18% of chronic headaches are cervicogenic in origin, ie result from a musculoskeletal dysfunction in the cervical spine.⁵¹

Cervicogenic headache consists of a unilateral or bilateral pain localised to the neck and occipital region which may project to regions on the head and/or face (see *Annex 2*).¹⁶ Pain may be precipitated or aggravated by particular neck movements or sustained neck postures and is associated with altered neck posture, movement, muscle tone contour and/or muscle tenderness.^{11,52} Manual examination identifying articular mobility, muscle extensibility and range of motion, in the form of flexion and extension may assist diagnosis.⁵¹ A headache may also be cervicogenic in origin if there is clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine (ICHD-II).¹⁶

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D Neck examination should be carried out in all patients presenting with headache including assessment of:

- neck posture
- range of movement
- muscle tone
- muscle tenderness.

3.3.4 RAISED INTRACRANIAL PRESSURE

Headache associated with raised intracranial pressure is usually worse when the patient is lying down and may awaken them from sleep. It may also be precipitated by valsalva manoeuvres (eg coughing, laughing, straining), sexual intercourse, or physical exertion.^{12,38} Visual obscurations, transient changes in vision with change in posture or valsalva, suggest raised CSF pressure.⁴⁵ Any of these symptoms should prompt referral for urgent specialist assessment.

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Intracranial tumours rarely produce headache until quite large, particularly in neurologically 'silent' areas such as the frontal lobes.¹¹ Pituitary and posterior fossa tumours are the exception to this. Haemorrhage into a tumour may cause sudden severe headache, but it is more common for these patients to present with seizures or neurological symptoms (eg cognitive change) or signs (eg homonymous hemianopia, hemiparesis). Heightened suspicion is appropriate if there is a history of cancer elsewhere in the body.¹¹

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In an audit of 324 patients with an imaging diagnosis of an intracranial tumour, headache was the first symptom in 23% but at the time of presentation was the sole symptom in only 0.2%. All other patients had focal symptoms or signs. Seizure was the most common focal symptom (21%).⁵³ In a large primary care case controlled study of 3,505 patients with primary brain tumour and 17,173 matched controls the positive predictive value (PPV) of isolated headache as the only symptom was 0.09% (95% CI 0.08 to 0.10). The PPV of new onset seizure was 1.2% (95% CI 1.0 to 1.4).⁵⁴

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Idiopathic intracranial hypertension (incidence 1-3/100,000 all; 21/100,000 in women aged 15-45) presents with symptoms and signs consistent with raised intracranial pressure, typically normal neuroimaging (including computerised tomography or magnetic resonance venography to exclude cerebral venous sinus thrombosis) and a raised CSF pressure. The headache is initially episodic then usually progresses over weeks to daily headache with features typical of raised intracranial pressure.⁴⁵ Other symptoms and signs commonly present include: transient visual obscurations, pulsatile tinnitus, sixth nerve palsy, enlarged blind spots and papilloedema. It is most frequently seen in obese women of childbearing age. The aetiology is unclear in the majority of cases, but secondary causes to consider include cerebral venous sinus thrombosis, various medications (eg tetracyclines and retinoids) and CSF inflammation, infection or malignancy.

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If a patient presents with headache and a combination of all or some of fever, neck stiffness, focal signs or seizures, then infection of the central nervous system (CNS) should be considered.^{35,49} This may be diffuse (meningitis or encephalitis) or localised (brain abscess). Heightened suspicion is appropriate if there is a history of HIV or immunosuppression.³⁸

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D Patients with headache and features suggestive of raised intracranial pressure should be referred urgently for specialist assessment.

D Patients with headache and features suggestive of CNS infection should be referred immediately for same day specialist assessment.

3.3.5 INTRACRANIAL HYPOTENSION (SPONTANEOUS OR IATROGENIC)

In patients with reduced CSF pressure there is a clear postural component to the headache. The headache develops or worsens soon after assuming an upright posture and lessens or resolves shortly after lying down.⁴⁴

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Once the headache becomes chronic it often loses its postural component. Low pressure headache is caused by CSF leakage. The commonest cause is a diagnostic lumbar puncture but spontaneous dural leakage can occur and is often not recognised.

D Intracranial hypotension should be considered in all patients with headache developing or worsening after assuming an upright posture.

3.3.6 GIANT CELL (TEMPORAL) ARTERITIS

Giant cell arteritis (GCA) should be considered in any patient over the age of 50 presenting with headache. Headache is usually diffuse rather than localised to the temple. It is generally persistent and may be severe. The patient may be systemically unwell. Scalp tenderness is common but has a low predictive value of a positive temporal artery biopsy. Jaw claudication is the most reliable predictor, but is not always present. Any patient with jaw claudication and headache should be considered to have GCA until proven otherwise. Visual disturbance is the next most reliable predictor. Prominent, beaded, or enlarged temporal arteries are the most predictive physical sign. A normal erythrocyte sedimentation rate (ESR) makes the diagnosis unlikely, but does not exclude it.⁴⁸

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D Giant cell arteritis should be considered in any patient over the age of 50 presenting with a new headache or change in headache.

☒ Patients with symptoms suggestive of giant cell arteritis should be referred urgently for specialist assessment.

3.3.7 ANGLE CLOSURE GLAUCOMA

Angle closure glaucoma is rare before middle age. Family history, female sex and hypermetropia are recognised risk factors. Presentation is variable. The patient may have a mid-dilated pupil and red eye with impaired vision, indicating acutely raised intraocular pressure. Alternatively angle closure glaucoma may present as non-specific headache, eye pain, halos around lights or headache mimicking migraine with aura.^{37,55} Intermittent angle closure glaucoma may precede acute angle closure and the eye may not be red.³⁷ The diagnosis should be considered in a patient with headache associated with a red eye, halos or unilateral visual symptoms.

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D Angle closure glaucoma should be considered in a patient with headache associated with a red eye, halos or unilateral visual symptoms.

☒ Acute angle closure glaucoma is an ophthalmological emergency.

3.3.8 CARBON MONOXIDE POISONING

Symptoms of sub-acute carbon monoxide poisoning include headaches, nausea, vomiting, dizziness, muscular weakness and blurred vision.¹¹

4

4 Assessment tools

A number of tools have been developed to aid headache diagnosis, assess headache impact and related disability and measure response to treatment. Table 2 summarises a number of tools which are readily available via the internet. In clinical practice physicians usually ask questions about headache symptoms. Whilst considering symptoms is important, asking questions about impact can change a clinician's perception of how severe a patient's headache or migraine is.⁵⁶ This information influences treatment choice and the need for follow up.

Patients, primary care clinicians and headache specialists commonly get the diagnosis wrong.^{19,20} This may be because of limited consultation time or poor patient recall. Clinician review and analysis of a prospective diary that records headache symptoms over a few weeks can improve diagnosis.^{11,19,20}

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D Practitioners should consider using headache diaries and appropriate assessment questionnaires to support the diagnosis and management of headache.

A sample weekly headache diary is displayed in Annex 5.

Table 2 Tools for headache diagnosis and assessment of impact.

Tool	Applications/Benefits	Format	Basis	Limitations
Headache Impact Test (HIT /HIT 6) www.headachetest.com/	- assess headache impact - determine diagnostic label - monitor treatment response ^{57,58} Patients with a high HIT-6 score are more likely to be correctly diagnosed and treated for migraine by their GP. Typical scores are chronic headache 57-63 migraine 54-59 TTH 34-45. ^{19,59-61}	Internet or paper based questionnaire 5/6 questions Computerised adaptive testing. ^{62,63}	Retrospective tool based on patient's experience of headache over the previous 4 weeks. It assesses: - pain - social role limitations - cognitive functioning - psychological distress - vitality	Limited sensitivity for measuring severity of pain⁶¹
Migraine Disability Assessment (MIDAS) www.midas-migraine.net/edu/question/Default.asp	- assess headache impact - monitor treatment response Scores correlate with diagnosis based on physicians' estimates of pain and disability based on patients' medical histories.⁶⁴ High internal consistency, test-retest reliability, accuracy and ease of use.^{26, 65-67}	5 item paper based questionnaire	Retrospective tool based on time lost in 3 activity domains over previous 3 months.⁶⁶ - work or school - household, work and family - social or leisure activities	Gives all patients with frequent headache a high score. One headache may count multiple times because of the scoring domains.^{65, 68-70} Domains exclude emotional impact.
ID Migraine www.migraineclinic.org.uk/	determine diagnostic label²⁸ Sensitivity for migraine of 0.81 (95% CI, 0.77 to 0.85), specificity of 0.75 (95% CI 0.64 to 0.84) and a positive predictive value of 0.93 (95% CI 0.90 to 0.96).	3 item paper based screening questionnaire	Retrospective based on experience of: - gastric symptoms - light sensitivity - functional impairment	False positive rate of 19%.

5 Investigations

5.1 NEUROIMAGING

When is neuroimaging required?

Investigation should be avoided in principle if it does not lead to a change in management or it is unlikely to reveal a relevant abnormality. Occasionally, neuroimaging may be required on an individual basis if a patient is disabled by fear of serious pathology.⁷¹

4

The vast majority of primary headaches do not require neuroimaging. In a prospective study where patients with headache for more than four weeks underwent neuroimaging (CT, MRI or both), significant intracranial abnormalities were found in 0.4% of patients with migraine, 0.8% of patients with tension-type headache, and in 5% (one out of 20 patients) of those with cluster headache. In a subgroup of 188 patients without clearly defined headache type, significant intracranial abnormality was found in 3.7%.⁷²

2+

A meta-analysis of neuroimaging studies estimated a 0.2% prevalence of significant intracranial abnormalities in patients with migraine and a normal neurological examination.¹² In a retrospective review of 402 patients with chronic headache without neurological symptoms or signs, relevant abnormalities on MRI were found in 0.6% of patients with migraine, 1.4% of patients with tension-type headache and 14.1% of patients with "atypical headache".⁷³ In another retrospective review MRI revealed relevant intracranial abnormalities in 0.7% of patients with chronic or recurrent headache and a normal neurological examination.⁷⁴

4
3

Neuroimaging in patients with headache and an abnormal neurological examination is significantly more likely to reveal an underlying cause.^{12,39,40} Further investigation is required to exclude secondary aetiology when headache is accompanied by red flags (see section 3.3).

4

Incidental abnormalities

Both MRI and CT can identify neurological abnormalities incidental to the patient's presenting complaint and which may result in heightened patient anxiety and clinician uncertainty.^{21,22} Cranial MRI in 2,536 healthy young males revealed incidental abnormalities in 6.55%.²² A prospective cohort study of 2,000 volunteers (mean age, 63.3 years; age range 45-96 years) who received brain MRI revealed incidental abnormalities in 13.5%.²¹

3
2+

Patient reassurance

A randomised controlled trial of 150 patients with chronic daily headache in a specialist clinic found that patients who received MRI had a decrease in anxiety levels at three months, but that the reduction in anxiety was not maintained at one year. Patients with high scores on the hospital anxiety and depression scale who did not receive a scan had significantly higher health service costs overall due to a greater use of healthcare resources such as psychiatric and psychology services than comparable patients who received a scan.⁷⁵

1+

CT versus MRI

In ruling out secondary causes of headache MRI is more sensitive than CT in identifying white matter lesions and developmental venous anomalies.¹² The European Federation of Neurological Societies guidelines suggest that MRI is the imaging modality of choice because of this greater sensitivity.⁷⁶ The US headache consortium concluded that MRI may be more sensitive than CT in identifying clinically insignificant abnormalities, but not more sensitive in identifying clinically significant pathology relevant to the cause of the headache.⁷¹

3

- D** Neuroimaging is not indicated in patients with a clear history of migraine, without red flag features for potential secondary headache, and a normal neurological examination.
- D** Clinicians requesting neuroimaging should be aware that both MRI and CT can identify incidental neurological abnormalities which may result in patient anxiety as well as practical and ethical dilemmas with regard to management.
- D** Brain CT should be performed in patients with headache who have unexplained abnormal neurological signs, unless the clinical history suggests MRI is indicated.

5.1.1 COMPUTERISED TOMOGRAPHY AND THUNDERCLAP HEADACHE

ICHD-II classification states that normal brain imaging and CSF are required before a diagnosis of primary thunderclap headache can be made.¹⁶ 4

When SAH is suspected, CT brain scan should be carried out as soon as possible to maximise sensitivity. Sensitivity of CT for subarachnoid haemorrhage is 98% at 12 hours dropping to 93% by 24 hours.⁵⁰ 4

A normal CT brain scan is insufficient to rule out SAH and a lumbar puncture is required in patients with normal CT scans (see section 5.3).

If negative results are obtained from both brain CT and lumbar puncture with cerebrospinal fluid analysis within two weeks of onset of thunderclap headache, then SAH can be excluded from diagnosis.^{35,38,50} 4

Sudden severe headaches precipitated by sexual activity can be diagnosed as primary if they cannot be attributed to another disorder.¹⁶ On first onset of this headache it is essential to exclude SAH and arterial dissection.⁷⁷ 4

- D** In patients with thunderclap headache, unenhanced CT of the brain should be performed as soon as possible and preferably within 12 hours of onset.

5.1.2 MAGNETIC RESONANCE IMAGING

Expert opinion suggests that MRI should be considered in patients with cluster headache, paroxysmal hemicrania or SUNCT, in order to exclude the wide variety of secondary causes.³² 4

In a review of 31 cases in which a TAC or TAC like syndrome was associated with a structural lesion and the treatment of the lesion resulted in significant clinical improvement, 11 out of 31 had a pituitary adenoma. Only 10 out of the 31 cases had atypical presenting features.⁷⁸ In a prospective study of 43 patients with SUNCT and nine patients with SUNA, cranial imaging was carried out in 36 with SUNCT and eight with SUNA. Twelve patients (11 with SUNCT, 1 with SUNA) of the 44 who received cranial imaging had significant intracranial abnormalities.³³ 3
2+

- D** Brain MRI should be considered in patients with cluster headache, paroxysmal hemicrania or SUNCT.

In a retrospective study in patients with cough-induced headaches (n = 30), exertional headaches (n = 28) and sexual headaches (n = 14); 17 out of 30 patients with cough-induced headache had chiari type 1 malformation; 10 out of 28 patients with headache induced by exertion had SAH, 1 had sinusitis and 1 had brain metastases; and 1 out of 13 patients with explosive orgasmic headache had SAH.⁷⁹ 3

Primary cough headache (Valsalva manoeuvre headache) which is precipitated rather than aggravated by coughing, laughing or straining may be diagnosed only after structural lesions are excluded by neuroimaging.¹⁶ Patients with cough headache should have an MRI brain scan to rule out posterior fossa lesion.⁷⁷ 4

- D** Brain MRI should be carried out in patients presenting with headache which is precipitated, rather than aggravated, by cough.

Benign exertional headache which is precipitated rather than aggravated by exertion can be diagnosed as primary if it is not associated with any other disorder (see Annex 2).¹⁶ ICHD-II classification states that on first occurrence subarachnoid haemorrhage or arterial dissection need to be excluded.¹⁶ Similar percentages of patients with benign thunderclap headache and confirmed SAH were provoked by exertion in two prospective case series so exertion alone does not predict SAH.^{35,41} Expert opinion suggests that neuroimaging should be carried out to exclude a structural cause or vascular abnormality in patients with exertional headache. If headaches are prolonged beyond a few hours, are accompanied by focal neurological symptoms or vomiting, or appear de novo after the age of 40 the chance of finding a relevant abnormality is increased.⁷⁷

4

- ☒ Further investigation should be considered in patients with headaches which are precipitated, rather than aggravated, by exercise.

A small case control study of spinal MRI in patients with post lumbar puncture headache and spontaneous intracranial hypotension concluded that venous plexus volume at C2 was significantly higher in patients than in the controls. Spinal hygromas were present in 67% of patients with spontaneous intracranial hypotension and 73% of patients with post lumbar puncture headache, but were not present in controls.⁸⁰

3

Several small case series show an association between spontaneous intracranial hypotension and diffuse pachymeningeal gadolinium enhancement on brain MRI.⁸¹⁻⁸³

3

- ☒ All patients with suspected low pressure headache should be referred to a specialist for consideration of the most appropriate investigation.

5.2 LUMBAR PUNCTURE IN SUBARACHNOID HAEMORRHAGE

Lumbar puncture (LP) with CSF analysis is appropriate for patients with thunderclap headache and normal neuroimaging to exclude a diagnosis of subarachnoid haemorrhage.^{35,50,84,85} One prospective study found that lumbar puncture was positive for subarachnoid haemorrhage in 21% of patients with thunderclap headache (5 out of 23 patients) who had a normal CT brain scan.³⁵

4

3

2⁺

In a case series, lumbar puncture was performed in 40 out of 81 patients presenting with thunderclap headache and a normal CT brain scan. 15% of these had a lumbar puncture positive for SAH.⁸⁵

3

Since xanthochromia (bilirubin and oxyhaemoglobin) can only be detected in CSF after 12 hours, lumbar puncture and CSF analysis should be delayed 12 hours from the onset of thunderclap headache.^{50,86,87} In patients presenting late, LP can be informative up to two weeks from the onset of the thunderclap headache.^{50,86}

3

Spectrophotometry is the recommended method of CSF analysis and should be performed on the final sample of CSF collected. Following lumbar puncture, the presence of CSF bilirubin is the key result suggestive of SAH, and is usually accompanied by oxyhaemoglobin.⁸⁷

4

Opening pressure should be measured routinely in all lumbar punctures.⁸⁷

4

C Patients with thunderclap headache and a normal CT should have a lumbar puncture.

D In patients who require a lumbar puncture for thunderclap headache, oxyhaemoglobin and bilirubin should be included in cerebrospinal fluid analysis.

☒ Opening pressure should be measured when lumbar puncture is indicated in patients with headache.

☒ In patients with suspected subarachnoid haemorrhage, neuroimaging should be performed prior to lumbar puncture.

☒ Lumbar puncture in CT negative patients with suspected subarachnoid haemorrhage should be carried out as soon as possible after 12 hours has elapsed from the onset of symptoms.

In delayed presentations, lumbar puncture can be performed up to two weeks from onset of symptoms.

5.3 ERYTHROCYTE SEDIMENTATION RATE, C-REACTIVE PROTEIN AND PLASMA VISCOSITY IN GIANT CELL ARTERITIS

Increased erythrocyte sedimentation rate (ESR) may be useful in predicting the presence or absence of GCA in patients with suggestive symptoms. Mean ESR in patients with GCA was 88 mm/hr compared with a mean ESR of 10 mm/hr in patients without GCA. The difference was not statistically significant.⁴⁸ Four per cent of patients with positive temporal artery biopsy results had a normal value ESR.⁴⁸

2+

A retrospective case series of 363 patients who underwent temporal artery biopsy for suspected GCA found that both ESR and C-reactive protein (CRP) had a high sensitivity for detection of GCA. C-reactive protein had a higher sensitivity than ESR (100% vs 92%). Combining ESR and CRP gave the highest specificity (97%) than CRP alone (83% in men and 79% in women).⁸⁸ In patients with suspected GCA, the odds of a positive biopsy were 3.2 times greater with CRP above 24.5 mg/l ($p=0.0208$); two times greater with an ESR between 47 and 107 mm/hr compared to an ESR less than 47 mm/hr ($p=0.0454$); the odds of a positive biopsy was 2.7 times greater than 107 mm/hr relative to an ESR less than 47 mm/hr ($p=0.0106$).⁸⁸

3

D ESR and/or CRP (but preferably a combination of these diagnostic tests to maximise sensitivity and specificity) should be measured in patients with suspected giant cell arteritis.

Plasma viscosity is used in the diagnosis of GCA, but no studies on its effectiveness were identified.

5.4 OTHER INVESTIGATIONS

No evidence was identified on the benefits of routine full blood count assessment or the use of X-ray of the cervical spine in the diagnosis of patients with headache.

6 Migraine

6.1 ACUTE TREATMENT

The treatment of acute migraine attacks should be selected for each patient according to severity and frequency of attacks, other symptoms, patient preference and history of treatment. A stepped approach can be used, commencing with an analgesic and anti-emetic, if required, and escalating to 5HT₁ receptor agonist (triptan) as required. A non-steroidal anti-inflammatory drug (oral/rectal or intramuscular) can be given following, or added to, a triptan for resistant attacks.¹¹

4

☒ Practitioners should recognise that a patient's standard therapy may not give a consistent response across all attacks. A strategy for managing resistant attacks should be planned with patients.

☒ When initiating acute treatment for migraine the risks of medication overuse headache should be discussed with the patient.

The proportion of patients who become pain free two hours post-dose has become the preferred and clinically most relevant primary end point. However, the ideal efficacy end point is sustained pain free: the proportion of patients who were pain free by two hours post-dose and who do not have a recurrence of moderate or severe headache and who do not use any rescue headache medication 2-24 hours post-dose.⁸⁹

1⁺

6.1.1 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (INCLUDING ASPIRIN) AND PARACETAMOL

Aspirin, ibuprofen and paracetamol are inexpensive and widely available over-the-counter therapies, making them a good option for first line treatment. Aspirin and ibuprofen should be avoided in patients with asthma or peptic ulceration.⁹⁰

Three well conducted RCTs showed that 48-52% of patients with acute migraine experienced pain relief at two hours after taking aspirin 900-1,000 mg.⁹¹⁻⁹³ A combination of paracetamol 1,000 mg, aspirin 1,000 mg and caffeine 260 mg may be more effective (84% pain relief at two hours) than aspirin 500 mg or sumatriptan 50 mg alone for patients with mild to moderate migraine.⁹⁴

1⁺⁺
1⁺

In an RCT ibuprofen 200-400 mg relieved pain in 41% of patients with migraine within two hours, although severe initial headache was only relieved by the 400 mg dose.⁹⁵ Ibuprofen 400 mg is as effective as aspirin 1,000 mg or sumatriptan 50 mg for pain relief at two hours.⁹¹ Ketoprofen 75-150 mg also provided relief to 62% of patients with migraine at two hours.⁹⁶

1⁺⁺

The NSAID tolfenamic acid rapid tablets 200 mg is licensed specifically for the treatment of acute attacks of migraine. Diclofenac, flurbiprofen, ibuprofen and naproxen are also licensed for use in migraine. For patients with nausea and vomiting, diclofenac suppositories 100 mg can be used for pain.⁹⁷

In a placebo-controlled RCT, paracetamol 1,000 mg relieved 57.8% of moderate (but not severe) attacks of migraine within two hours.⁹⁸

1⁺⁺

A Aspirin 900 mg is recommended for acute treatment in patients with all severities of migraine.

A Ibuprofen 400 mg is recommended for acute treatment in patients with migraine.

☒ Other NSAIDs (tolfenamic acid, diclofenac, naproxen and flurbiprofen) can be used in the treatment of acute migraine attacks.

B Paracetamol 1,000 mg is recommended as acute treatment for mild to moderate migraine.

6.1.2 TRIPTANS

Triptans provide significant pain relief to patients with acute migraine within two hours of administration and improve patients' quality of life.⁹⁹⁻¹⁰³ 1++
1+

Triptans vs pharmacy and over-the-counter medicines

Sumatriptan 100 mg achieved significantly less headache relief compared with aspirin 900 mg and metoclopramide 10 mg in patients presenting after their first migraine attack.¹⁰² Sumatriptan 50 mg also achieved significantly less headache relief at two hours compared with a combination of aspirin 1,000 mg, paracetamol 1,000 mg and caffeine 260 mg for patients with mild to moderate headache.^{94, 102} It was statistically equipotent with aspirin (1,000 mg) and ibuprofen (400 mg) in reducing headache severity at two hours, but significantly better than aspirin for pain-free outcome at two hours (37.1% of patients pain free versus 27.1%).⁹¹ 1+
1++

Triptans vs ergots

Eletriptan 40 mg and 80 mg had significantly better headache response rate and pain-free rate at two hours than cafergot[®], a combination of ergotamine 1 mg and caffeine 100 mg.¹⁰⁰ 1+

Triptan vs triptan

The following comparison of various triptans is based largely on three systematic reviews. In a large review and meta-analysis, the activities of all oral triptans (except frovatriptan) were compared with sumatriptan 100 mg.¹⁰⁴ Another systematic review compared efficacy and tolerability of triptans with placebo.¹⁰⁵ A systematic review of RCTs examined efficacy and tolerability of frovatriptan compared with placebo.¹⁰⁶ 1++
1+

Sumatriptan 50 mg is available from the community pharmacist without prescription to treat previously diagnosed migraine.

Table 3: Comparison of the main efficacy and tolerability measures for the oral triptans versus 100 mg sumatriptan.*

	Initial 2h relief	Sustained pain free	Consistency	Tolerability
Sumatriptan 25 mg	-	=/-	-	+
Sumatriptan 50 mg	=	=	=/-	=
Zolmitriptan 2.5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=
Naratriptan 2.5 mg	-	-	-	++
Rizatriptan 5 mg	=	=	=	=
Rizatriptan 10 mg	+	+	+(+)	=
Eletriptan 20 mg	-	-	-	=
Eletriptan 40 mg	=/+	=/+	=	=
Eletriptan 80 mg	+(+)	+	=	-
Almotriptan 12.5 mg	=	+	+	++
= indicates no difference when compared with sumatriptan 100 mg + indicates better when compared with sumatriptan 100 mg - indicates inferior when compared with sumatriptan 100 mg				

* Table cited from Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials Lancet, 2001; 358(9294): 1674.

Response at two hours

Compared with 100 mg sumatriptan, 10 mg of rizatriptan and 80 mg of eletriptan showed higher initial two hour relief.¹⁰⁴ 1++

Sustained pain-free at two hours

Compared with sumatriptan 100 mg, 80 mg eletriptan, 12.5 mg almotriptan, and 10 mg rizatriptan showed higher sustained pain-free rates at two hours post-dose.¹⁰⁴ 1++

Rizatriptan 10 mg (number needed to treat (NNT)=3.1) showed higher pain-free rates at two hours than sumatriptan 50 mg (NNT=4.0), sumatriptan 100 mg (NNT=4.3) and naratriptan 2.5 mg (NNT=9.2).⁹⁹ 1+

Frovatriptan 2.5 mg was more effective than placebo for pain-free rate at two hours (relative risk (RR) 3.70, 95% CI 2.59-5.29, $p < 0.0001$) and at four hours post-dose (RR 2.67, 95% CI 2.21-3.22, $p < 0.0001$).¹⁰⁶ 1+

Recurrence rates 2-24 hours

Comparison of headache recurrence rates for different triptans is problematic. Less potent, slower acting triptans which only relieve milder headaches tend to show lower recurrence rates because mild headaches may be less likely to recur. Compared with sumatriptan 100 mg (30%, 95% CI 27-33), recurrence rates were lower for 40-80 mg eletriptan and higher for 5 and 10 mg rizatriptan.¹⁰⁴ The risk of headache recurrence within 24 hours was reduced by frovatriptan, (RR 0.74, 95% CI 0.59-0.93, $p = 0.009$) but this apparent benefit needs to be assessed in the light of confounding by headache severity.¹⁰⁶ 1++
1+

Sustained pain-free rates

Compared with sumatriptan 100 mg (rate =20%, 95% CI 18-21), sustained pain-free rates were higher for 10 mg rizatriptan, 80 mg eletriptan and 12.5 mg almotriptan and lower for 20 mg eletriptan.¹⁰⁴ 1++

Consistency

Triptans produced a response to headache at two hours in at least one of three treated attacks in 79-89% of patients, compared with around 50% in placebo, two of three treated attacks in 47-72% of patients, compared with 17-33% in placebo and three of three treated attacks in 16-47% of patients compared with up to 9% in placebo.¹⁰⁴ 1++

Triptan use led to freedom from pain at two hours in 51-59% of patients, compared with 18% in placebo. Sustained pain-free response in two of three treated attacks was achieved in 14-42% of patients compared with 3-13% with placebo and three of three treated attacks in 1-17% of patients compared with <2% with placebo.¹⁰⁴ 1++

Compared with placebo, the highest consistency rates were for 100 mg sumatriptan and 12.5 mg almotriptan.¹⁰⁴

Adverse event rates

100 mg sumatriptan had a mean placebo subtracted rate of any adverse events of 13% (95% CI 8-18). Rates for other triptans overlap, except for lower values for 2.5 mg naratriptan and 12.5 mg almotriptan; these rates also do not differ from placebo.¹⁰⁴ 1++

Recommendations on triptan use

Triptans are contraindicated in patients with ischaemic heart disease, previous myocardial infarction, coronary vasospasm or uncontrolled or severe hypertension. Triptans should be used with caution in hemiplegic migraine.⁹⁰

A Oral triptans are recommended for acute treatment in patients with all severities of migraine if previous attacks have not been controlled using simple analgesics.

A Almotriptan 12.5 mg, eletriptan 40-80 mg or rizatriptan 10 mg, are the preferred oral triptans for acute migraine.

The response to individual triptans is idiosyncratic. Patients who do not respond to one triptan may have a good response to a different triptan.¹⁰⁷ 1++

B If a patient does not respond to one triptan an alternative triptan should be offered.

Triptans should not be taken during the aura and should be taken at or soon after the onset of the headache phase of a migraine attack.¹¹ 4

D Triptans should be taken at, or soon after, the onset of the headache phase of a migraine attack.

Triptan nasal sprays/subcutaneous injections

Sumatriptan nasal spray is not useful if vomiting precludes oral therapy as its bioavailability depends on ingestion. Zolmitriptan nasal spray may be useful if vomiting is already occurring as 30% is absorbed through the nasal mucosa. In patients with severe attacks of migraine which are resistant to oral or nasal triptans, subcutaneous injection of sumatriptan 6 mg remains an option.¹¹ This offers the fastest and highest level of pain relief, but carries an increased risk of adverse events which may limit its use for some patients. 4

☒ Nasal zolmitriptan or subcutaneous sumatriptan should be considered in severe migraine or where vomiting precludes oral route or where oral triptans have been ineffective.

Triptan and NSAID combinations

Two replicate double blind RCTs have compared the efficacy and safety of a fixed dose combination of 85 mg sumatriptan and 500 mg naproxen sodium with placebo and with monotherapy with sumatriptan succinate or naproxen sodium in the acute treatment of migraine.¹⁰⁸ The incidence of headache relief two hours after dosing (the reduction of pain from moderate/severe intensity to mild/no pain without use of rescue medication) were 65%, 55%, 44% and 28% with sumatriptan-naproxen sodium, sumatriptan monotherapy, naproxen sodium monotherapy and placebo, respectively in study 1 ($p < 0.001$ for sumatriptan-naproxen sodium, sumatriptan and naproxen sodium versus placebo; $p = 0.009$ for sumatriptan naproxen sodium versus sumatriptan). The corresponding percentages in study 2 were 57%, 50%, 43% and 29% ($p = 0.03$ for sumatriptan-naproxen sodium versus sumatriptan). Sumatriptan-naproxen sodium was significantly more effective than monotherapy with sumatriptan or naproxen sodium for the incidence of 24 hour sustained pain-free response in both studies. In study 1, the incidence of sustained pain-free response was 25% with sumatriptan-naproxen sodium compared with 16% with sumatriptan monotherapy ($p < 0.01$), 10% with naproxen sodium monotherapy ($p < 0.001$) and 8% with placebo ($p < 0.001$). The corresponding incidences in study 2 were 23% with sumatriptan-naproxen sodium compared with 14% with sumatriptan monotherapy ($p < 0.001$), 10% with naproxen monotherapy ($p < 0.001$) and 7% with placebo ($p < 0.001$). 1+

C A combination of sumatriptan 50-100 mg and naproxen sodium 500 mg may be helpful in acute migraine particularly in prolonged attacks which are associated with recurrence.

6.1.3 ANTI-EMETICS

Anti-emetics such as prochlorperazine 3-6 mg buccal tablets or domperidone 10 mg oral or 30 mg rectal, may be used for symptoms of nausea and vomiting associated with migraine. Anti-emetics such as metoclopramide 10 mg or domperidone 20 mg are also useful as a prokinetic to promote gastric emptying.¹¹

4

D Oral and rectal anti-emetics can be used in patients with acute migraine attacks to reduce symptoms of nausea and vomiting and to promote gastric emptying.

A systematic review identified six double blind RCTs evaluating the combination of aspirin and metoclopramide for the treatment of acute migraine attacks.¹⁰⁹ The dose of metoclopramide (10 mg) was constant in all trials, but the dose of aspirin varied from 650–900 mg. Four compared the combination with placebo, two with oral sumatriptan (100 mg) one with oral dihydroergotamine mesilate (5 mg) and one with aspirin (650 mg) alone. The combination was significantly better than placebo for pain relief at two hours in all four RCTs. Sumatriptan was better in one RCT and equivalent in the other for pain relief at two hours. Improvement in nausea was not significantly different. The combination was significantly better than oral dihydroergotamine for pain relief at two hours. In the only RCT to compare the combination with aspirin alone, there was no difference in pain relief at two hours. The number of patients in this RCT was small.

1+

B A combination of aspirin and metoclopramide can be used for the treatment of patients with acute migraine attacks.

A double blind crossover RCT compared the fixed combination droperamol® (paracetamol 500 mg and domperidone 10 mg) with 50 mg sumatriptan. There was no significant difference in headache relief at two (36.4% vs 33.3%) and four (49.2% vs 41.9%) hours between the two treatments. Improvement in nausea was the same with both treatments. Fewer side effects were reported with droperamol®.¹¹⁰ Headache improvement using the fixed combination paramax® (paracetamol 500 mg and metoclopramide 5 mg) was not significantly different to placebo.¹⁰² Two double blind RCTs have compared the fixed combination migramax® (lysine acetylsalicylate 1620 mg and metoclopramide 10 mg) with placebo. In both headache relief was superior with migramax® compared to placebo (56% vs 28%, 57% vs 24%). The second study also compared migramax® with sumatriptan 100 mg. There was no significant difference. Fewer side effects were reported in the migramax® group.¹⁰²

1+

B Fixed analgesic/anti-emetic combinations can be used for the treatment of patients with acute migraine attacks.

Intravenous anti-emetic can be used in a hospital setting for migraine which is not responsive to standard treatment.

A well conducted meta-analysis of RCTs of variable quality showed that intravenous metoclopramide is more effective than placebo in reducing headache pain from acute migraine (odds ratio (OR) 2.84, 95% CI 1.05 to 7.68).¹¹¹

1++

Metoclopramide is not licensed for treatment of pain in migraine.

An RCT demonstrated that haloperidol IV 5 mg significantly relieves migraine headache in 80% of patients compared to 15% of patients treated with sodium chloride ($p < 0.0001$). Haloperidol is associated with a high level of adverse events such as sedation and restlessness which limits its use in patients with migraine.¹¹²

1+

B IV metoclopramide can be used in the acute management of patients with migraine.

6.1.4 ERGOTAMINE

Ergotamine is superior in efficacy to placebo but is less effective in relieving acute migraine symptoms than triptans, NSAIDs, isometheptene or opioid comparators. It is not well tolerated.¹⁰² A combination of ergotamine and caffeine (Cafergot®) also performed less well than eletriptan for better headache response and pain-free rates.¹⁰⁰

1++

Ergotamine can cause side effects such as nausea, vomiting, abdominal pain and muscular cramps. It should not be used in patients who have cerebrovascular or cardiovascular disease.⁹⁰

A

Ergotamine is not recommended for patients with acute migraine.

6.1.5 CAFFEINE

Evidence on the use of caffeine as a treatment for headaches was limited to the inclusion of caffeine with combinations of other therapies (see sections 6.1.1 and 6.1.4).

6.1.6 OTHER THERAPIES

No evidence was identified for the efficacy of COX-2 inhibitors, corticosteroids, indometacin or opioids.

There is a risk of medication overuse with all acute treatments for migraine (see section 9.1). This risk is greatest for opioid-containing analgesics eg Migrave® , Syndol® and Solpadeine®.¹¹³

2+

D

Opioid analgesics should not be routinely used for the treatment of patients with acute migraine due to the potential for development of medication overuse headache.

6.2 PHARMACOLOGICAL PROPHYLAXIS

Preventive pharmacological treatment for migraine should be considered in patients with recurring migraines that significantly interfere with their daily routine, in the presence of contraindication to, failure of, or overuse of acute therapies and in uncommon forms of migraine (hemiplegic migraine, basilar artery migraine or migraine with prolonged aura). The goal of preventive therapy is to reduce the attack frequency, severity and duration, improve responsiveness to treatment of acute attacks and reduce migraine associated disability.

4

General principles for preventive treatment for migraine:

- most preventive drugs should be titrated slowly to an effective or maximum dose in order to minimise side effects¹¹
- preventive medication should be given a trial of at least six to eight weeks following dose titration¹¹
- the choice of preventive medication should be guided by their side effect profile and the patient's comorbid conditions
- after six to 12 months of effective prophylaxis, gradual withdrawal should be considered.¹¹⁴

4
1+

☒

Alongside preventive migraine treatment patients should also have access to appropriate medications for treatment of acute attacks of migraine.

A suggested guide to the use of prophylaxis is outlined in Table 4.^{11,90}

Table 4 Prophylactic therapies for patients with migraine

Preventive drug	Use with caution in patients with: (not an exhaustive list)	May be preferred in patients with:
Beta blockers	Asthma	Comorbid anxiety
	Diabetes	
	Bradycardia	
	Peripheral vascular disease	
	Comorbid depression	
Tricyclics	Angle closure glaucoma	Comorbid depression
		Comorbid tension-type headache
		Sleep disturbance
Topiramate	Renal stones	Comorbid obesity
	Angle closure glaucoma	
	Pregnancy	
Valproate	Obesity	Comorbid depression
	Liver disease	
	Pregnancy	

- ☑ When considering antiepileptic medication for prophylaxis of migraine in women of reproductive age, advice and counselling regarding the potential teratogenic side effects of these drugs should be given.

6.2.1 BETA BLOCKERS

Propranolol 80-240 mg per day is effective in reducing the frequency of migraine.¹¹⁵ A Cochrane review found that the overall relative risk of response to treatment for propranolol was 1.94 (95% CI, 1.61 to 2.35) indicating that propranolol is approximately twice as effective as placebo in reducing headache frequency.¹¹⁶ Data on headache intensity were reported inconsistently. The US Headache Consortium considers potential placebo response to be at least 20%.¹¹⁵

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1++

The US Headache Consortium found a high degree of certainty that propranolol provides moderate reduction in headache frequency, intensity and/or duration. Timolol, atenolol and nadolol are likely to be beneficial based upon comparison with placebo or propranolol. Direct comparison of metoprolol and propranolol suggests that metoprolol is as effective as propranolol in the prevention of migraine.¹¹⁵

4

Atenolol is not licensed for use in migraine.

When propranolol is prescribed to a patient using rizatriptan, the patient should be advised to halve the dose of rizatriptan and in addition not to take rizatriptan within two hours of taking propranolol.⁹⁰

4

A Propranolol 80-240 mg per day is recommended as first line therapy for prophylaxis in patients with migraine.

D Timolol, atenolol, nadolol and metoprolol can be used as alternatives to propranolol as prophylaxis in patients with migraine.

6.2.2 ANTIEPILEPTICS

A Cochrane review has shown that, as a class, antiepileptics can reduce the frequency of migraine by 1.4 attacks per 28 days. Patients are 2.4 times more likely to experience a 50% or greater reduction in migraine frequency when using antiepileptics compared with placebo. The NNT to achieve a 50% or greater reduction in migraine frequency for each are:¹¹⁷

- all antiepileptics: 3.9 (95% CI 3.4 to 4.7)
- topiramate: 3.9 (95% CI 3.4 to 5.1)
- sodium valproate: 3.1 (95% CI 1.9 to 8.9)
- gabapentin: 3.3 (95% CI 2.1 to 8.4).

1++

Topiramate significantly reduces the number of acute migraine episodes from 5.26 to 2.60 per 28 days ($p < 0.001$)¹¹⁸ as well as causing a greater mean reduction in migraine frequency than placebo (1.55 vs 0.47, $p = 0.001$).^{119, 120} The mean monthly frequency decreased significantly for patients receiving 100 mg per day of topiramate (from 5.4 to 3.3, $p < 0.001$) or 200 mg per day of topiramate (from 5.6 to 2.6, $p < 0.001$) as compared to placebo. There was a trend towards higher adverse incidents in patients who received 200 mg per day of topiramate.¹²¹

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1+

Topiramate 100 mg per day is similar to propranolol 160 mg with respect to reductions in migraine frequency, responder rates and daily use of rescue medication.¹²²

1+

In another study comparing topiramate therapy with placebo in patients with chronic migraine, treatment with topiramate resulted in a statistically significant mean reduction of days with migraine when compared with placebo (topiramate 6.4 versus placebo 4.1, $p = 0.032$).¹²³

1+

Three well conducted RCTs assessing the role of topiramate in migraine prevention were pooled. The data were analysed with regard to the number of headache days during the final four weeks of the treatment. The number of headache days per month in the topiramate versus placebo treated groups was 7.3 ± 3.0 versus 7.3 ± 3.1 during baseline and 4.1 ± 4.2 versus 5.6 ± 4.9 during the final four weeks ($p < 0.001$). At the end of the study eight versus 16 patients fulfilled ICHD-II criteria for chronic headache ($p = 0.082$). A significantly lower number of patients receiving topiramate reported an increase in headache days per month by the end of the study when compared with placebo (66 versus 88 patients, respectively, $p < 0.05$).¹²⁴

1+

Topiramate improves health related quality of life measures in patients with migraine taking part in RCTs when compared with placebo.¹²⁵

1+

Topiramate is licensed for use in the preventive treatment of migraine but its initiation is restricted to those offering specialist care with treatment managed under specialist supervision or shared care arrangements.

In a small study with a short follow-up period there was no significant difference in beneficial effects between topiramate and valproate in terms of number of days with migraine or MIDAS scores, when given to patients with chronic migraine.¹²⁶

1-

No significant difference in the number of patients reporting a 50% reduction in migraine frequency was observed when divalproex sodium (valproic acid) was compared with propranolol and when sodium valproate was compared with flunarizine (see section 6.2.4).¹¹⁷

1++

In a study comparing the effect of 400 mg of sodium valproate with 50 mg of topiramate in patients with episodic migraine, treatment with sodium valproate reduced the mean monthly frequency of attacks from 5.4 to 4.0 and the headache intensity from 7.7 to 5.8 ($p < 0.001$).¹²⁷ In patients treated with topiramate the mean monthly headache frequency was reduced from 5.4 to 3.2 and headache intensity from 6.9 to 3.7 ($p < 0.001$ in each case). There was no significant difference in these outcome measures between the two drugs.¹²⁷

1+

Gabapentin is more effective than placebo for patients with episodic migraine, with a median four week migraine rate of 2.7 for patients treated with gabapentin compared to 3.5 for patients treated with placebo ($p=0.006$).¹²⁸ The study had a high drop-out rate in the treatment group.

1⁺

A In patients with episodic migraine and chronic migraine topiramate 50-200 mg per day is recommended to reduce headache frequency and severity.

A In patients with episodic migraine sodium valproate 800-1,500 mg per day is recommended to reduce headache frequency and severity.

C Patients with episodic and chronic migraine can be treated with gabapentin 1,200 -2,400 mg per day to reduce headache frequency.

6.2.3 ANTIDEPRESSANTS

In a meta-analysis of 38 trials of antidepressants in patients with chronic headache only amitriptyline was studied in sufficient numbers of patients to demonstrate statistically significant effect. It reduced headache index (measure of headache burden calculated from frequency and severity) in both migraine and tension-type headache. The six studies of selective serotonin reuptake inhibitors (SSRIs) that measured effects on headache burden found no significant benefits.¹²⁹

1⁺

A Cochrane review showed no significant difference between the use of SSRIs and placebo in the reduction of migraine frequency or severity.¹³⁰ Fluoxetine was the most commonly studied SSRI.

1⁺⁺

There is consistent good evidence that amitriptyline is significantly better than placebo in reducing headache index and frequency and it is effective in the prophylaxis of migraine at a dose of 25-150 mg per day.¹¹⁵

4

An RCT found that venlafaxine 150 mg is superior to placebo and to venlafaxine 75 mg in the prophylaxis of patients with migraine without aura.¹³¹ There was a significant reduction in the number of days patients on venlafaxine 150 mg had headaches, compared to placebo ($p=0.006$). They consumed considerably fewer analgesics and there was greater patient satisfaction with venlafaxine 150 mg or 75 mg compared to placebo. When the global efficacy was considered 80% of patients in the venlafaxine 75 mg group and 88.2% of patients in the 150 mg group evaluated treatment benefits as either good or very good.¹³²

1⁺

The prophylactic effect of venlafaxine has been compared to amitriptyline in patients with migraine. In this crossover RCT the pain parameters were significantly improved in both groups compared to the washout period ($p<0.05$) but there was no significant difference between the groups ($p>0.05$).¹³²

1⁺

B SSRIs are not recommended in the prophylaxis of migraine.

B Amitriptyline 25-150 mg per day is recommended for patients requiring prophylaxis of migraine.

B Venlafaxine 75-150 mg per day is an effective alternative to tricyclic antidepressants for prophylaxis of migraine.

6.2.4 OTHER THERAPIES

Pizotifen

Pizotifen is a long established prophylactic agent and is commonly used in the UK. Most of the studies on pizotifen were conducted in the 1970s. Between 30 and 50% of patients have reported that using pizotifen reduces the number of attacks.¹³³

Two multicentre studies, one a double blind placebo-controlled (study 1) and the other an open study (study 2) were conducted to assess if pizotifen prophylaxis (in doses of 1.5 mg per day) improved migraine. The median of the monthly attack rate was lower in patients receiving pizotifen and sumatriptan than in those receiving placebo and sumatriptan (study 1; 3.5 versus 3.9, $p=0.008$), or sumatriptan alone (study 2; 2.9 versus 3.2, $p=0.23$). They also conclude that pizotifen may be better reserved for those patients who have four or more attacks per month.¹³³

1+

☒ Pizotifen is of limited value in prophylaxis of migraine.

Methysergide

Methysergide was one of the first drugs to be used for the prevention of migraine but its use is limited by the potential for causing retroperitoneal and retropleural fibrosis with prolonged use.⁹⁰ In four placebo-controlled trials methysergide was significantly better than placebo at reducing migraine frequency.¹¹⁵

1+

☒ Methysergide should only be used under specialist supervision.

Flunarizine

Flunarizine in doses of 5 mg and 10 mg a day has been compared to propranolol 160 mg for the prophylactic treatment of patients with migraine. Both flunarizine groups were at least as effective as propranolol in reducing attack frequency ($p<0.001$). No significant differences between the three treatments were found with regard to safety.¹³⁴

1+

Botulinum toxin A

The efficacy of botulinum toxin A for prophylaxis of episodic migraine was studied in a multicentre RCT. The primary efficacy end point was the mean reduction in the frequency of migraine days at day 180. All groups improved with no significant differences ($p=0.817$). At day 180 the frequency of migraine episodes was reduced from baseline means by 1.6, 1.7, 1.5 and 1.4 for Botulinum toxin A 225U, 150U and 75U and placebo respectively.¹³⁵

1+

A Botulinum toxin A is not recommended for the prophylactic treatment of migraine.

Candesartan

In one small study candesartan performed well against placebo with a relative reduction of 22% in the number of days patients experienced migraine.¹³⁶

1+

Aspirin

One study showed that aspirin may be associated with a small prophylactic effect in migraine among middle aged women, but this was not statistically significant (self reported improvement in frequency at 36 months, 59.6% vs 56.4% for placebo, OR 1.13).¹³⁷

1+

Montelukast

Montelukast given over three months to patients with migraine resulted in 15.4% patients reporting at least a 50% reduction in migraine attack frequency, as compared to 10.3% for placebo ($p=0.304$).¹³⁸

1+

Acetazolamide

Acetazolamide is poorly tolerated in patients with migraine and does not offer any beneficial prophylactic effect when compared to placebo.¹³⁹ | 1-

Hyperbaric oxygen

Hyperbaric oxygen has no role in the preventive treatment of migraine.¹⁴⁰ | 1-

Lanepitant

Lanepitant (a neurokinin NK1 antagonist) is no better than placebo for the preventive treatment of migraine. The number of patients with a 50% reduction in days with headache was 41% for lanepitant compared to 22% for placebo ($p=0.065$).¹⁴¹ Lanepitant is not licensed for use in the UK. | 1+

Buspirone

Patients with migraine and anxiety disorder treated with buspirone showed a 43.3% reduction in headache frequency compared to 10.3% with placebo ($p=0.0025$). There was no association of the headache response with the anxiolytic effect.¹⁴² | 1-

7 Tension-type headache

7.1 ACUTE TREATMENT

A large RCT (n = 638) showed that aspirin had a high response rate for relief of pain at two hours in patients with episodic tension-type headache (75% for 1,000 mg; p = 0.0009 and 70% for 500 mg p = 0.011). Paracetamol 1,000 mg had a similar rate (71% p = 0.007) and both performed well compared with response to placebo (54.5%).¹⁴³

1++

No studies were identified on any other therapies for the acute treatment of patients with tension-type headache.

A Aspirin and paracetamol are recommended for acute treatment in patients with tension-type headache.

7.2 PHARMACOLOGICAL PROPHYLAXIS

7.2.1 ANTIHYPERTENSIVES

High blood pressure does not usually cause headache, although blood pressure lowering treatments can reduce the prevalence of headache.¹⁴⁴

2++

A meta-analysis indicated that angiotensin II receptor antagonists reduce the frequency of headache.¹⁴⁵ An RCT showed that lisinopril has a significant effect on the reduction of hours and days with headache and migraine.¹⁴⁶ Neither of these studies specified headache type or identified patients with hypertension within the trial.

1-

1+

7.2.2 ANTIEPILEPTICS

One RCT was identified which showed a 9.1% difference in headache free rates benefiting patients with chronic daily headache who were treated with gabapentin versus those on placebo (p = 0.0005).¹⁴⁷

1+

7.2.3 ANTIDEPRESSANTS

A Cochrane review has shown no significant difference between treatment with placebo and fluoxetine for reduction in headache frequency and severity.¹³⁰

2++

Tricyclic antidepressants are more effective in reducing chronic headache than SSRIs.^{129,130} A significantly higher intake of analgesic medication was seen in patients treated with SSRIs than in patients treated with tricyclic antidepressants, equivalent to five or more doses per month (95% CI 1 to 9). Tricyclic antidepressants also reduced headache duration by 1.26 hours per day and headache index scores based on frequency and severity. Amitriptyline in doses of 25-75 mg was the most commonly studied tricyclic antidepressant.¹²⁹

1+

A Tricyclic antidepressants, particularly amitriptyline, 25-150 mg per day, are recommended as the agents of choice where prophylactic treatment is being considered in a patient with chronic tension-type headache.

A small RCT (n = 24) of mirtazapine in patients with chronic tension-type headache showed a significant reduction in headache frequency (p = 0.005), duration (p = 0.03) and intensity (p = 0.03) compared to placebo.¹⁴⁸

1-

Sertraline did not show a significant improvement on severity and frequency of chronic tension-type headache when compared to placebo.¹⁴⁹

1+

A small RCT (n = 60) on the efficacy of venlafaxine extended release tablets (150 mg per day) in the prophylactic treatment of patients with tension-type headache showed that the median number of days with headache decreased from baseline in the venlafaxine group in two out of the three periods studied, but not in the placebo group (p = 0.05 and 0.033). The number needed to treat for responders (> 50% reduction in days with headache) was 3.48.¹⁵⁰

1+

7.2.4 OTHER THERAPIES

A multicentre RCT assessing the efficacy of botulinum toxin A in the prophylactic treatment of chronic tension-type headaches showed no statistically significant difference between placebo and the four botulinum toxin A groups in the number of TTH free days per month.¹⁵¹ A statistically significant difference favouring placebo versus botulinum toxin A 150U was observed (4.5 versus 2.8 tension headache free days per month, $p = 0.007$). 1⁺

Botulinum toxin A has been shown to be effective for the treatment of patients with headache associated with neck dystonias.¹⁵² 1⁺

B Botulinum toxin A is not recommended for the preventive treatment of chronic tension-type headache.

Tizanidine has been shown to be superior to placebo in reducing headache (as measured by combination of frequency, duration and intensity) in patients with a chronic daily headache (migraine and tension-type, $p = 0.0025$).¹⁵³ 1⁺

8 Trigeminal autonomic cephalalgias

8.1 ACUTE TREATMENT OF CLUSTER HEADACHE

Few well conducted trials have been carried out on patients with cluster headache, possibly due to the spontaneous course of the condition.¹⁵⁴

8.1.1 TRIPTANS

Subcutaneous injection of 6 mg sumatriptan relieves pain in 73-96% of patients with acute cluster headache within 15 minutes.¹⁵⁵⁻¹⁵⁸ Nasal administration of 20 mg sumatriptan acts more slowly, relieving pain in 57% of patients at 30 minutes.¹⁵⁹

2-
1++

Nasal zolmitriptan 5 mg and 10 mg provide acute attack relief at 30 minutes in 50% and 63% of cluster headache patients respectively.¹⁶⁰ Oral zolmitriptan 10 mg relieves acute attack pain in 47% patients with episodic cluster headache at 30 minutes.¹⁶¹

1++

A Subcutaneous injection of 6 mg sumatriptan is recommended as the first choice treatment for the relief of acute attacks of cluster headache.

A Nasal sumatriptan or zolmitriptan is recommended for treatment of acute attacks of cluster headache in patients who cannot tolerate subcutaneous sumatriptan.

8.1.2 OXYGEN

In a small double blind crossover study conducted over 20 years ago, 19 men with cluster headache were treated with 100% oxygen versus air inhalation at 6 l/minute via a non-rebreathable mask over 15 minutes. The average relief score for all oxygen treated patients was 1.93 ± 0.22 (out of a possible score of 3.0). For air the treatment relief score was 0.77 ± 0.23 .¹⁶² In a previous study it was reported that 75% of 52 randomly selected patients with cluster headaches, reported significant pain relief when treated with 100% oxygen at a rate of 7 l/min for 15 minutes.¹⁶³

1+

A tight fitting, non-rebreathing mask should be used. Information on availability of suitable masks and loan of appropriate regulator equipment is available from www.ouchuk.org/html/

☒ 100% oxygen (7-12 litres per minute) should be considered for the treatment of acute attacks in all patients with cluster headache.

Trials have been conducted on the use of hyperbaric oxygen but no consistent prophylactic effect has been demonstrated.^{140,164,165}

1++
1+
1-

8.1.3 LIDOCAINE

An RCT demonstrated that 10% nasal drops of lidocaine brought pain relief within 37 minutes in patients with acute cluster headache, compared to 59 minutes for those on a saline placebo ($p < 0.001$).¹⁶⁶

1+

☒ For patients whose attacks of cluster headache are not well relieved by subcutaneous or nasal triptan and inhaled 100% oxygen, 10% intranasal lidocaine drops can be considered to help speed relief for acute attacks.

8.2 PHARMACOLOGICAL PROPHYLAXIS

8.2.1 CALCIUM CHANNEL BLOCKERS

Open label studies show that verapamil reduces the frequency and severity of cluster headaches.³² 4

In a small double blind study 86% of patients receiving verapamil (360 mg per day) showed an improvement of > 50% reduction in headache frequency while the placebo group showed no response.¹⁶⁷ 1+

Higher doses of verapamil (up to 960 mg per day) have been used and are recommended for the preventive treatment of cluster headaches. Regular electrocardiogram monitoring is required.¹⁶⁸ 4

B Verapamil 240-960 mg is recommended for the prophylaxis of cluster headache.

8.2.2 LITHIUM

A small double blind placebo-controlled trial using lithium (800 mg per day) in patients with cluster headache was stopped early because superiority over placebo could not be established.¹⁶⁹ 1-
Both lithium and verapamil have been shown to be superior to placebo in one small trial.³² 4

8.2.3 ERGOTS

Ergotamine has previously been used for the preventive treatment of cluster headaches but no trial evidence for this is available.³² 4

8.2.4 5-HT ANTAGONISTS

There are no contemporary placebo-controlled trials on the use of methysergide in cluster headaches. A small trial found pizotifen to be effective for cluster headaches but a further review has concluded that the effect is minimal.¹⁶⁸ 4

8.2.5 MELATONIN

In a small double blind study (20 patients with cluster headache) melatonin significantly reduced headache frequency compared with placebo ($p < 0.03$).¹⁷⁰ 1-

8.2.6 ANTIEPILEPTICS

A double blind placebo-controlled trial of valproate for treatment of cluster headaches found no beneficial effect. The study had an unusually high placebo response rate.¹⁷¹ 1-

In open label studies topiramate and gabapentin have been found to be effective for patients with cluster headaches.³² 4

8.2.7 STEROIDS

A double blind placebo-controlled trial compared suboccipital injection of a mixture of long and rapid acting betamethasone with the injection of physiological saline in patients with episodic and chronic cluster headache. Eighty five per cent of patients injected with steroid became headache free in the first week after injection compared to none in the placebo group ($p = 0.0001$). At four weeks eight of 11 responders remained attack free ($p = 0.0026$).¹⁷² 1+

Expert opinion suggests that oral steroids can be used for the short term preventive treatment of cluster headaches although no contemporary trial evidence is available.¹⁶⁸ 4

8.3 **TREATMENT OF PAROXYSMAL HEMICRANIA, HEMICRANIA CONTINUA AND SUNCT**

Responsiveness to indometacin is integral to the diagnosis of paroxysmal hemicrania and hemicrania continua. Indometacin is effective in doses of up to 225 mg per day.³² | 4

Lamotrigine may be effective for the treatment of the SUNCT syndrome.^{32,168} | 4

D Indomethacin up to 225mg is recommended for the prophylaxis of paroxysmal hemicrania and hemicrania continua.

9 Medication overuse headache

9.1 DEFINITIONS AND ASSESSMENT

Medication overuse headache (MOH) is defined as headache which is present for 15 days or more per month and which has developed or worsened while taking regular symptomatic medication (see Annex 2). ^{16,27,173}	4
Medication overuse headache is reported in migraine, tension-type headache, hemicrania continua, new daily persistent headache, cluster headache and SUNCT. ^{33,174-177} Patients with cluster headache and SUNCT who develop MOH usually have a personal or family history of migraine. ^{33,176}	3 4
ICHD-II criteria suggest medication overuse headache should be considered with use on ten days per month for triptans, ergots, opioids or combination analgesics and on 15 days per month for simple analgesics. ¹⁷³	4
Patients with a history of migraine headache who frequently use pain medications for non-headache pain are at increased risk of developing chronic daily headache. ¹⁷⁴	3
Patients who overuse medications are more likely to develop chronic daily headache. ^{113,178} The risk depends on which medication is being overused (opioid OR 4.4; triptan OR 3.7; ergot OR 2.9; analgesics OR 2.7). ¹¹³	3
In an audit of nine GP practices fewer than 16.2% of patients who were using triptans for headache met ICHD-II criteria for triptan overuse. ¹⁷⁹	3
Patients with frequent headache are at increased risk of developing chronic daily headache. ¹¹³ The more frequent the headache the greater the risk (5-9 headaches per month = OR 7.6; 10-15 headaches per month = OR 25.4).	3
Patients with chronic daily headache meeting the criteria for medication overuse headache evolving from episodic tension-type headache were found to be more likely to have a mood disorder than those with chronic tension-type headache without medication overuse. Patients with chronic daily headache meeting the criteria for medication overuse headache evolving from migraine were found to be more likely to have a mood disorder, depression, anxiety disorder or obsessive compulsive disorder than chronic tension-type headache without medication overuse. ¹⁸⁰	2+
In patients with chronic daily headache the DSM-IV criteria for dependence behaviour were significantly more common in those who met ICHD-II criteria for medication overuse headache. ¹⁸⁰	2+

D Medication overuse headache must be excluded in all patients with chronic daily headache (*headache ≥ 15 days / month for > 3 months*).

D Clinicians should be aware that patients using any acute or symptomatic headache treatment are at risk of medication overuse headache. Patients with migraine, frequent headache and those using opioid-containing medications or overusing triptans are at most risk.

C When diagnosing medication overuse headache, psychiatric comorbidity and dependence behaviour should be considered.

C Patients with medication overuse headache who have psychiatric comorbidity or dependence behaviour should have these conditions treated independently. Referral to a psychiatrist or a clinical psychologist should be considered.

9.2 TREATMENT

Abrupt withdrawal of the precipitating agent is the treatment of choice in the majority of patients with medication overuse headache.^{177,181-185}

In a case series of 98 patients who underwent withdrawal from medication all but three patients experienced an improvement in headache frequency at 14 days. 85% of patients taking triptan, 57% of patients taking ergot and 23% of patients taking analgesic achieved headache freedom at 14 days. Duration of withdrawal symptoms was shortest in the triptan group.¹⁸¹ These findings were confirmed in a second study which also found that migraine was more likely to improve than tension-type headache.¹⁸⁶

Follow up of patients with successful withdrawal showed a relapse rate of 45% at one and four years. Of those who relapsed 94% did so in the first year. Relapse rate varied with headache type (22% for migraine, 73% for TTH and 77% for mixed headache). Analgesics had the highest relapse rate (52%). Only 22% of ergot and 17% of triptan overusers relapsed.¹⁸⁷ A group looking at disability following medication withdrawal found a sustained improvement in MIDAS disability scores during three year follow up.¹⁸⁸

Duration of withdrawal headache depends on the medication overused.^{181,186} Duration is shorter and withdrawal more likely to be successful in patients taking triptans and ergots than in patients taking opioids, simple or combination analgesics. Withdrawal symptoms are also shorter for triptans.

Abrupt withdrawal from medication initially results in worsening of headache.^{181,184,186}

No studies were identified comparing abrupt versus gradual withdrawal. Expert opinion emphasises the need to withdraw opioids (and benzodiazepines and barbiturates) gradually.^{177,184}

Structured advice about medication overuse, benefits of medication withdrawal and withdrawal symptoms is as good as inpatient and outpatient detoxification programmes, in patients not overusing opioids.¹⁸³ There is similar reduction in headache frequency with abrupt withdrawal with education alone when compared with patients also given prednisolone or naratriptan.¹⁸²

A number of intravenous inpatient treatments are used in specialist centres. There is limited information based on small case series of selected patients available for dihydroergotamine, sodium valproate and lidocaine.¹⁷⁷ No recommendation can be made on the basis of these, but referral to a specialist service should be considered if outpatient withdrawal is not successful.

☒ Medication withdrawal should be attempted in all patients with medication overuse headache.

C Patients with medication overuse headache caused by simple analgesics or triptans should be advised to abruptly withdraw the overused medication. In the majority of patients this can be as an outpatient with structured advice.

D Patients with medication overuse headache caused by opioids and opioid-containing analgesics should be considered for gradual withdrawal of the overused medications.

A well conducted RCT in patients admitted to hospital for abrupt medication withdrawal, showed that there was no difference in the frequency or severity of withdrawal headache in patients given prednisolone (60 mg), followed by a six day taper compared with placebo. Symptomatic medication use, to alleviate withdrawal symptoms, was the same in both groups (no analgesics were allowed).¹⁸⁹ It has been argued that this dose of prednisolone was not sufficient.¹⁹⁰ A smaller RCT showed that a larger dose of prednisolone (100 mg for five days) significantly reduced withdrawal headache compared with placebo. There was also a trend to less use of symptomatic medication, but this was not significant.¹⁹⁰ A quasi-randomised cohort study in patients abruptly withdrawing symptomatic medication as outpatients, showed that patients given prednisolone or naratriptan had fewer withdrawal symptoms, used fewer symptomatic medications and used symptomatic medications for a shorter time than patients given structured advice alone.¹⁸² No significant difference was found between prednisolone and naratriptan.

Three small RCTs (two well conducted) have shown that topiramate is useful in medication overuse headache.^{118,191,192} Topiramate reduced the mean number of monthly migraine days by 3.5 ± 7.1 despite ongoing medication overuse.¹⁹¹ A similar response to topiramate was seen in a second study in which patients were instructed to significantly restrict medication use during the study period. Those treated with topiramate showed a significantly lower 28 day headache frequency when compared to placebo (8.1 vs 20.6, $p < 0.0007$).¹⁹²

1+
1-

Topiramate is not licensed in the UK for use in medication overuse headache.

Amitriptyline and sodium valproate reduce headache during abrupt withdrawal in patients with medication overuse headache, in small randomised controlled and uncontrolled trials.^{118,184,193} Naproxen has been shown to ameliorate withdrawal symptoms in ergotamine-induced headache.¹⁸⁴

1-
2-
3

A prospective cohort study in patients who had no response to various prophylactic treatments when overusing symptomatic medications found that the efficacy of prophylactic treatment returned after successful medication withdrawal.¹⁸⁵

3

D If frequent headache persists after symptomatic medications have been withdrawn, prophylactic agents may be effective and should be considered.

C In patients with medication overuse headache, topiramate may be considered in order to reduce the total number of headache days.

10 Pregnancy, contraception, menstruation and the menopause

10.1 PREGNANCY

Where possible, the use of medication in pregnancy should be avoided, particularly in the first trimester. Paracetamol, however, has been used routinely during all stages of pregnancy for relief of headache and overall there seems to be no clear evidence of harmful effects on the fetus.¹⁹⁴⁻¹⁹⁷ If drug treatment is considered essential then paracetamol, at the recommended therapeutic doses, is the analgesic of choice for the short term relief of mild to moderate pain during pregnancy.^{195,197} As with any medication used during pregnancy, paracetamol should be taken at the lowest effective dose for the shortest time necessary.

4

If short term analgesia with an NSAID is required in the first or second trimester, ibuprofen or aspirin can be used.¹⁹⁵ Aspirin is contraindicated during the third trimester of pregnancy.⁹⁰ Whilst limited, the available evidence does not indicate that exposure to ibuprofen before 20 weeks of pregnancy is associated with an increased risk of birth defects or spontaneous abortions. Long term exposure or exposure to high doses in late pregnancy is associated with an increased risk of fetal complications.¹⁹⁵

4

Three systematic reviews found no robust evidence of an increased risk of fetal abnormalities in babies born to mothers who took sumatriptan during pregnancy.¹⁹⁸⁻²⁰⁰ There is a non-significant trend to an increased risk of pre-term births (before 37 weeks) and miscarriages following the use of sumatriptan during pregnancy.^{198,199} There is insufficient evidence to advocate the use of triptans during pregnancy.

2+
2-

Some anti-emetics can be used with caution in pregnancy. There is no evidence for teratogenicity for buclizine and cyclizine.⁹⁰ Prochlorperazine is safe in the first two trimesters.⁹⁰

4

☒ Paracetamol 1,000 mg is the treatment of choice in pregnancy for all patients with migraine and tension-type headache when the pain is sufficient to require analgesia.

☒ If paracetamol provides insufficient analgesia aspirin 300 mg or ibuprofen 400 mg can be used in the first and second trimester of pregnancy.

10.2 ORAL CONTRACEPTION

Migraine and the use of the combined oral contraceptive pill (COCP) are both independent risk factors for stroke. It is important to discuss stroke risk with women with migraine who require oral contraception.

The risk of stroke in women aged 25 to 44 is very low. The annual incidence of all types of cerebral infarction has been estimated as four per 100,000 in women aged 25-34 and 11 per 100,000 in women aged 35-44.²⁰¹ The annual incidence of ischaemic stroke in women aged 25-44 has been estimated as 4.4 per 100,000.²⁰²

4
2++

A WHO collaborative showed that for women with migraine the overall odds ratio for all stroke was 1.78 (95% CI 1.14 to 2.77), 3.54 (95% CI 1.30 to 9.61) for ischaemic stroke and 1.10 (95% CI 0.63 to 1.94) for haemorrhagic stroke. The odds ratio for stroke in women with migraine with aura was 3.81 (95% CI 1.26 to 11.5) and for migraine without aura 2.97 (95% CI 0.66 to 13.5).²⁰³ Evidence from other meta-analyses and systematic reviews also suggests a significant increased risk of ischaemic stroke among women with migraine, with a relative risk of between 1.85 (95% CI 1.44 to 2.36) to 2.16 (95% CI 1.89-2.48).^{204,205}

2++

The increased risk of ischaemic stroke with a COCP is related to dose. Studies show an odds ratio varying between 2.08 (95% CI 1.55-2.80) to 2.74 (95% CI 2.24-3.35).²⁰⁶ | 2++

Women with migraine with aura using a COCP have a relative risk of 8.72 (95% CI 5.05 -15.05) for developing stroke.²⁰⁴ | 2++

B Women with migraine with aura should not use a combined oral contraceptive pill.

The WHO advises that women over the age of 35 suffering from migraine without aura also have an increased risk of ischaemic stroke if they take COCP.^{206,207} | 4

D Patients with migraine without aura who are over the age of 35 should not use a combined oral contraceptive pill.

No evidence was identified on the safety or the efficacy of reducing the frequency and severity of menstrual migraine in patients using progesterone or long-acting implantable contraceptives.

10.3 MENSTRUATION

More than 50% of women with migraine report an increased frequency and severity of migraine attacks around the time of menstruation. Evidence suggests that this is related to the withdrawal of oestrogen in the late luteal phase of the menstrual cycle.²⁰⁸⁻²¹³ Standard acute migraine drugs work for the majority of women. Fewer than 10% of women report migraine "exclusively" with menstruation and at no other time of the month. | 2+
1+
2-

10.3.1 SIMPLE ANALGESICS

A meta-analysis of three RCTs looking at the use of a fixed formulation of aspirin, paracetamol and caffeine in the acute treatment of patients with menstrual migraine attacks showed that the treatment relieved 61% of headaches at two hours, compared with 29% of patients given placebo ($p=0.05$).²¹⁴ | 1++

A single RCT showed that mefenamic acid gave 79% of patients effective relief at two hours, compared to 16% with placebo ($p<0.03$).²¹⁵ | 1++

A Patients with acute menstrual migraine can be treated with mefenamic acid or a combination of aspirin, paracetamol and caffeine.

10.3.2 TRIPTANS

Zolmitriptan, sumatriptan, naratriptan and rizatriptan have been shown to be effective in relieving symptoms in patients with acute attacks of menstrual migraine.²¹⁶⁻²¹⁹ | 1++
2-

A Sumatriptan, zolmitriptan, naratriptan and rizatriptan are recommended for the acute treatment of patients with menstrual migraine.

10.3.3 PROPHYLAXIS FOR MENSTRUAL MIGRAINE

Specific menstrual migraine prophylaxis should only be considered in women with regular and predictable menstrual cycles.

Hormone manipulation

A systematic review of four small case studies, three for the prevention of menstrually related migraine and one for the prevention of pure menstrual migraine, concluded that perimenstrual supplementation with oestradiol can reduce the risk of menstrual migraine (RR 0.78, 95% CI 0.62 to 0.99) but can cause a rebound increase in migraine after the treatment phase.^{211,220} The risk of rebound headache was 68% for oestradiol 1.5 mg gel and five per cent for oestradiol 1.5 mg patches. Due to significant clinical heterogeneity, meta-analyses of these trials was not possible. The studies alone are too small to make a recommendation on using oestradiol for the prevention of menstrual migraine. | 4

There is insufficient evidence to make any recommendations on the use of phyto-oestrogens.

Triptans

Frovatriptan 2.5 mg per day or naratriptan 1 mg twice per day significantly reduces the risk of menstrual migraine if taken for two days before the onset of menses and then for a further four days, or five days respectively.^{221,222} 1++

Two studies of naratriptan showed that the number of days with menstrually associated migraine in women given treatment versus placebo were five days versus 6.5 days ($p=0.005$) and 5.3 days versus six days ($p=0.018$). Eleven per cent of patients experienced no migraine versus three per cent on placebo ($p<0.05$). In both studies patients experienced rebound headache after stopping the naratriptan.²⁷⁵ 1++

A Frovatriptan 2.5 mg/day or naratriptan 1 mg twice daily taken two days before day one of the menstrual cycle then for a further four or five days respectively is recommended for the prophylaxis of menstrual migraine.

NSAIDs

No evidence was identified on the possible prophylactic effect of NSAIDs for treating patients with menstrual migraine, although this is a widely used strategy. There is limited evidence that mefenamic acid and naproxen can be effective for headache associated with dysmenorrhoea.²¹³

10.4 MENOPAUSE

The perimenopause is the time of peak prevalence of migraine without aura in women.^{211, 223-226} This is thought to be due to oestrogen fluctuations associated with disrupted menstrual cycles. Migraine declines after spontaneous menopause in women who are vulnerable to hormone change such as those with premenstrual syndrome.^{226,227} Women who had a surgical menopause had a higher prevalence of migraine.²²⁶

The perimenopause often results in climacteric symptoms (eg vasomotor symptoms such as night sweats, hot flushes, and insomnia, as well as memory loss/forgetfulness and mood swings) that might get better with hormone replacement therapy (HRT).²²³

HRT has been shown to increase the risk of stroke in all women. The women's health initiative RCT showed a hazard ratio of 1.41 for HRT and stroke (95% CI 1.07-1.85).²²⁸ 2++

No studies have assessed the relationship between migraine, HRT and stroke. An editorial review concluded that there is no compelling evidence that HRT increases or decreases the risk of ischaemic stroke in women with migraine.²²⁹ Migraine is not a risk factor for stroke in women older than 45 and is not a contraindication for HRT.²³⁰⁻²³² 4
2-
4

HRT can make migraine worse. Current users of HRT had an odds ratio for migraine without aura of 1.42 (95% CI 1.41-1.76).^{225, 233} One small study has shown that the transdermal route for oestrogen administration is less likely than the oral route to make migraine worse.²³³ This is supported by expert opinion.²³² 3
2-
4

D HRT can be prescribed to menopausal and perimenopausal women with migraine.

D If a patient taking HRT experiences worsening migraine, HRT should be considered as a possible cause.

☒ If the patient is using oral HRT and experiences worsening migraine, transdermal HRT should be considered.

11 Lifestyle factors

The studies reviewed for this section involve combinations of interventions, making assessment of their individual contribution to headaches difficult.

11.1 DIET

Although many patients report that various foods trigger their migraine, an editorial review found no good quality published evidence to support this.²³⁴ No evidence was identified to support the prophylactic effect of general avoidance of cheese or chocolate, or for any other dietary manipulation in patients with migraine.^{11,235,236} | 1-43

Dietary supplementation with omega-3 fatty acids does not reduce the incidence of migraine.²³⁷ | 1+

Expert opinion suggests that omission or altered timing of meals may be associated with migraine in some patients, eg missing breakfast may trigger a late morning attack, and so patients should be encouraged to eat regularly.¹¹ | 4

☒ Patients with migraine should be encouraged not to miss meals.

11.2 TRIGGER AVOIDANCE

Limited and low quality evidence was identified in relation to possible trigger factors for headache.

A survey of patients with headache suggested that a reduction in caffeine intake and addressing sleep problems may reduce disability associated with headache.²³⁸ | 3

No good quality evidence was identified on whether mobile phone signals relate to headache symptoms.

11.3 EXERCISE

The evidence on exercise was mainly limited to exercise included in combined therapies programmes.

For patients with cervicogenic headache, low load cervical exercise and manipulation were effective in reducing frequency and intensity of headache, but there was no additional statistically significant benefit when therapies were combined.²³⁹ This effect may relate to patients' belief in the therapy or therapist.²⁴⁰ | 1+

For patients with migraine, multidisciplinary intervention including group supervised exercise therapy sessions (along with stress management and relaxation therapy lectures, dietary advice and massage therapy) provided improvements in frequency, intensity and duration of headache and quality of life.²⁴¹ | 1+

11.4 SLEEP

No good quality evidence was found relating to sleep and headache. There may be an association between obstructive sleep apnoea and chronic headache, although studies did not include headache as a primary symptom.^{242,243} Changes in sleep pattern, eg sleeping longer at weekends or sleep disturbance due to stress, may be associated with migraine, although there may be confounding factors related to the altered sleep.^{11,235,236} | 2-4

11.5 STRESS MANAGEMENT

In a prospective analysis of the factors related to headache in migraineurs, tension and stress were associated with increased risk of migraine, whereas holidays, relaxation after stress and after divorce decreased the hazard.²³⁶ 3

Multidisciplinary intervention, including stress management was effective in patients with migraine.²⁴¹ Results from a survey of patients with migraine suggest that reduction in stress can relieve headache symptoms.²⁴⁴ 1+
3

B Stress management should be considered as part of a combined therapies programme to help patients reduce the frequency and severity of migraine headaches.

For patients with chronic TTH, stress management was more effective when combined with antidepressant medication, although stress management alone was still more effective than placebo. This study had a high drop-out rate.²⁴⁵ 1-

12 Psychological therapies

Various methodological problems have been encountered with the research identified in this area. These include:^{246,247}

- difficulties in blinding trials in this area of research
- lack of standardisation and description of patient groups, interventions and their delivery and outcome measures
- use of inappropriate self selected patient groups
- ethical issues around pharmacological versus psychological interventions.

For patients with migraine, a single RCT suggests multidisciplinary intervention, including exercise, stress management, relaxation, diet and massage are effective in reducing pain frequency duration and intensity and improving quality of life, but it is unclear which specific intervention has the greatest benefit.²⁴¹ Stress management is discussed in section 11.5.

1+

No good quality contemporary evidence was identified for cognitive behavioural therapy or any specific relaxation therapy or biofeedback technique. The US Headache Consortium guidelines for migraine headache included evidence from 1966-1996 and recommended that relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback and cognitive behavioural therapy may be considered as treatment options for prevention of migraine.²⁴⁸

4

No good quality evidence was identified for hypnotherapy.

13 Physical therapies

It is not possible to conduct blinded trials of physical therapies. Studies are subject to attention and placebo effects which may introduce bias. A number of studies examine the effects of combinations of treatments making the effectiveness of the individual therapies difficult to ascertain. The role of exercise is discussed in section 11.3.

13.1 MANUAL THERAPY

Manual therapy covers a number of interventions including spinal manipulation therapy (SMT) and spinal mobilisation.

Cervicogenic headache

In a Cochrane systematic review five studies of spinal manipulation therapy for cervicogenic headache were described. SMT was compared with placebo, mobilisation, NSAIDs, exercise and massage plus placebo laser.²⁴⁹ Although the studies were too dissimilar for results to be pooled, there was moderate evidence that SMT is superior to no treatment in reducing headache pain and frequency one week and 12 months following six weeks of treatment and superior to placebo SMT for pain, disability and number of headache sites three weeks after treatment. A comparison with massage plus placebo laser found SMT produced a significantly greater decrease in pain intensity (effect size 0.6; 95% CI 0.1-1.1).

1++

B Spinal manipulation therapy should be considered in patients with cervicogenic headache.

Migraine

A Cochrane systematic review identified three studies of effectiveness of spinal manipulation in migraine compared with amitriptyline, spinal mobilisation and placebo electrotherapy.²⁴⁹ The studies were too dissimilar for results to be pooled and the evidence of effectiveness is too limited to lead to recommendation.

1++

Tension-type headache

Two studies of SMT in patients with chronic tension-type headache were included in a Cochrane systematic review.²⁴⁹ In one study SMT was inferior to amitriptyline for effect on pain intensity during six weeks of treatment, although this was reversed at four weeks post-treatment. The second study examined the immediate effects of a single treatment and found more pain reduction in the SMT group than in a no-treatment control group.

1++

A systematic review of a range of manual therapies for pain reduction in tension-type headache found no rigorous positive effect of manual therapies.²⁵⁰

1+

A small single blind RCT (n=26) found that three osteopathic treatments, one each week for three weeks, plus relaxation exercises, increased the number of headache free days per week in patients with TTH compared with relaxation exercises alone (0.21 days to 1.79 days, p=0.016).²⁵¹

1+

An RCT in a mixed group of patients with episodic and chronic TTH compared a craniocervical training programme combined with physiotherapy with physiotherapy alone. There was a positive and clinically relevant effect on headache frequency at six months following a six week programme. 85% of patients in the treatment group (n=39) experienced a reduction of ≥50% in their headache frequency at six months compared to 35% in the control group.²⁵²

1+

13.2 MASSAGE

For patients with episodic TTH the benefit of massage as part of soft tissue manipulation is inconclusive.²⁵⁰ | 1⁺⁺

As part of a multidisciplinary intervention for patients with migraine massage appears effective with statistically significant reductions in frequency, intensity and duration of pain, and improved quality of life compared to controls which is maintained three months post-intervention.²⁴¹ The separate effect of massage is not clear. | 1⁺

There is insufficient evidence to make a recommendation on the use of massage in the treatment of patients with headache.

13.3 TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

A Cochrane review identified two trials where transcutaneous electrical nerve stimulation (TENS) was used as part of a combined physical therapies intervention.²⁴⁹ In a single RCT in patients with transformed migraine (MOH), TENS resulted in a statistically significant reduction in number of headache days per month, 21 days at baseline versus 11 days one month after TENS, ($p < 0.05$) but this benefit was not evident at four months.²⁵³ | 1⁺⁺
1⁺

There is insufficient evidence to make a recommendation on the use of TENS in the treatment of patients with headache.

13.4 ACUPUNCTURE

Interpretation of the evidence base for acupuncture is complicated by the lack of standardisation of interventions, the choice of control and comparison groups and the range of outcome measures employed. In addition to difficulties in blinding and concealment, trials very often have high drop-out rates ($> 10\%$). A review examining the methodology of 13 studies noted that the majority of studies of acupuncture in patients with migraine are of poor quality, with conflicting results.²⁵⁴ | 1⁺

A Cochrane systematic review of 26 studies found that the majority of trials had methodological and/or reporting shortcomings and suggested there was no conclusive evidence for the use of acupuncture in patients with migraine or TTH, although trends were towards benefit.²⁵⁵ | 1⁺⁺

In a large ($n = 401$), well conducted RCT in patients with chronic headache disorder, predominantly migraine, headache scores at 12 months were significantly reduced in patients having acupuncture compared to usual care.²⁵⁶ | 1⁺

A number of RCTs in patients with a range of chronic headache types found that sham acupuncture (eg needling superficially at points distant from the segments of true treatment points) was as effective as real acupuncture. This may be mediated through generation of non-specific physiological effects.²⁵⁷⁻²⁶⁰ | 1⁺
1⁻

B

Acupuncture should be considered for preventive management in patients with migraine.

13.5 ORAL REHABILITATION

No good quality evidence was found to determine whether the use of acrylic splints is effective for patients with migraine.

Temporomandibular disorders (TMD) include symptoms such as joint clicking, facial pain and limitation of mandibular movement. Headache is included as one of the diagnostic criteria for TMD (but is not diagnostic alone). There is inconsistency in criteria between studies and headache type may not be defined.^{261,262} A Cochrane review found no evidence from RCTs that occlusal adjustment treats or prevents headache in patients with temporomandibular disorders.²⁶²

1++

One study showed that occlusal splint therapy may be effective for headache as part of TMD but there are concerns about cases of aspiration of small splints and changes in tooth positions.²⁶³

1+

B

Occlusal adjustment is not recommended for treatment of patients with headache associated with temporomandibular disorders.

14 Complementary therapies

14.1 HOMEOPATHY

A systematic review of four randomised placebo-controlled double blind trials concluded that homeopathy is not effective in the prophylaxis of migraine beyond a placebo effect.²⁶⁴

1⁺

14.2 REFLEXOLOGY

No evidence was identified for the effectiveness of reflexology in reducing the frequency and severity of headaches.

14.3 MINERALS, VITAMINS AND HERBS

A Cochrane review concluded that there is insufficient evidence that feverfew is efficacious beyond placebo for preventing migraine. In four trials of acceptable size two showed that the frequency of migraine reduced with feverfew while two trials did not.²⁶⁵ A CO₂ extract of feverfew was shown to reduce the migraine frequency by 1.9 attacks per month as compared to 1.3 attacks in the placebo group ($p=0.0456$).²⁶⁶

1⁺⁺
1⁻

A Feverfew is not recommended for preventive treatment of patients with migraine.

Petasites hybridus root (butterbur) in a dose of 75 mg per day has been shown to reduce migraine attack frequency by 48% over four months as compared to a 28% reduction with placebo ($p=0.0012$).²⁶⁷

1⁻

In a small study coenzyme Q10 was shown to be superior to placebo for attack frequency, headache days, and days with nausea. The responder rate for attack frequency was 14.4% for placebo and 47.6% for CoQ10 (NNT = 3).²⁶⁸

1⁻

Niacin (oral or intravenous) may have beneficial effects for patients with migraine and tension-type headaches.²⁶⁹

4

Intravenous magnesium has an analgesic effect similar to IV metoclopramide and to placebo when administered for the treatment of patients with an acute migraine attack.²⁷⁰ A double blind RCT found no significant difference between the group receiving placebo or magnesium. The patients receiving magnesium had significantly more ($p=0.03$) side effects as compared to placebo.²⁷¹

1⁺

B Intravenous magnesium is not recommended as treatment in patients with acute migraine attack.

Riboflavin in a dose of 200 mg per day has been compared to placebo and found to have a responder rate of 56% versus 9% for attack frequency and 59% versus 15% for the number of migraine days.²⁷²

1⁻

A combination of riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg was not found to be more effective than placebo containing riboflavin 25 mg.²⁷³

1⁻

15 Information provision

15.1 FREQUENTLY ASKED QUESTIONS

These frequently asked questions and suggested answers are intended as a prompt for discussion between healthcare professionals and patients with headache concerns. They are not designed for direct distribution to patients, but might be incorporated into locally developed patient information materials. General patient information leaflets and further patient information is available from the organisations listed in section 15.2.

What is the difference between headache and migraine?

There are many different types of headache. The most common is tension-type headache which causes mild to moderate pain on both sides of the head.

Migraine usually causes moderate to severe pain on one side of the head and many people also feel or are sick. They may feel uncomfortable with bright light or noise. Sometimes people with migraine experience 'aura' which can cause changes to their sight, such as flashing lights or spots, and numbness or 'pins and needles' in their hands and face.

Is a brain tumour causing my headache?

Most common headaches are not caused by tumours. It is very unusual for headache to be the sole symptom of a brain tumour.

Is it going to go away?

People have different experiences of how often headaches and migraines occur, and how long they last. There are treatments which can help to prevent headaches occurring as frequently and which can help reduce the severity of the pain. Keeping a headache diary may help as it can show whether there are any patterns in your headaches.

Why me?

A tendency to troublesome headaches often runs in families. Many headache disorders are genetically linked. Headaches affect over 90% of the population in the UK at some time in their life, although some people experience much worse or more frequent headaches than others.

When should I consult my GP?

If you experience new severe headache, sudden headache, prolonged headache or a change in your usual headache pattern you should see your doctor.

If you have been prescribed medication and your headaches continue you should go back to your GP to discuss trying different treatment, and to make sure that the medicine itself is not causing more headaches (known as medication overuse headache).

What treatments are available?

There are many medicines available without prescription which can relieve headache and migraine, such as aspirin, paracetamol and ibuprofen.

If your headaches are more severe or occur frequently your GP can prescribe drugs to reduce the pain or prevent headaches occurring so often. If your treatment is not helping, go back to your GP as there may be another treatment which will work better for you.

Other therapies, such as acupuncture, or a combined programme of relaxation and exercise, may also help to reduce the frequency of your headaches.

Are there any problems with taking medicines for headache?

Taking medication too frequently can cause headaches known as medication overuse headache. Medicines for immediate pain relief should not generally be taken on more than 10 days per month. You should consult your GP if you are worried that your medication is causing more headaches or any side effects.

Women who are pregnant are advised to discuss headache medication with their pharmacist or GP.

15.2 SOURCES OF FURTHER INFORMATION

The British Association for the Study of Headache

www.bash.org.uk/

BASH is the United Kingdom national society member of the International Headache Society and the European Headache Federation. It is open to all healthcare professionals with an interest in headache.

The British Pain Society

Third Floor, Churchill House

35 Red Lion Square

London, WC1R 4SG

Tel: 020 7269 7840 • Fax: 020 7831 0859

Email: info@britishpainsociety.org

The British Pain Society has published a number of booklets aimed specifically for patients. Each publication is available to download free of charge, in PDF format.

The Migraine Action Association

27 East Street

Leicester, LE1 6NB

Tel: 0116 275 8317 • Fax: 0116 254 2023

Email: info@migraine.org.uk • Website: www.migraine.org.uk/

The Migraine Action Association provides information for healthcare professionals and patients on the causes, diagnosis and treatment of migraine.

Migraine in Primary Care Advisers

www.mipca.org.uk/

MIPCA is a UK society dedicated to the management of headache in primary care, and has strong links with the Migraine Action Association (the UK patient support group), academic societies and governmental groups. It runs three special interest groups, on research, education and how to set up a headache clinic.

The Migraine Trust

55-56 Russell Square

London, WC1B 4HP

Tel: 020 7436 1336 • Helpline: 020 7462 6601, Monday to Friday 10am - 5pm

Fax: 020 7436 2880

Email: info@migrainetrust.org • www.migrainetrust.org/

The Migraine Trust is a medical research and patient support charity for the condition. It supports sufferers and their families by funding and promoting research, providing information and raising awareness of migraine as a significant public health problem.

Organisation for the Understanding of Cluster Headache

OUCH (UK), Pyramid House

956 High Road

London, N12 9RX

Helpline: 01646 651 979

www.ouchuk.org

Provides support, information and advice on coping with cluster headaches. Can assist with supply of and contacts for appropriate equipment for oxygen treatment.

Pain Association Scotland

Cramond House

Cramond Glebe Road

Edinburgh, EH4 6NS

Tel (Enquiries only): 0800 783 6059 • Tel (Office): 0131 312 7955 • Fax: 0131 312 6007

www.chronicpaininfo.org

Runs local support groups for people with chronic pain.

Pain Concern

PO Box 13256

Haddington, EH41 4YD

Tel: 01620 822572 • Fax: 01620 829138

Email: info@painconcern.org.uk • www.painconcern.org.uk

Provides information and support for pain sufferers and their carers, factsheets and leaflets to help manage pain and a helpline.

16 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

16.1 RESOURCE IMPLICATIONS

The guideline development group did not identify any significant resource implications associated with implementing the recommendations.

16.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

16.2.1 PRIMARY CARE

GPs should review all patients who are prescribed 12 or more triptans a month to consider the diagnosis of medication overuse headache. Reducing triptan use may help to reduce headache frequency.

Audit how often patient information leaflets are given to patients. Patient understanding of headache improves management of the headache.

16.2.2 SECONDARY CARE

Review all patients with admission for thunderclap headache and audit how many have had an LP if the CT scan is negative.

The number of patients in the health board area with cluster headache that are known to the specialist headache services.

16.3 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

The SMC has approved certain formulations of sumatriptan.

Frovatriptan has been accepted for the treatment of patients during the headache phase of migraine attacks with or without aura.

Topiramate is accepted for restricted use within NHSScotland for the prophylaxis of migraine headache in adults.

Further information is available from the SMC website, www.scottishmedicines.org.uk/

There are no MTAs relevant to this guideline.

17 The evidence base

17.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using search strategies devised by a SIGN information specialist. Databases searched include Medline, Embase, CINAHL, PsycINFO, and the Cochrane Library. For most searches, the year range covered was 2001-2007. Internet searches were carried out on various websites including the US National Guideline Clearinghouse, NLH Guidelines Finder, and Guidelines International Network (G-I-N). The Medline version of the database search strategies for each key question can be found on the SIGN website in the section covering supplementary guideline material (www.sign.ac.uk/guidelines/published/support/). The main searches were supplemented by material identified by individual members of the guideline development group.

17.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- Comparison of acute versus gradual withdrawal of overused medications in medication overuse headache. Which is the best strategy for use in primary care?
- Does education on headache diagnosis and management change GPs' pattern of referral to secondary care neurological and headache services? What is appropriate headache education?
- Does open access to CT brain scanning change GPs' pattern of referral to secondary care neurological and headache services?
- Does the use of headache diaries by GPs in routine clinical practice improve diagnostic accuracy of headache type?

17.3 REVIEW AND UPDATING

This guideline was issued in 2008 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

18 Development of the guideline

18.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. The views and interests of NHS Quality Improvement Scotland as the funding body have not influenced any aspect of guideline development, including the final recommendations. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

18.2 THE GUIDELINE DEVELOPMENT GROUP

Dr David P B Watson (Chair)	General Practitioner, Hamilton Medical Group, Aberdeen
Dr Callum Duncan (Secretary)	Consultant Neurologist, Aberdeen Royal Infirmary
Dr Anne Coker	General Practitioner, Dundee
Ms Arlene Coulson	Principal Clinical Pharmacist, Ninewells Hospital, Dundee
Dr Roger Cull	Honorary Consultant Neurologist, Western General Hospital, Edinburgh
Ms Helen Duncan	Lay representative, Haddington
Dr Murray Fleming	General Practitioner, Clydebank Health Centre
Ms Penelope Fraser	Lead Clinician/Consultant Clinical Psychologist, Ninewells Hospital, Dundee
Mrs Suzie Harrold	Senior Physiotherapist, Glasgow Royal Infirmary
Ms Michele Hilton Boon	Information Officer, SIGN
Dr Gillian Smith	Oral Medicine Consultant, Glasgow Dental Hospital
Ms Ailsa Stein	Programme Manager, SIGN
Dr Lorna Thompson	Programme Manager, SIGN
Dr Alok Tyagi	Consultant Neurologist, Southern General Hospital, Glasgow
Ms Heather Wallace	Chairman, Pain Concern, Haddington

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

18.3 CONSULTATION AND PEER REVIEW

18.3.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 5 September 2007 and was attended by 123 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

18.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

Dr Anish Bahra	<i>Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London</i>
Mr Richard Bowen	<i>Patient representative, Lanarkshire</i>
Dr Rodney Burnham	<i>Registrar, Royal College of Physicians, London</i>
Dr Richard Coleman	<i>Consultant Neurologist, Aberdeen Royal Infirmary</i>
Dr Richard J Davenport	<i>Consultant Neurologist, Western General Hospital, Edinburgh</i>
Dr Paul Davies	<i>Consultant Neurologist, Northampton General Hospital</i>
Mrs Ruth M Edwards	<i>Lecturer in Pharmacy Practice, The Robert Gordon University, Aberdeen</i>
Dr John Gibson	<i>Consultant in Oral Medicine, Dundee Dental Hospital and School</i>
Mr David Gill	<i>Head of Pharmacy, Angus Community Health Partnership</i>
Professor Donald M Hadley	<i>Consultant Neuroradiologist and Professor in Radiology, Southern General Hospital, Glasgow</i>
Dr Chris Isles	<i>Consultant Physician, Dumfries and Galloway Royal Infirmary</i>
Dr Avinash Kanodia	<i>Consultant Radiologist, Perth Royal Infirmary</i>
Dr E Anne MacGregor	<i>Honorary Research Director, The City of London Migraine Clinic</i>
Dr Alan Merry	<i>General Practitioner, Ardrossan</i>
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18.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

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Abbreviations

CAT	Computerised adaptive testing
CH	Cluster headache
CI	Confidence interval
CNS	Central nervous system
COCAP	Combined oral contraceptive pill
CPH	Chronic paroxysmal hemicrania
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerised tomography
CTTH	Chronic tension-type headache
DSM-IV	Diagnostic and Statistical Manual, 4 th edition
ESR	Erythrocyte sedimentation rate
ETTH	Episodic tension-type headache
GCA	Giant cell arteritis
GP	General practitioner
HIT	Headache impact test
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
LP	Lumbar puncture
MIDAS	Migraine Disability Assessment Questionnaire
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
MTA	Multiple technology appraisal
NDPH	New daily-persistent headache
NHS QIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NSAIDS	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PH	Paroxysmal hemicrania
PPV	Positive predictive value
RCT	Randomised controlled trial
RR	Relative risk
SAH	Subarachnoid haemorrhage

SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMT	Spinal manipulation therapy
SSRI	Selective serotonin reuptake inhibitor
SUNA	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TA	Temporal arteritis
TAC	Trigeminal autonomic cephalalgia
TENS	Transcutaneous electrical nerve stimulation
TMD	Temporomandibular disorder
TTH	Tension-type headache
UK	United Kingdom
WHO	World Health Organisation

Annex 1

Key questions used to develop the guideline

DIAGNOSIS AND INVESTIGATION	
Key question	See guideline section
1. In patients > 18 yrs presenting with primary or secondary headache what are the critical signs and symptoms that help determine headache diagnosis and which patients should be referred?	3, 9.1
2. In patients with migraine or chronic headache, what tools are most effective in assessing headache severity, frequency and social and economic impact? Include: MIDAS (migraine disability and assessment score) HIT (headache impact test) SF36	4
3. In patients presenting with headache what is the evidence that the following investigations are effective in confirming diagnosis? a) CT scan b) MRI c) X-ray of the cervical spine d) full blood count e) ESR/CRP/plasma viscosity f) lumbar puncture	5
MANAGEMENT	
4. In patients with the following types of headache: Migraine with or without aura Tension headache Cluster headache and its variants (trigeminal autonomic cephalalgia, paroxysmal hemicrania, hemicrania continua) Jolts and jabs (primary stabbing headache) Medication overuse Cervicogenic – secondary headache Low pressure headache Oromandibular Benign intracranial hypertension / idiopathic intracranial hypertension what lifestyle factors have been shown to be effective in reducing frequency and severity of acute and chronic headache? a) diet b) exercise c) sleep d) stress management e) trigger avoidance	11

5. In patients with the following types of headache: Migraine with or without aura Tension headache Cluster headache and its variants (trigeminal autonomic cephalalgia, paroxysmal hemicrania, hemicrania continua) Jolts and jabs (primary stabbing headache) Medication overuse Cervicogenic – secondary headache Low pressure headache Oromandibular Benign intracranial hypertension/idiopathic intracranial hypertension which pharmacological therapies for acute attack are the most effective for immediate pain freedom or pain freedom at 24 hours? a) aspirin b) paracetamol c) NSAIDs d) COX-2 inhibitors e) anti-emetics f) corticosteroids g) triptans h) oxygen i) intranasal lidocaine j) indomethacin k) ergotamine l) opiates m) caffeine Outcomes: Scale used is 0 1 2 3 where 0 = no headache 1 = mild headache 2 = moderate headache 3 = severe headache pain free is score down to 0 pain relief is 2 or 3 headache to 1 [consider comorbidities]	6.1, 7.1, 8.1, 8.3, 9.2

6. In patients with the following types of headache: - Migraine with or without aura - Tension headache - Cluster headache and its variants (trigeminal autonomic cephalalgia, paroxysmal hemicrania, hemicrania continua - Jolts and jabs (primary stabbing headache) - Medication overuse - Cervicogenic – secondary headache - Low pressure headache - Oromandibular - Benign intracranial hypertension/idiopathic intracranial hypertension which prophylactic pharmacological therapies are most effective in reducing frequency and severity of headaches? a) beta blockers b) antiepileptics c) serotonin antagonists (pizotifen, methysergide, cyproheptadine) d) antidepressants e) ACE inhibitors f) angiotensin-II receptor antagonists g) low-dose aspirin h) lithium i) verapamil and other calcium channel blockers j) indomethacin and other NSAIDs k) corticosteroids l) ergotamine Outcomes: Scale used is 0 1 2 3 where 0 = no headache 1 = mild headache 2 = moderate headache 3 = severe headache pain free is score down to 0 pain relief is 2 or 3 headache to 1 [consider comorbidities]	6.2, 7.2, 8.2, 9.2
7. In patients with chronic headache are psychological therapies effective in reducing frequency and severity of headaches? Consider: a) cognitive behavioural therapy (CBT) b) biofeedback and relaxation c) stress management d) hypnotherapy	12

8. In patients with chronic headache are physical therapies effective in reducing frequency and severity of headaches? Consider: a) cervical manual therapy (manipulation or mobilisation) b) osteopathy c) chiropracty d) physiotherapy e) massage f) transcutaneous electrical nerve stimulation (TENS) g) postural or exercise advice h) acupuncture i) occlusal splint therapy/oral rehabilitation	13
9. In patients with chronic headache are complementary therapies effective in reducing frequency and severity of headaches? Consider: a) homeopathy b) reflexology c) minerals, vitamins and herbs d) magnesium e) riboflavin f) butterbur g) feverfew h) coenzyme Q	14
10. In patients with medication overuse headache what management strategies are effective?	9
HORMONAL HEADACHE AND HEADACHE IN PREGNANCY	
11. In women experiencing predominantly menstrual migraine what drugs are safe and effective in reducing the frequency and severity of headaches? a) combined oral contraceptives b) progesterone c) oestrogen supplementation d) long-acting implantable contraceptives e) triptans f) mefenamic acid and other NSAIDs	10.3
12. In women who are menopausal and experiencing migraine is hormone replacement therapy (HRT) safe and effective in reducing the frequency and severity of headaches?	10.4

13. In pregnant women with headache what is the safety of the following treatments: a) aspirin b) paracetamol c) NSAIDs d) COX-2 inhibitors e) anti-emetics f) corticosteroids g) triptans h) oxygen i) intranasal lidocaine j) indomethacin k) ergotamine l) opiates m) caffeine n) beta blockers o) antiepileptics p) serotonin antagonists (pizotifen, methysergide, cyproheptadine) q) tricyclic antidepressants r) SSRIS s) ace inhibitors t) angiotensin-II receptor antagonists u) low-dose aspirin v) lithium w) verapamil and other calcium channel blockers	10.1

Annex 2

Selected Diagnostic Criteria from International Headache Society Classification (ICHD-II)^{*16,27}

1 Migraine

1.1 Migraine without aura

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

- A. At least 5 attacks, 1 fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
 - 1. unilateral location
 - 2. pulsating quality
 - 3. moderate or severe pain intensity
 - 4. aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)
- D. During headache at least one of the following:
 - 1. nausea and/or vomiting
 - 2. photophobia and phonophobia
- E. Not attributed to another disorder

1.2 Migraine with aura

Description: Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
- C. Not attributed to another disorder

^{*}Cited from International Headache Society. The International classification of headache disorders, 2nd edition. Cephalgia 2004;24 (Supp 1): 8-160.

1.2.1 *Typical aura with migraine headache*

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
 - 1. fully reversible visual symptoms including positive features (eg flickering lights, spots or lines) and/or negative features (ie loss of vision)
 - 2. fully reversible sensory symptoms including positive features (ie pins and needles) and/or negative features (ie numbness)
 - 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
 - 1. homonymous visual symptoms¹ and/or unilateral sensory symptoms
 - 2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 - 3. each symptom lasts ≥ 5 and < 60 minutes
- D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder

1.5.1 *Chronic migraine*

- A. Headache (tension-type and/or migraine) on ≥ 15 days per month for at least 3 months*
- B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 Migraine without aura
- C. On ≥ 8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura
 - 1. Has at least two of a–d
 - (a) unilateral location
 - (b) pulsating quality
 - (c) moderate or severe pain intensity
 - (d) aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)
 - and at least one of a or b
 - (a) nausea and/or vomiting
 - (b) photophobia and phonophobia
 - 2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above
- D. No medication overuse and not attributed to another causative disorder

2 Tension-type headache

2.1 Infrequent episodic tension-type headache

Description: Infrequent episodes of headache lasting minutes to days. The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity, and it does not worsen with routine physical activity. There is no nausea but photophobia or phonophobia may be present.

Diagnostic criteria:

- A. At least 10 episodes occurring on < 1 day per month on average (< 12 days per year) and fulfilling criteria B–D
 - B. Headache lasting from 30 minutes to 7 days
 - C. Headache has at least two of the following characteristics:
 - 1. bilateral location
 - 2. pressing/tightening (non-pulsating) quality
 - 3. mild or moderate intensity
 - 4. not aggravated by routine physical activity such as walking or climbing stairs
 - D. Both of the following:
 - 1. no nausea or vomiting (anorexia may occur)
 - 2. no more than one of photophobia or phonophobia
 - E. Not attributed to another disorder
- ± Increased pericranial tenderness on manual palpation

2.2 Frequent episodic tension-type headache

Diagnostic criteria:

As for 2.1 Infrequent episodic tension-type headache except:

- A. At least 10 episodes occurring on ≥ 1 but < 15 days per month for at least 3 months (≥ 12 and < 180 days per year) and fulfilling criteria B–D (2.1)

2.3 Chronic tension-type headache

Diagnostic criteria:

As for 2.1 Infrequent episodic tension-type headache except:

- A. Headache occurring on ≥ 15 days per month on average for > 3 months (≥ 180 days per year) and fulfilling criteria B–D (2.1)

3 Cluster headache and other trigeminal autonomic cephalalgias

3.1 Cluster headache

Description: Attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15–180 minutes and occurring from once every other day to 8 times a day. The attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, eyelid oedema. Most patients are restless or agitated during an attack.

Diagnostic criteria:

- A. At least 5 attacks fulfilling criteria B–D
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes if untreated
- C. Headache is accompanied by at least one of the following:
 - 1. ipsilateral conjunctival injection and/or lacrimation
 - 2. ipsilateral nasal congestion and/or rhinorrhoea
 - 3. ipsilateral eyelid oedema
 - 4. ipsilateral forehead and facial sweating
 - 5. ipsilateral miosis and/or ptosis
 - 6. a sense of restlessness or agitation
- D. Attacks have a frequency from one every other day to 8 per day
- E. Not attributed to another disorder

3.1.1 Episodic cluster headache

At least two cluster periods lasting 7–365 days and separated by pain-free remission periods of ≥ 1 month

3.1.2 Chronic cluster headache

Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

3.2 Paroxysmal hemicrania

Description: Attacks with similar characteristics of pain and associated symptoms and signs to those of cluster headache, but they are shorter-lasting, more frequent, occur more commonly in females and respond absolutely to indometacin.

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B–D
- B. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting 2–30 minutes
- C. Headache is accompanied by at least one of the following:
 - 1. ipsilateral conjunctival injection and/or lacrimation
 - 2. ipsilateral nasal congestion and/or rhinorrhoea
 - 3. ipsilateral eyelid oedema
 - 4. ipsilateral forehead and facial sweating
 - 5. ipsilateral miosis and/or ptosis

- D. Attacks have a frequency above 5 per day for more than half of the time, although periods with lower frequency may occur
- E. Attacks are prevented completely by therapeutic doses of indometacin
- F. Not attributed to another disorder

3.2.1 Episodic paroxysmal hemicrania

At least two attack periods lasting 7–365 days and separated by pain-free remission periods of ≥ 1 month

3.2.2 *Chronic paroxysmal hemicrania (CPH)*

Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

3.3 Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)

Description: This syndrome is characterised by short-lasting attacks of unilateral pain that are much briefer than those seen in any other TAC and very often accompanied by prominent lacrimation and redness of the ipsilateral eye.

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B–D
- B. Attacks of unilateral orbital, supraorbital or temporal stabbing or pulsating pain lasting 5–240 seconds
- C. Pain is accompanied by ipsilateral conjunctival injection and lacrimation
- D. Attacks occur with a frequency from 3 to 200 per day
- E. Not attributed to another disorder

Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms (SUNA)

Description: This syndrome is characterised by short-lasting attacks of unilateral pain that are much briefer than those seen in any other TAC and very often accompanied by prominent cranial autonomic features.

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B–D
- B. Attacks of unilateral orbital, supraorbital or temporal stabbing or pulsating pain lasting from 2 seconds to 10 minutes
- C. Pain is accompanied by one of:
 1. conjunctival injection and/or lacrimation
 2. nasal congestion and/or rhinorrhoea
 3. eyelid oedema
- D. Attacks occur with a frequency of > 1 per day for more than half the time
- E. No refractory period follows attacks triggered from trigger areas
- F. Not attributed to another disorder

4 Other primary headaches

4.1 Primary stabbing headache

Description: Transient and localised stabs of pain in the head that occur spontaneously in the absence of organic disease of underlying structures or of the cranial nerves.

Diagnostic criteria:

- A. Head pain occurring as a single stab or a series of stabs and fulfilling criteria B–D
- B. Exclusively or predominantly felt in the distribution of the first division of the trigeminal nerve (orbit, temple and parietal area)
- C. Stabs last for up to a few seconds and recur with irregular frequency ranging from one to many per day
- D. No accompanying symptoms
- E. Not attributed to another disorder

4.2 Primary cough headache

Description: Headache precipitated by coughing or straining in the absence of any intracranial disorder.

Diagnostic criteria:

- A. Headache fulfilling B and C
- B. Sudden onset, lasting from one second to 30 minutes
- C. Brought on by and occurring only in association with coughing, straining and/or valsalva manoeuvre
- D. Not attributable to another disorder

4.3 Primary exertional headache

Description: Headache precipitated by any form of exercise.

Diagnostic criteria:

- A. Pulsating headache fulfilling criteria B and C
- B. Lasting from five minutes to 48 hours
- C. Brought on by and occurring only during or after physical exertion
- D. Not attributed to another disorder

4.4 Primary headache associated with sexual activity

Description: Headache precipitated by sexual activity, usually starting as a dull bilateral ache as sexual excitement increases and suddenly becoming intense at orgasm, in the absence of any intracranial disorder.

4.4.1 Preorgasmic headache

Diagnostic criteria:

- A. Dull ache in the head and neck associated with awareness of neck and/or jaw muscle contraction and fulfilling criterion B
- B. Occurs during sexual activity and increases with sexual excitement
- C. Not attributed to another disorder

4.4.2 Orgasmic headache

Diagnostic criteria:

- A. Sudden severe headache fulfilling criterion B
- B. Occurs at orgasm
- C. Not attributed to another disorder

4.5 Hypnic headache

Description: Attacks of dull headache that always awaken the patient from asleep.

Diagnostic criteria:

- A. Dull headache fulfilling criteria B–D
- B. Develops only during sleep, and awakens patient
- C. At least two of the following characteristics:
 1. occurs > 15 times per month
 2. lasts ≥ 15 minutes after waking
 3. first occurs after age of 50 years
- D. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
- E. Not attributed to another disorder

4.6 Primary thunderclap headache

Description: High-intensity headache of abrupt onset mimicking that of ruptured cerebral aneurysm.

Diagnostic criteria:

- A. Severe head pain fulfilling criteria B and C
- B. Both of the following characteristics:
 1. sudden onset, reaching maximum intensity in < 1 minute
 2. lasting from 1 hour to 10 days
- C. Does not recur regularly over subsequent weeks or months
- D. Not attributed to another disorder

4.7 Hemicrania continua

Description: Persistent strictly unilateral headache responsive to indometacin.

Diagnostic criteria:

- A. Headache for > 3 months fulfilling criteria B–D
- B. All of the following characteristics:
 1. unilateral pain without side-shift
 2. daily and continuous, without pain-free periods
 3. moderate intensity, but with exacerbations of severe pain

- C. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
 - 1. conjunctival injection and/or lacrimation
 - 2. nasal congestion and/or rhinorrhoea
 - 3. ptosis and/or miosis
- D. Complete response to therapeutic doses of indometacin
- E. Not attributed to another disorder

4.8 New daily-persistent headache (NDPH)

Description: Headache that is daily and unremitting from very soon after onset (within 3 days at most). The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity. There may be photophobia, phonophobia or mild nausea.

Diagnostic criteria:

- A. Headache for > 3 months fulfilling criteria B–D
- B. Headache is daily and unremitting from onset or from < 3 days from onset
- C. At least two of the following pain characteristics:
 - 1. bilateral location
 - 2. pressing/tightening (non-pulsating) quality
 - 3. mild or moderate intensity
 - 4. not aggravated by routine physical activity such as walking or climbing stairs
- D. Both of the following:
 - 1. no more than one of photophobia, phonophobia or mild nausea
 - 2. neither moderate or severe nausea nor vomiting
- E. Not attributed to another disorder

Secondary Headaches

8.2 Medication overuse headache

Diagnostic criteria:

- A. Headache present on ≥ 15 days/month
- B. Regular overuse for > 3 months of one or more acute/symptomatic treatment drugs as defined under sub forms of 8.2.
 - 1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥ 10 days/month on a regular basis for > 3 months
 - 2. Simple analgesics or any combination of ergotamine, triptans, analgesics opioids on ≥ 15 days/month on a regular basis for > 3 months without overuse of any single class alone
- C. Headache has developed or markedly worsened during medication overuse

11.2.1 Cervicogenic Headache

Diagnostic Criteria:

- A. Pain referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C & D
- B. Clinical, laboratory &/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache
- C. Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following
 - 1. Demonstration of clinical signs that implicate a source of pain in the neck
 - 2. Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo or other adequate control
- D. Pain resolves in 3 months after successful treatment of the causative disorder or lesion.

11.7 Headache or facial pain attributed to temporomandibular joint (TMJ) disorder

Diagnostic Criteria:

- A. Recurrent pain in one or more regions of the head and/or face fulfilling criteria C and D
- B. X-ray, MRI and/or bone scintigraphy demonstrate TMJ disorder
- C. Evidence that pain can be attributed to the TMJ disorder, based on at least one of the following:
 - 1. pain is precipitated by jaw movements and/or chewing of hard or tough food
 - 2. reduced range of or irregular jaw opening
 - 3. noise from one or both TMJs during jaw movements
 - 4. tenderness of the joint capsule(s) of one or both TMJs
- D. Headache resolves within 3 months, and does not recur, after successful treatment of the TMJ disorder

Annex 3

Differentiation between trigeminal autonomic cephalalgias

The following differentiate trigeminal autonomic cephalalgias from each other:^{32, 33, 274}

- Gender: CH is more common in men (M:F 3.5-7:1); PH is more common in women (M:F 1:2.13-2.36); SUNCT is more common in men (M:F 2:1)
- Duration: CH 15min-3hr; PH 2-45min; SUNCT 2-250s
- Frequency: CH 1 every other day – 8/day; PH 1-40/day; SUNCT 1/day – 30/hour
- Restlessness during an attack: 100% in cluster headache, 50% in paroxysmal hemicrania, 50% in SUNCT
- Episodic form predominates in CH, Chronic form predominates in PH
- Response to indometacin is absolute in paroxysmal hemicrania, but indometacin is ineffective in CH or SUNCT
- Alcohol frequently triggers CH, occasionally triggers PH and does not trigger SUNCT.

3
4

Differentiation from trigeminal neuralgia

The following differentiate trigeminal autonomic cephalalgias from trigeminal neuralgia:^{23,32,33}

- Trigeminal neuralgia may coexist with cluster headache and paroxysmal hemicrania (cluster-tic, and paroxysmal hemicrania-tic syndromes)
- Location: Orbital, supra-orbital, temporal in TACs; in trigeminal neuralgia the pain occurs in the maxillary and mandibular divisions of the trigeminal nerve in 90%, when present in the ophthalmic division it has usually been in the other two divisions for many years
- Duration: In trigeminal neuralgia pain duration is brief (few seconds) easily distinguishing it from CH and PH
- Autonomic symptoms are not prominent in trigeminal neuralgia and when present the disorder has usually been established for many years, distinguishing it from SUNCT where autonomic features are very prominent.

3
4

Annex 4

Headache history¹¹

1. How many different headache types does the patient experience?

Separate histories are necessary for each. It is reasonable to concentrate on the most bothersome to the patient but others should always attract some enquiry in case they are clinically important.

2. Time questions

- a) Why consulting now?
- b) How recent in onset?
- c) How frequent, and what temporal pattern (especially distinguishing between episodic and daily or unremitting)?
- d) How long lasting?

3. Character questions

- a) Intensity of pain
- b) Nature and quality of pain
- c) Site and spread of pain
- d) Associated symptoms

4. Cause questions

- a) Predisposing and/or trigger factors
- b) Aggravating and/or relieving factors
- c) Family history of similar headache

5. Response questions

- a) What does the patient do during the headache?
- b) How much is activity (function) limited or prevented?
- c) What medication has been and is used, and in what manner?

6. State of health between attacks

- a) Completely well, or residual or persisting symptoms?
- b) Concerns, anxieties, fears about recurrent attacks, and/or their cause

Annex 5

Weekly Headache Diary

WEEK 1	Please score the pain of your headache out of 10 and indicate if you have any other symptoms as listed.						
	Sun	Mon	Tue	Wed	Thur	Fri	Sat
Headache (0 = none 10 = worse)							
Feeling sick (Yes/No)							
Vomiting (Yes/No)							
Other symptoms (Yes/No)							
Duration of attack (hours)							
Had to lie down (Yes/No)							
Time away from normal activities (hours)							
Number of tablets of medicine taken:							
Prescribed							
Over the counter							
Menstruation (Yes/No)							

Annex 6

Drug licensing status

All the drugs recommended in this guideline are licensed for the indication in the recommendation with the following exceptions:

Section	Drug
6.1.2	Sumatriptan/naproxen sodium fixed combination is not licensed for the treatment of acute migraine.
6.2.1	Atenolol is not licensed for the prophylaxis of patients with migraine.
6.2.2	Gabapentin and sodium valproate are not licensed for the treatment of migraine.
6.2.3	Amitriptyline and venlafaxine are not licensed for the prophylaxis of migraine.
7.2.3	Tricyclic antidepressants are not licensed for the prophylaxis of tension-type headache.
8.1.3	Lidocaine is not licensed for the treatment of headache.
8.2.1	Verapamil is not licensed for the prophylaxis of cluster headache.

References

- Boardman HF, Thomas E, Croft PR, Millson DS. Epidemiology of headache in an English district. *Cephalalgia* 2003;23(2):129-37.
- Latinovic R, Gulliford M, Ridsdale L. Headache and migraine in primary care: consultation, prescription, and referral rates in a large population. *J Neurol Neurosurg Psychiatry* 2006;77(3):385-7.
- Lamer AJ. Guidelines for primary headache disorders in primary care: an "intervention" study. *Headache Care* 2006;3(1):1-2.
- Patterson VH, Esmonde TF. Comparison of the handling of neurological outpatient referrals by general physicians and a neurologist. *J Neurol Neurosurg Psychiatry* 1993;56(7):830.
- Martin V, Elkind A. Diagnosis and classification of primary headache disorders. In: *Standards of care for headache diagnosis and treatment*. Chicago (IL): National Headache Foundation; 2004. p.4-18.
- Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia* 2003;23(7):519-27.
- World Health Organisation. The world health report 2001 - mental health: new understanding, new hope. Geneva: World Health Organisation; 2001.
- Anon. Migraine: costs and consequences. *Bandolier* 1999;6(9):5-6.
- BMJ Clinical Evidence. Headache (chronic tension-type). [cited 16 Oct 2008]. Available from url: <http://clinicalevidence.bmj.com/ceweb/conditions/nud/1205/1205.jsp>
- Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27(3):193-210.
- British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache, 3rd edition. Hull; 2007.
- US Headache Consortium, Frishberg BM, Rosenberg JH, Matchar DB, McCrory DC, Pietrzak MP, et al. Evidence based guidelines in the primary care setting: neuroimaging in patients with non-acute headache. [cited 16 Oct 2008]. Available from url: <http://www.aan.com/professionals/practice/pdfs/gl0088.pdf>
- Dowson AJ, Lipscombe S, Sender J, Rees T, Watson D, MIPCA Migraine Guidelines Development Group, et al. New guidelines for the management of migraine in primary care. *Curr Med Res Opin* 2002;18(7):414-39.
- Edmeads J, Láinez JM, Brandes JL, Schoenen J, Freitag F. Potential of the Migraine Disability Assessment (MIDAS) Questionnaire as a public health initiative and in clinical practice. *Neurology* 2001;56(6 Suppl 1):S29-34.
- MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment patterns: the global Migraine and Zolmitriptan Evaluation survey. *Headache* 2003;43(1):19-26.
- International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia* 2004;24(Suppl 1):8-160.
- Diamond ML. The role of concomitant headache types and non-headache co-morbidities in the underdiagnosis of migraine. *Neurology* 2002;58(9 Suppl 6):S3-9.
- Lipton RB, Stewart WF, Celentano DD, Reed ML. Undiagnosed migraine headaches. A comparison of symptom-based and reported physician diagnosis. *Arch Intern Med* 1992;152(6):1273-8.
- Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C. Diagnostic lessons from the spectrum study. *Neurology* 2002;58(9 Suppl 6):S27-31.
- Tepper SJ, Dahlof CG, Dowson A, Newman L, Mansbach H, Jones M, et al. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. *Headache* 2004;44(9):856-64.
- Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al. Incidental findings on brain MRI in the general population. *N Engl J Med* 2007;357(18):1821-8.
- Weber F, Knopf H. Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci* 2006;240(1-2):81-4.
- Smetana GW. The diagnostic value of historical features in primary headache syndromes: a comprehensive review. *Arch Intern Med* 2000;160(18):2729-37.
- Dodick DW. Diagnosing headache: clinical clues and clinical rules. *Adv Stud Med* 2003;3(2):87-92.
- Fisher CM. Late-life migraine accompaniments—further experience. *Stroke* 1986;17(5):1033-42.
- Lipton RB, Goadsby PJ, Sawyer JPC, Blakeborough P, Stewart WF. Migraine: diagnosis and assessment of disability. *Rev Contemp Pharmacother* 2000;11(2):63-73.
- Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006;26(6):742-6.
- Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J, Hettiarachchi J, et al. A self-administered screener for migraine in primary care: the ID Migraine-super(TM) Validation Study. *Neurology* 2003;61(3):375-82.
- Maizels M, Burchette R. Rapid and sensitive paradigm for screening patients with headache in primary care settings. *Headache* 2003;43(5):441-50.
- Mulleners WM, Aurora SK, Chronicle EP, Stewart R, Gopal S, Koehler PJ. Self-reported photophobic symptoms in migraineurs and controls are reliable and predict diagnostic category accurately. *Headache* 2001;41(1):31-9.
- Russell MB, Fenger K, Olesen J. The family history of migraine. Direct versus indirect information. *Cephalalgia* 1996;16(3):156-60.
- Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003;63(16):1637-77.
- Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) - a prospective clinical study of SUNCT and SUNA. *Brain* 2006;129(10):2746-60.
- Goadsby PJ, Boes C. New daily persistent headache. *J Neurol Neurosurg Psychiatry* 2002;72(Suppl II):ii6-ii9.
- Landtblom AM, Fridriksson S, Boivie J, Hillman J, Johansson G, Johansson I. Sudden onset headache: a prospective study of features, incidence and causes. *Cephalalgia* 2002;22(5):354-60.
- Locker TE, Thompson C, Rylance J, Mason SM. The utility of clinical features in patients presenting with nontraumatic headache: an investigation of adult patients attending an emergency department. *Headache* 2006;46(6):954-61.
- Maggioni F, Dainese F, Mainardi F, Lisotto C, Zanchin G. Intermittent angle-closure glaucoma in the presence of a white eye, posing as retinal migraine. *Cephalalgia* 2005;25(8):622-6.
- American College for Emergency Physicians (ACEP). Critical issues in the evaluation and management of patients presenting to the emergency department with acute headache. *Ann Emerg Med* 2002;39:108-22.
- Aygun D, Bildik F. Clinical warning criteria in evaluation by computed tomography the secondary neurological headaches in adults. *Eur J Neurol* 2003;10:437-42.
- Shibata T, Kubo M, Kuwayama N, Hirashima Y, Endo S. Warning headache of subarachnoid hemorrhage and infarction due to vertebralbasilar artery dissection. *Clin J Pain* 2006;22(2):193-6.
- Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998;65(5):791-3.
- Agostoni E. Headache in cerebral venous thrombosis. *Neurol Sci* 2004;25(3 Suppl Oct):S206-10.
- Joseph R, Cook GE, Steiner TJ, Clifford Rose F. Intracranial space-occupying lesions in patients attending a migraine clinic. *Practitioner* 1985;229(1403):477-81.
- Schievink WI. Misdiagnosis of spontaneous intracranial hypotension. *Arch Neurol* 2003;60(12):1713-8.
- Skau M, Brennum J, Gjerris F, Jensen R. What is new about idiopathic intracranial hypertension? An updated review of mechanism and treatment. *Cephalalgia* 2006;26(4):384-99.
- Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. *J Neurol Neurosurg Psychiatry* 2005;76(8):1084-7.
- Iurlaro S, Beghi E, Massetto N, Guccione A, Autunno M, Colombo B, et al. Does headache represent a clinical marker in early diagnosis of cerebral venous thrombosis? A prospective multicentric study. *Neurol Sci* 2004;25(Suppl 3):S298-9.
- Smetana GW, Shmerling RH. Does this patient have temporal arteritis? *JAMA* 2002;287(1):92-101.
- van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *New Engl J Med* 2004;351(18):1849-59.
- Al-Shahi R, White PM, Davenport RJ, Lindsay KW. Subarachnoid haemorrhage. *BMJ* 2006;333(7561):235-40.

51. Zito G, Jull G, Story I. Clinical tests of musculoskeletal dysfunction in the diagnosis of cervicogenic headache. *Man Ther* 2006;11(2):118-29.
52. Sjaastad O, Fredriksen TA, Pfaffenrath V. Cervicogenic headache: diagnostic criteria. The Cervicogenic Headache International Study Group. *Headache* 1998;38(6):442-5.
53. Grant R. Overview: brain tumour diagnosis and management/Royal College of Physicians guidelines. *J Neurol Neurosurg Psychiatry* 2004;75(Suppl 2):ii18-23.
54. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. *Br J Gen Pract* 2007;57(542):695-9.
55. Coleman AL. Glaucoma. *Lancet* 1999;354(9192):1803-10.
56. Holmes WF, MacGregor EA, Sawyer JP, Lipton RB. Information about migraine disability influences physicians' perceptions of illness severity and treatment needs. *Headache* 2001;41(4):343-50.
57. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. *J Clin Epidemiol* 2006;59(4):374-80.
58. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Jr., Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12(8):963-74.
59. Bayliss MS, Dewey JE, Dunlap I, Batenhorst AS, Cady R, Diamond ML, et al. A study of the feasibility of Internet administration of a computerized health survey: the headache impact test (HIT). *Qual Life Res* 2003;12(8):953-61.
60. De Diego EV, Lanteri-Minet M. Recognition and management of migraine in primary care: influence of functional impact measured by the headache impact test (HIT). *Cephalalgia* 2005;25(3):184-90.
61. Kilminster SG, Dowson A, Bundy M. The Headache Impact Test 1 and the Short Pain Inventory: outcome measures compared. *Int J Pharmaceutical Med* 2003;17(1):23-32.
62. Bjorner JB, Kosinski M, Ware JE, Jr. Calibration of an item pool for assessing the burden of headaches: an application of item response theory to the headache impact test (HIT). *Qual Life Res* 2003;12(8):913-33.
63. Ware JE, Jr., Kosinski M, Bjorner JB, Bayliss MS, Batenhorst A, Dahlof CG, et al. Applications of computerized adaptive testing (CAT) to the assessment of headache impact. *Qual Life Res* 2003;12(8):935-52.
64. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) questionnaire. *Headache* 2001;41(9):854-61.
65. Dowson AJ. Assessing the impact of migraine. *Curr Med Res Opin* 2001;17(4):298-309.
66. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 1999;19(2):107-14.
67. Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology* 1999;53(5):988-94.
68. Stewart WF, Lipton R. Need for care and perceptions of MIDAS among headache sufferers study. *CNS Drugs* 2002;16(Suppl 1):5-11.
69. Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. *Headache* 2003;43(4):336-42.
70. Stewart WF, Lipton RB, Kolodner K. Migraine disability assessment (MIDAS) score: relation to headache frequency, pain intensity, and headache symptoms. *Headache* 2003;43(3):258-65.
71. US Headache Consortium. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. [cited 16 Oct 2008]. Available from url: <http://www.americanheadachesociety.org/professionalresources/USHeadacheConsortiumGuidelines.asp>
72. Sempere AP, Porta-Etessam J, Medrano V, Garcia-Morales I, Concepcion L, Ramos A, et al. Neuroimaging in the evaluation of patients with non-acute headache. *Cephalalgia* 2005;25(1):30-5.
73. Wang HZ, Simonson TM, Greco WR, Yuh WTC. Brain MR imaging in the evaluation of chronic headache in patients without other neurologic symptoms. *Acad Radiol* 2001;8(5):405-8.
74. Tsushima Y, Endo K. MR imaging in the evaluation of chronic or recurrent headache. *Radiology* 2005;235(2):575-9.
75. Howard L, Wessely S, Leese M, Page L, McCrone P, Husain K, et al. Are investigations anxiolytic or anxiogenic? A randomised controlled trial of neuroimaging to provide reassurance in chronic daily headache. *J Neurol Neurosurg Psychiatry* 2005;76(11):1558-64.
76. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A and Sandor, PS. EFNS guideline on the drug treatment of migraine – report of an EFNS task force. *Eur J Neurol* 2006;13(6):560-72.
77. Cutrer MF, Boes CJ. Cough, exertional, and sex headaches. *Neurol Clin N Am* 2004;22:133-49.
78. Favier I, van Vliet JA, Roon KI. Trigeminal autonomic cephalgias due to structural lesions: a review of 31 cases. *Arch Neurol* 2007;64(1):25-31.
79. Pascual J, Iglesias F, Oterino A, Vázquez-Barquero A, Berciano J. Cough, exertional, and sexual headaches: an analysis of 72 benign and symptomatic cases. *Neurology* 1996;46(6):1520-24.
80. Yousry I, Forderreuther S, Moriggl B, Holtmannspotter M, Naidich TP, Straube A, et al. Cervical MR imaging in postural headache: MR signs and pathophysiological implications. *ANJR Am J Neuroradiol* 2001;22(7):1239-50.
81. Moayeri NN, Henson JW, Schaefer PW, Zervas NT. Spinal dural enhancement on magnetic resonance imaging associated with spontaneous intracranial hypotension. Report of three cases and review of the literature. *J Neurosurg* 1998;88(5):912-8.
82. Pannullo SC, Reich JB, Krol G, Deck MD, Posner JB. MRI changes in intracranial hypotension. *Neurology* 1993;43(5):919-26.
83. Rabin BM, Roychowdhury S, Meyer JR, Cohen BA, LaPat KD, Russell EJ. Spontaneous intracranial hypotension: spinal MR findings. *ANJR Am J Neuroradiol* 1998;19(6):1034-9.
84. Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging? *JAMA* 2006;296(10):1274-83.
85. O'Neill J, McLaggan S, Gibson R. Acute headache and subarachnoid haemorrhage: a retrospective review of CT and lumbar puncture findings. *Scott Med J* 2005;50(4):151-3.
86. Webb S, Bone I, Lindsay K. The investigation of acute severe headache suggestive of probable subarachnoid haemorrhage: a hospital-based study. *Br J Neurosurg* 2003;17(6):580-4.
87. Davenport R. Sudden headache in the emergency department. *Pract Neurol* 2005;5:132-43.
88. Hayreh SS, Podhajsky PA, Raman R, Zimmerman B. Giant cell arteritis: validity and reliability of various diagnostic criteria. *Am J Ophthalmol* 1997;123(3):285-96.
89. Ferrari MD. Current perspectives on effective migraine treatments: are small clinical differences important for patients? *Drugs Today* 2003;39:37-41.
90. British National Formulary. 56th ed. London: BMJ Publishing; 2008.
91. Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 2004;24(11):947-54.
92. Lipton RB, Goldstein J, Baggish JS, Yataco AR, Sorrentino JV, Quiring JN. Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005;45(4):283-92.
93. MacGregor EA, Dowson A, Davies PT. Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002;42(4):249-55.
94. Goldstein J, Silberstein SD, Saper JR, Elkind AH, Smith TR, Gallagher RM, et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache* 2005;45(8):973-82.
95. Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. A randomized controlled trial. *Headache* 2001;41(7):665-79.
96. Dib M, Massiou H, Weber M, Henry P, Garcia-Acosta S, Bousser MG, et al. Efficacy of oral ketoprofen in acute migraine: a double-blind randomized clinical trial. *Neurology* 2002;58(11):1660-5.
97. Electronic medicines compendium. [cited 16 Oct 2008]. Available from url: <http://www.emc.medicines.org.uk/>
98. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000;160(22):3486-92.
99. Belsey J. The clinical and financial impact of oral triptans in the management of migraine in the UK: a systematic review. *J Med Economics* 2000;3:35-47.
100. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ, et al. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafertgot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *Eur Neurol* 2002;47(2):99-107.

101. Edmeads J. Defining response in migraine: which endpoints are important? *Eur Neurol* 2005;1:22-8.
102. Loder E. Fixed drug combinations for the acute treatment of migraine: place in therapy. *CNS Drugs* 2005;19(9):769-84.
103. Mannix LK. Effect of triptans on the quality of life of patients with migraine. *Headache Q* 2002;13(3):11-21.
104. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22(8):633-58.
105. Pascual J, Mateos V, Roig C, Sanchez-Del-Rio M, Jimenez D. Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. *Headache* 2007;47(8):1152-68.
106. Poolsup N, Leelasangaluk V, Jittangtrong J, Rithlamlert C, Ratanapantamane N, Khanthong M. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005;30(6):521-32.
107. Diener HC. Efficacy of almotriptan 12.5 mg in achieving migraine-related composite endpoints: a double-blind, randomized, placebo-controlled study in patients with previous poor response to sumatriptan 50 mg. *Curr Med Res Opin* 2005;21(10):1603-10.
108. Brandes JL, Kudrow D, Stark SR, O'Carroll CP, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007;297(13):1443-54.
109. Chabriot H, Danchot J, Hugues FC, Joire JE. Combined aspirin and metoclopramide in the acute treatment of migraine attacks: a review. *Headache Q* 1997;8(2):118-21.
110. Dowson A, Ball K, Haworth D. Comparison of a fixed combination of domperidone and paracetamol (Domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Curr Med Res Opin* 2000;16(3):190-7.
111. Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004;329(7479):1369-72.
112. Honkaniemi J, Liimatainen S, Rainesalo S, Sulavuori S. Haloperidol in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2006;46(5):781-7.
113. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology* 2004;62(5):788-90.
114. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2007;6(12):1054-62.
115. US Headache Consortium, Ramadan NM, Silberstein SD, Freitag F, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. [cited 16 Oct 2008]. Available from url: <http://www.aan.com/professionals/practice/pdfs/gl0090.pdf>
116. Linde K, Rosnagel K. Propranolol for migraine prophylaxis (Cochrane Review). In: *The Cochrane Library*, Issue 1. London: Wiley; 2006.
117. Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis (Cochrane Review). In: *The Cochrane Library*, Issue 3. London: Wiley; 2004.
118. Mei D, Ferraro D, Zelano G, Capuano A, Vollono C, Gabriele C, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol* 2006;29(5):269-75.
119. Edwards KR, Potter DL, Wu SC, Kamin M, Hulihan J. Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. *CNS spectrums* 2003;8(6):428-32.
120. Nadin C. Topiramate: the evidence for its therapeutic value in the prevention of migraine. *Core Evidence* 2005;1(2):103-24.
121. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The effect of migraine on daily activities: effect of topiramate compared with placebo. *Curr Med Res Opin* 2006;22(6):1021-9.
122. Diener HC, Tfelt-Hansen P, Dahlof C, Lainez MJ, Sandrini G, Wang SJ, et al. Topiramate in migraine prophylaxis—results from a placebo-controlled trial with propranolol as an active control. *J Neurol* 2004;251(8):943-50.
123. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007;47(2):170-80.
124. Limmroth V, Biondi D, Pfeil J, Schwalen S. Topiramate in patients with episodic migraine: reducing the risk for chronic forms of headache. *Headache* 2007;47(1):13-21.
125. Diamond M, Dahl AC, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache Care* 2005;45(8):1023-30.
126. Bartolini M, Silvestrini M, Taffi R, Lanciotti C, Luconi R, Capecci M, et al. Efficacy of topiramate and valproate in chronic migraine. *Clin Neuropharmacol* 2005;28(6):277-9.
127. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. *Headache* 2006;46(4):642-48.
128. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, et al. Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001;41(2):119-28.
129. Tomkins GE, Jackson JL, O'Malley PG, Balden E, Santoro JE. Treatment of chronic headache with antidepressants: a meta-analysis. *Am J Med* 2001;111(1):54-63.
130. Moja PL, Cusi C, Sterzi RR, Canepari C. Selective serotonin reuptake inhibitors (SSRIs) for preventing migraine and tension-type headaches (Cochrane Review). In: *The Cochrane Library*, Issue 3. London: Wiley; 2005.
131. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertaş M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005;45(2):144-52.
132. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg* 2004;107(1):44-8.
133. Cleland PG, Barnes D, Elrington GM, Loizou LA, Rawes GD. Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997;38(1):31-8.
134. Diener HC, Matias-Guiu J, Hartung E, Pfaffenrath V, Ludin HP, Nappi G, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002;22(3):209-21.
135. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia* 2007;27(6):492-503.
136. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;289(1):65-9.
137. Bensenor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. Low-dose aspirin for migraine prophylaxis in women. *Cephalalgia* 2001;21(3):175-83.
138. Brandes JL, Visser WH, Farmer MV, Schuhl AL, Malbecq W, Vrijens F, et al. Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. *Headache Care* 2004;44(6):581-6.
139. Vahedi K, Taupin P, Djomby R, El-Amrani M, Lutz G, Filippetti V, et al. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. *J Neurol* 2002;249(2):206-11.
140. Eftedal OS, Lydersen S, Helde G, White L, Brubakk AO, Stovner LJ. A randomized, double blind study of the prophylactic effect of hyperbaric oxygen therapy on migraine. *Cephalalgia* 2004;24(8):639-44.
141. Goldstein DJ, Offen WW, Klein EG, Phebus LA, Hipskind P, Johnson KW, et al. Lanepitant, an NK-1 antagonist, in migraine prevention. *Cephalalgia* 2001;21(2):102-6.
142. Lee ST, Park JH, Kim M. Efficacy of the 5-HT_{1A} agonist, buspirone hydrochloride, in migraineurs with anxiety: a randomized, prospective, parallel group, double-blind, placebo-controlled study. *Headache* 2005;45(8):1004-11.
143. Steiner TJ, Lange R, Voelker M. Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* 2003;23(1):59-66.
144. Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure: results from a meta-analysis of 94 randomized placebo-controlled trials with 24,000 participants. *Circulation* 2005;112(15):2301-6.
145. Etminan M, Levine MA, Tomlinson G, Rochon PA. Efficacy of angiotensin II receptor antagonists in preventing headache: a systematic overview and meta-analysis. *Am J Med* 2002;112(8):642-6.
146. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001;322(7277):19-22.

147. Spira PJ, Beran RG, Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003;61(12):1753-9.
148. Bendtsen L, Jensen R. Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. *Neurology* 2004;62(10):1706-11.
149. Singh NN, Misra S. Sertraline in chronic tension-type headache. *J Assoc Physicians India* 2002;50:873-8.
150. Zisis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, et al. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. *Cephalalgia* 2007;27(4):15-24.
151. Silberstein SD, Gobel H, Jensen R, Elkind AH, DeGryse R, Walcott JM, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalalgia* 2006;26(7):790-800.
152. Sycha T, Kranz G, Auff E, Schnider P. Botulinum toxin in the treatment of rare head and neck pain syndromes: a systematic review of the literature. *J Neurol* 2004;251(Suppl 1):119-30.
153. Saper JR, Lake IA, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002;42(6):470-82.
154. Ekblom K. Treatment of cluster headache: clinical trials, design and results. *Cephalalgia* 1995;15(Suppl):33-6.
155. Ekblom K, Krabbe A, Miciceli G, Prusinski A, Cole JA, Pilgrim AJ, et al. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). Sumatriptan Cluster Headache Long-term Study Group. *Cephalalgia* 1995;15(3):230-6.
156. Ekblom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. *Acta Neurol Scand* 1993;88(1):63-9.
157. Ekblom K, Waldenlind E, Levi R, Andersson B, Boivie J, Dizdar N, et al. Treatment of acute cluster headache with sumatriptan. *New Engl J Med* 1991;325(5):322-6.
158. Gobel H, Lindner V, Heinze A, Ribbat M, Deuschl G. Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. *Neurology* 1998;51(3):908-11.
159. van Vliet JA, Bahra A, Martin V, Ramadan N, Aurora SK, Mathew NT, et al. Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. *Neurology* 2003;60(4):630-3.
160. Rapoport AM, Mathew NT, Silberstein SD, Dodick D, Tepper SJ, Sheftell FD, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007;69(9):821-6.
161. Bahra A, Gawe MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000;54(9):1832-9.
162. Fogar L. Treatment of cluster headache. A double-blind comparison of oxygen v air inhalation. *Arch Neurol* 1985;42(4):362-3.
163. Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache* 1981;21(1):1-4.
164. Nilsson Remahl AI, Ansjon R, Lind F, Waldenlind E. Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. *Cephalalgia* 2002;22(9):730-9.
165. Di Sabato F, Rocco M, Martelletti P, Giacobozzo M. Hyperbaric oxygen in chronic cluster headaches: influence on serotonergic pathways. *Undersea Hyperb Med* 1997;24(2):117-22.
166. Costa A, Pucci E, Antonaci F, Sances G, Granella F, Broich G, et al. The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000;20(2):85-91.
167. Leone M, D'Amico D, Frediani F, Moschiano F, Grazi L, Attanasio A, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000;54(6):1382-5.
168. May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006;13(10):1066-77.
169. Steiner TJ, Hering R, Couturier EG, Davies PT, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997;17(6):673-5.
170. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 1996;16(7):494-96.
171. El Amrani M, Massiou H, Bousser MG. A negative trial of sodium valproate in cluster headache: methodological issues. *Cephalalgia* 2002;22(3):205-8.
172. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Pain* 2005;118(1-2):92-6.
173. Silberstein SD, Olesen J, Bousser MG, Diener HC, Dodick D, First M, et al. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia* 2005;25(6):460-5.
174. Bahra A, Walsh M, Menon S, Goadsby PJ. Does chronic daily headache arise de novo in association with regular use of analgesics? *Headache* 2003;43(3):179-90.
175. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002;59(7):1011-4.
176. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. *Neurology* 2006;67(1):109-13.
177. Paemeleire K, Crevits L, Goadsby PJ, Kaube H. Practical management of medication-overuse headache. *Acta Neurol Belg* 2006;106(2):43-51.
178. Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J. Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT Study. *Neurology* 2003;61(2):160-4.
179. Williams D, Cahill T, Dowson A, Fearon H, Lipscombe S, O'Sullivan E, et al. Usage of triptans among migraine patients: an audit in nine GP practices. *Curr Med Res Opin* 2002;18(1):1-9.
180. Atasoy HT, Atasoy N, Unal AE, Emre U, Sumer M. Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. *Eur J Pain* 2005;9(3):285-91.
181. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57(9):1694-8.
182. Krymchantowski AV, Moreira PF. Out-patient detoxification in chronic migraine: comparison of strategies. *Cephalalgia* 2003;23(10):982-93.
183. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia* 2006;26(9):1097-105.
184. Zed PJ, Loewen PS, Robinson G. Medication-induced headache: overview and systematic review of therapeutic approaches. *Ann Pharmacother* 1999;33:61-72.
185. Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. *Cephalalgia* 2006;26(10):1192-8.
186. Zeeberg P, Olesen J, Jensen R. Probable medication-overuse headache: the effect of a 2-month drug-free period. *Neurology* 2006;66(12):1894-8.
187. Katsarava Z, Limmroth V, Finke M, Diener HC, Fritsche G. Rates and predictors for relapse in medication overuse headache: a 1-year prospective study. *Neurology* 2003;60(10):1682-3.
188. Andrasik F, Grazi L, Usai S, D'Amico D, Kass S, Bussone G. Disability in chronic migraine with medication overuse: treatment effects at 3 years. *Headache* 2007;47(9):1277-81.
189. Boe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology* 2007;69(1):26-31.
190. Pageler L, Katsarava Z, Diener HC, Limmroth V. Prednisone vs. placebo in withdrawal therapy following medication overuse headache. *Cephalalgia* 2008;28(2):152-6.
191. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007;27(7):814-23.
192. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalalgia* 2003;23(8):820-4.
193. Descombes S, Brefel-Courbon C, Thalameas C, Albucher JF, Rascol O, Montastruc JL, et al. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. *Headache* 2001;41(2):178-82.
194. Briggs G, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2005.
195. Lee A, Inch S, Finnigan D, editors. Therapeutics in pregnancy and lactation. Abingdon: Radcliffe Medical Press; 2000.
196. Rubin P, editor. Prescribing in pregnancy. 3rd ed. London: BMJ Publishing; 2000.

197. Schaefer D, editor. Drugs during pregnancy and lactation. 1st ed. Amsterdam: Elsevier Science B.V.; 2001.
198. Fox AW, Chambers CD, Anderson PO, Diamond ML, Spierings ELH. Evidence-based assessment of pregnancy outcome after sumatriptan exposure. *Headache* 2002;42(1):8-15.
199. Hilaire ML, Cross LB, Eichner SF. Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004;38:1726-30.
200. Loder E. Safety of sumatriptan in pregnancy: a review of the data so far. *CNS Drugs* 2003;17(1):1-7.
201. Buse DC, Loder EW, Golub JR. Use of oral contraceptives in women with migraine. *Headache Care* 2005;2(3):183-94.
202. MacGregor EA. Migraine and use of combined hormonal contraceptives: a clinical review. *J Fam Plann Reprod Health Care* 2007;33(3):159-69.
203. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *BMJ* 1999;318(7175):13-8.
204. Etmann M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 2005;330(7482):63-5.
205. Mendizabal JE, Herbert DE. Risk of ischemic stroke in migraineurs: a meta-analysis. *Headache & Pain: Diagnostic Challenges, Current Therapy* 2004;15(4):197-200.
206. Curtis KM, Mohllajee AP, Peterson HB. Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception* 2006;73(2):189-94.
207. Faculty of Family Planning and Reproductive Health Care. UK medical eligibility criteria for contraceptive use 2005/2006. [cited 17 Oct 2008]. Available from url: http://www.ffprhc.org.uk/admin/uploads/298_UKMEC_200506.pdf
208. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA* 2006;295(15):1824-30.
209. Burke BE, Olson RD, Cusack BJ. Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. *Biomed Pharmacother* 2002;56(6):283-8.
210. Ferrante F, Fusco E, Calabresi P, Cupini LM. Phyto-oestrogens in the prophylaxis of menstrual migraine. *Clin Neuropharmacol* 2004;27(3):137-40.
211. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology* 2006;67(12):2159-63.
212. Martin V, Wernke S, Mandell K, Zoma W, Bean J, Pinney S, et al. Medical oophorectomy with and without estrogen add-back therapy in the prevention of migraine headache. *Headache* 2003;43(4):309-21.
213. MacGregor EA. Menstrual migraine: a clinical review. *J Fam Plann Reprod Health Care* 2007;33(1):36-47.
214. Silberstein SD, Armellino JJ, Hoffman HD, Battikha JP, Hamelsky SW, Stewart WF, et al. Treatment of menstruation-associated migraine with the nonprescription combination of acetaminophen, aspirin, and caffeine: results from three randomized, placebo-controlled studies. *Clin Ther* 1999;21(3):475-91.
215. Al-Waili NS. Treatment of menstrual migraine with prostaglandin synthesis inhibitor mefenamic acid: double-blind study with placebo. *Eur J Med Res* 2000;5(4):176-82.
216. Loder E, Silberstein SD, Abu-Shakra S, Mueller L, Smith T. Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache* 2004;44(2):120-30.
217. Massiou H, Jamin C, Hinzeln G, Bidaut-Mazel C, The French Naramig Collaborative Study Group. Efficacy of oral naratriptan in the treatment of menstrually related migraine. *Eur J Neurol* 2005;12(10):774-81.
218. Nett R, Landy S, Shackelford S, Richardson MS, Ames M, Lener M. Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstet Gynecol* 2003;102(4):835-42.
219. Silberstein SD, Massiou H, McCarroll KA, Lines CR. Further evaluation of rizatriptan in menstrual migraine: retrospective analysis of long-term data. *Headache* 2002;42(9):917-23.
220. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headaches: evidence-based review. *Neurology* 2008;70(17):1555-63.
221. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004;63(2):261-9.
222. Newman L, Mannix LK, Landy S, Silberstein S, Lipton RB, Putnam DG, et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2001;41(3):248-56.
223. Ashkenazi A, Silberstein SD. Hormone-related headache: pathophysiology and treatment. *CNS Drugs* 2006;20(2):125-41.
224. MacGregor EA, Barnes D. Migraine in a specialist menopause clinic. *Climacteric* 1999;2(3):218-23.
225. Misakian AL, Langer RD, Bensenor IM, Cook NR, Manson JE, Buring JE, et al. Postmenopausal hormone therapy and migraine headache. *J Womens Health (Larchmt)* 2003;12(10):1027-36.
226. Wang SJ, Fuh JL, Lu SR, Juang KD, Wang PH. Migraine prevalence during menopausal transition. *Headache* 2003;43(5):470-8.
227. Neri I, Granella F, Nappi R, Manzoni GC, Facchinetti F, Genazzani AR. Characteristics of headache at menopause: a clinico-epidemiologic study. *Maturitas* 1993;17(1):31-7.
228. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-33.
229. Kittner SJ, Bousser MG. Post-menopausal hormone replacement therapy and stroke risk. *Cephalalgia* 2000;20:208-13.
230. Tzourio C, Iglesias S, Hubert JB, Visy JM, Alperovitch A, Tehindrazanarivelo A, et al. Migraine and risk of ischaemic stroke: a case-control study. *BMJ* 1993;307(6899):289-92.
231. MacGregor EA. Migraine and the menopause. *J Br Menopause Soc* 2006;12:104-8.
232. Silberstein SD. Headache and female hormones: what you need to know. *Curr Opin Neurol* 2001;14(3):323-33.
233. Nappi RE, Cagnacci A, Granella F, Piccinini F, Polatti F, Facchinetti F. Course of primary headaches during hormone replacement therapy. *Maturitas* 2001;38(2):157-63.
234. Crawford P, Simmons M. What dietary modifications are indicated for migraines? *J Fam Pract* 2006;55(1):62-6.
235. Wober C, Holzhammer J, Zeitlhofer J, Wessely P, Wober-Bingol C. Trigger factors of migraine and tension-type headache: experience and knowledge of the patients. *J Headache Pain* 2006;7(4):188-95.
236. Wober C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia* 2007;27(4):304-14.
237. Pradalier A, Bakouche P, Baudesson G, Delage A, Cornaille-Lafage G, Launay JM, et al. Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: a double-blind study versus placebo. *Cephalalgia* 2001;21(8):818-22.
238. Boardman HF, Thomas E, Millson DS, Croft PR. The natural history of headache: predictors of onset and recovery. *Cephalalgia* 2006;26(9):1080-8.
239. Jull G, Trott P, Potter H, Zito G, Niere K, Shirley D, et al. A randomized controlled trial of exercise and manipulative therapy for cervicogenic headache. *Spine* 2002;27(17):1835-43.
240. Stanton WR, Jull GA. Cervicogenic headache: locus of control and success of treatment. *Headache* 2003;43(9):956-61.
241. Lemstra M, Stewart B, Olszynski WP. Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. *Headache* 2002;42(9):845-54.
242. Nobre ME, Leal AJ, Filho PM. Investigation into sleep disturbance of patients suffering from cluster headache. *Cephalalgia* 2005;25(7):488-92.
243. Sand T, Hagen K, Schrader H. Sleep apnoea and chronic headache. *Cephalalgia* 2003;23(2):90-5.
244. Vos J, Passchier J. Reduced impact of migraine in everyday life: an observational study in the Dutch Society of Headache Patients. *Headache* 2003;43(6):645-50.
245. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001;285(17):2208-15.
246. Symvoulakis EK, Clark LV, Dowson AJ, Jones R, Ridsdale L. Headache: a 'suitable case' for behavioural treatment in primary care? *Br J Gen Pract* 2007;57(536):231-7.
247. Andrasik F. What does the evidence show? Efficacy of behavioural treatments for recurrent headaches in adults. *Neurol Sci* 2007;28 Suppl 2:S70-7.
248. US Headache Consortium. Evidence-based guidelines for migraine headache: behavioral and physical treatments. [cited 17 Oct 2008]. Available from url: <http://www.aan.com/professionals/practice/pdfs/g10089.pdf>

249. Bronfort G, Nilsson N, Haas M, Evans R, Goldsmith CH, Assendelft WJ, et al. Non-invasive physical treatments for chronic/recurrent headache (Cochrane Review). In: The Cochrane Library, Issue 3. London: Wiley; 2004.
250. Fernandez-de-Las-Penas C, Alonso-Blanco C, Cuadrado ML, Miangolarra JC, Barriga FJ, Pareja JA. Are manual therapies effective in reducing pain from tension-type headache?: a systematic review. *Clin J Pain* 2006;22(3):278-85.
251. Anderson RE, Seniscal C. A comparison of selected osteopathic treatment and relaxation for tension-type headaches. *Headache* 2006;46(8):1273-80.
252. van Ettekovén H, Lucas C. Efficacy of physiotherapy including a craniocervical training programme for tension-type headache; a randomized clinical trial. *Cephalalgia* 2006;26(8):983-91.
253. Allais G, De Lorenzo C, Quirico PE, Lupi G, Airola G, Mana O, et al. Non-pharmacological approaches to chronic headaches: transcutaneous electrical nerve stimulation, lasertherapy and acupuncture in transformed migraine treatment. *Neurol Sci* 2003;24 Suppl 2:S138-42.
254. Griggs C, Jensen J. Effectiveness of acupuncture for migraine: critical literature review. *J Adv Nurs* 2006;54(4):491-501.
255. Melchart D, Linde K, Berman B, White A, Vickers A, Allais G, et al. Acupuncture for idiopathic headache (Cochrane Review). In: The Cochrane Library, Issue 1. London: Wiley; 2001.
256. Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, et al. Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis. *Health Technol Assess* 2004;8(48):1-50.
257. Alecrim-Andrade J, Maciel-Junior JA, Cladellas XC, Correa-Filho HR, Machado HC. Acupuncture in migraine prophylaxis: a randomized sham-controlled trial. *Cephalalgia* 2006;26(5):520-9.
258. Diener HC, Kronfeld K, Boewing G, Lungenhausen M, Maier C, Molsberger A, et al. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurol* 2006;5(4):310-6.
259. Karst M, Reinhard M, Thum P, Wiese B, Rollnik J, Fink M. Needle acupuncture in tension-type headache: a randomized, placebo-controlled study. *Cephalalgia* 2001;21(6):637-42.
260. Melchart D, Streng A, Hoppe A, Brinkhaus B, Witt C, Wagenpfeil S, et al. Acupuncture in patients with tension-type headache: randomised controlled trial. *BMJ* 2005;331(7513):376-82.
261. Al-Ani MZ, Davies SJ, Gray RJ, Sloan P, Glenny AM. Stabilisation splint therapy for temporomandibular pain dysfunction syndrome (Cochrane Review). In: The Cochrane Library, Issue 1. London: Wiley; 2004.
262. Koh H, Robinson PG. Occlusal adjustment for treating and preventing temporomandibular joint disorders (Cochrane Review). In: The Cochrane Library, Issue 1. London: Wiley; 2003.
263. Jokstad A, Mo A, Krogstad BS. Clinical comparison between two different splint designs for temporomandibular disorder therapy. *Acta Odontol Scand* 2005;63(4):218-26.
264. Ernst E. Homeopathic prophylaxis of headaches and migraine: a systematic review. *J Pain Symptom Manage* 1999;18:353-7.
265. Pittler MH, Ernst E. Feverfew for preventing migraine (Cochrane Review). In: The Cochrane Library, Issue 1. London: Wiley; 2004.
266. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH. Efficacy and safety of 6.25 mg t.i.d. feverfew CO₂-extract (MIG-99) in migraine prevention—a randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia* 2005;25(11):1031-41.
267. Lipton RB, Göbel H, Einhüpl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004;63(12):2240-4.
268. Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005;64(4):713-5.
269. Prousky J, Seely D. The treatment of migraines and tension-type headaches with intravenous and oral niacin (nicotinic acid): systematic review of the literature. *Nutrition J* 2005;4:3.
270. Cete Y, Dora B, Ertan C, Ozdemir C, Oktay C. A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the emergency department. *Cephalalgia* 2005;25(3):199-204.
271. Frank LR, Olson CM, Shuler KB, Gharib SF. Intravenous magnesium for acute benign headache in the emergency department: a randomized double-blind placebo-controlled trial. *Can J Emerg Med* 2004;6(5):327-32.
272. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50(2):466-70.
273. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004;44(9):885-90.
274. Zidverc-Trajkovic J, Pavlovic AM, Mijajlovic M, Jovanovic Z, Sternic N, Kostic VS. Cluster headache and paroxysmal hemicrania: differential diagnosis. *Cephalalgia* 2005;25(4):244-8.
275. Mannix LK, Savani N, Landy S, Valade D, Shackelford S, Ames M, et al. Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. *Headache* 2007;47(7):1037-1049.

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[Intervention Review]

Non-invasive physical treatments for chronic/recurrent headache

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ABSTRACT

Background

Non-invasive physical treatments are often used to treat common types of chronic/recurrent headache.

Objectives

To quantify and compare the magnitude of short- and long-term effects of non-invasive physical treatments for chronic/recurrent headaches.

Search strategy

We searched the following databases from their inception to November 2002: MEDLINE, EMBASE, BIOSIS, CINAHL, Science Citation Index, Dissertation Abstracts, CENTRAL, and the Specialised Register of the Cochrane Pain, Palliative Care and Supportive Care review group. Selected complementary medicine reference systems were searched as well. We also performed citation tracking and hand searching of potentially relevant journals.

Selection criteria

We included randomized and quasi-randomized controlled trials comparing non-invasive physical treatments for chronic/recurrent headaches to any type of control.

Data collection and analysis

Two independent reviewers abstracted trial information and scored trials for methodological quality. Outcomes data were standardized into percentage point and effect size scores wherever possible. The strength of the evidence of effectiveness was assessed using pre-specified rules.

Main results

Twenty-two studies with a total of 2628 patients (age 12 to 78 years) met the inclusion criteria. Five types of headache were studied: migraine, tension-type, cervicogenic, a mix of migraine and tension-type, and post-traumatic headache. Ten studies had methodological quality scores of 50 or more (out of a possible 100 points), but many limitations were identified. We were unable to pool data because of study heterogeneity.

For the prophylactic treatment of migraine headache, there is evidence that spinal manipulation may be an effective treatment option with a short-term effect similar to that of a commonly used, effective drug (amitriptyline). Other possible treatment options with weaker evidence of effectiveness are pulsating electromagnetic fields and a combination of transcutaneous electrical nerve stimulation [TENS] and electrical neurotransmitter modulation.

For the prophylactic treatment of chronic tension-type headache, amitriptyline is more effective than spinal manipulation during treatment. However, spinal manipulation is superior in the short term after cessation of both treatments. Other possible treatment options with weaker evidence of effectiveness are therapeutic touch; cranial electrotherapy; a combination of TENS and electrical neurotransmitter modulation; and a regimen of auto-massage, TENS, and stretching. For episodic tension-type headache, there is evidence that adding spinal manipulation to massage is not effective.

For the prophylactic treatment of cervicogenic headache, there is evidence that both neck exercise (low-intensity endurance training) and spinal manipulation are effective in the short and long term when compared to no treatment. There is also evidence that spinal manipulation is effective in the short term when compared to massage or placebo spinal manipulation, and weaker evidence when compared to spinal mobilization.

There is weaker evidence that spinal mobilization is more effective in the short term than cold packs in the treatment of post-traumatic headache.

Authors' conclusions

A few non-invasive physical treatments may be effective as prophylactic treatments for chronic/recurrent headaches. Based on trial results, these treatments appear to be associated with little risk of serious adverse effects. The clinical effectiveness and cost-effectiveness of non-invasive physical treatments require further research using scientifically rigorous methods. The heterogeneity of the studies included in this review means that the results of a few additional high-quality trials in the future could easily change the conclusions of our review.

PLAIN LANGUAGE SUMMARY

Non-invasive physical treatments for chronic/recurrent headaches

Various physical treatments are often used instead of, or in addition to, medications to treat headaches. Evidence from controlled trials suggests that several non-invasive physical treatments may help prevent chronic/recurrent headaches. Spinal manipulation may be effective for migraine and chronic tension-type headache. Both spinal manipulation and neck exercises may be effective for cervicogenic headache. Weaker evidence suggests that other treatments may also be effective: pulsating electromagnetic fields and transcutaneous electrical nerve stimulation (TENS) for migraine, and therapeutic touch, cranial electrotherapy, TENS, and a combination of self-massage/TENS/stretching for tension-type headache. Although none of these treatments has conclusive evidence for effectiveness, all appear to be associated with little risk of serious adverse effects.

BACKGROUND

Headache is an extremely common complaint in the industrialized world, with a 1-day prevalence in the general population of approximately 16% (Rasmussen 1991). Migraine affects 10% to 12% of the population annually (Stewart 1992), while ten-

sion-type headache affects over 38% (Schwartz 1998). Although headache is normally a benign disorder and most cases are moderate or mild, the human and socioeconomic impact is considerable due to lost work days and days with reduced work efficiency (Pryse-

EVIDENCE-BASED GUIDELINES FOR THE CHIROPRACTIC TREATMENT OF ADULTS WITH HEADACHE

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ABSTRACT

Objective: The purpose of this manuscript is to provide evidence-informed practice recommendations for the chiropractic treatment of headache in adults.

Methods: Systematic literature searches of controlled clinical trials published through August 2009 relevant to chiropractic practice were conducted using the databases MEDLINE; EMBASE; Allied and Complementary Medicine; the Cumulative Index to Nursing and Allied Health Literature; Manual, Alternative, and Natural Therapy Index System; Alt HealthWatch; Index to Chiropractic Literature; and the Cochrane Library. The number, quality, and consistency of findings were considered to assign an overall strength of evidence (strong, moderate, limited, or conflicting) and to formulate practice recommendations.

Results: Twenty-one articles met inclusion criteria and were used to develop recommendations. Evidence did not exceed a moderate level. For migraine, spinal manipulation and multimodal multidisciplinary interventions including massage are recommended for management of patients with episodic or chronic migraine. For tension-type headache, spinal manipulation cannot be recommended for the management of episodic tension-type headache. A recommendation cannot be made for or against the use of spinal manipulation for patients with chronic tension-type headache. Low-load craniocervical mobilization may be beneficial for longer term management of patients with episodic or chronic tension-type headaches. For cervicogenic headache, spinal manipulation is recommended. Joint mobilization or deep neck flexor exercises may improve symptoms. There is no consistently additive benefit of combining joint mobilization and deep neck flexor exercises for patients with cervicogenic headache. Adverse events were not addressed in most clinical trials; and if they were, there were none or they were minor.

Conclusions: Evidence suggests that chiropractic care, including spinal manipulation, improves migraine and cervicogenic headaches. The type, frequency, dosage, and duration of treatment(s) should be based on guideline recommendations, clinical experience, and findings. Evidence for the use of spinal manipulation as an isolated intervention for patients with tension-type headache remains equivocal. (*J Manipulative Physiol Ther* 2011;34:274-289)

Key Indexing Terms: *Spinal Manipulation; Migraine Disorders; Tension-Type Headache; Post-traumatic Headache; Practice Guideline; Chiropractic*

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Wearable Cardiac Defibrillator Vests

Question: Should wearable cardiac defibrillator vests be included on the Prioritized List?

Question source: Tracy Muday, MD; Medical Director of Western Oregon Advanced Health CCO

Issue: DMAP was asked about whether wearable cardiac defibrillator vests (WCDs) are currently covered. While they are currently not on the fee schedule nor covered, a number of requests have been approved. The Medicare allowable is \$2704.94/month, and these are frequently used for about 3 months.

Muday shared that most of the requests are for patients who have had an MI and are in the recommended waiting period after MI before an implantable defibrillator is placed or with cardiomyopathy and EF <35% but still undergoing optimization of medical therapy. Waiting periods required in current Medicare coverage criteria include the following (CMS 2005): 40 days after acute MI, 3 months after CABG or PCI or NICM.

WCDs are used by patients at high risk of arrhythmias to attempt to prevent sudden cardiac death (SCD). High risk patients include certain patients with structural heart disease, history of myocardial infarction, certain types of cardiomyopathy, or who have undergone revascularization for coronary artery stenosis. Implantable cardioverter-defibrillators (ICDs) are the standard tool used for secondary prevention for individuals who already experienced (and survived) cardiac arrest or for the primary prevention of SCD among these high risk patients. For some of these conditions, a waiting period is recommended before implantation of an ICD, either because randomized trials have not shown a benefit of ICD during the waiting period, or because ventricular function may improve during the waiting period, making implantation of the ICD unnecessary. In addition, there are circumstances in which an ICD is temporarily contraindicated, such as when infection requires removal of an implanted ICD. There may also be logistical reasons for a delay in implantation of an ICD. In these circumstances, it has been proposed that these patients receive a wearable cardioverter-defibrillator (WCD) to reduce their risk for SCD.

The only WCD device on the market, the LifeVest®, was approved by the US Food and Drug Administration (US FDA) in 2002. The vest includes an elastic belt and shoulder straps that hold four dry, non-adhesive sensing electrodes and three defibrillator electrodes. A monitor worn around the waist holds a battery, the defibrillator, an alarm system, and response buttons that prevent the device from shocking inappropriately.

Wearable Cardiac Defibrillator Vests

Current List Status

Code	Code Description	Placement
K0606	Automatic external defibrillator, with integrated electrocardiogram analysis, garment type	Ancillary
K0607	Replacement battery for automated external defibrillator, garment type only, each	Ancillary
K0608	Replacement garment for use with automated external defibrillator, each	Ancillary
K0609	Replacement electrodes for use with automated external defibrillator, garment type only, each	Ancillary
93745	Initial set-up and programming by a physician or other qualified health care professional of wearable cardioverter-defibrillator includes initial programming of system, establishing baseline electronic ECG, transmission of data to data repository, patient instruction in wearing system and patient reporting of problems or events	Ancillary

Lines including ICD placement (October 1, 2014/January 1, 2015 Prioritized Lists)

76/73 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION
 109/103 CARDIOMYOPATHY, HYPERTROPHIC MUSCLE
 (122)/115 CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART [note: not on line 122 for October 1, 2014]
 195/193 CHRONIC ISCHEMIC HEART DISEASE
 304/286 LIFE-THREATENING CARDIAC ARRHYTHMIAS
 376/350 CARDIAC ARRHYTHMIAS

Wearable Cardiac Defibrillator Vests

Evidence summary

MED, 2014

- 1) N=2 technology assessments, BCBS 2010 and Hayes 2012.
 - a. Most authors of included studies had significant conflicts of interest
- 2) Evidence is limited by the lack of controlled trials
- 3) The WCD correctly identifies and effectively defibrillates VT and VF. However, device use requires correct assembly by the patient, which may limit effectiveness. Compliance with wearing the device ranges from an average of 14 to 21 hours per day, and device discomfort and inconvenience results in a significant number of patients who discontinue use.
- 4) There is not sufficient evidence about the ability of the WCD, used either as bridge or destination therapy, to affect mortality. Extrapolation from randomized trials of ICDs may be informative for WCD, but have not shown that an ICD implanted fewer than 40 days post-MI improve mortality. There is no evidence to suggest that WCD would perform better. The same is true for early implantation of an ICD in patients who are post-CABG. Implantation at the time of CABG compared to no implantation resulted in no mortality benefit but an increase in wound infections. Similarly, there is no evidence to suggest that WCD would perform differently. There is no evidence specifically addressing patients post-MI more than 40 days or post-CABG either more or less than 90 days
- 5) Harms: Inappropriate shocks from the WCD occur at a rate of approximately 0.67% to 1.4% per month. Burns from inappropriate shocks have been reported, and shock delivery can be interfered with by pacemakers or incorrect assembly of the device.

California Technology Assessment Forum 2009

- 1) Review included uncontrolled case series and case reports and one multicenter prospective trial; conclusions based mainly on the one trial
- 2) The limited scientific evidence does not permit conclusions concerning the effectiveness of the WCD regarding health outcomes for persons at risk of SCD
- 3) The WCD has not been shown to be as effective as the ICD in treatment of patients who would have otherwise qualified for one
- 4) The current literature is insufficient to conclude if the WCD should be offered to patients as an alternative to the ICD when use of an ICD is not feasible.
- 5) The peer reviewed, published data are not sufficient to conclude that the efficacy and safety of the WCD has been established in the investigational setting, let alone under conditions of usual medical practice.
- 6) It is recommended that the use of a wearable cardioverter defibrillator (WCD) for patients at risk for sudden cardiac arrest and who are not candidates for or refuse an implantable cardioverter defibrillator (ICD) does not meet CTAF TA criteria for efficacy and improvement in health outcomes.

Wearable Cardiac Defibrillator Vests

Medicare LCD for Automatic External Defibrillators

Automatic external defibrillators are covered for beneficiaries at high risk for sudden cardiac death (SCD) due to one of the conditions described under I or II. It is expected the ordering physician be experienced in the management of beneficiaries at risk for SCD.

- I. A wearable defibrillator (K0606) is covered for beneficiaries if they meet one of the criteria (1-4), described below:
 1. A documented episode of ventricular fibrillation or a sustained, lasting 30 seconds or longer, ventricular tachyarrhythmia. These dysrhythmias may be either spontaneous or induced during an electrophysiologic (EP) study, but may not be due to a transient or reversible cause and not occur during the first 48 hours of an acute myocardial infarction; or
 2. Familial or inherited conditions with a high risk of life-threatening ventricular tachyarrhythmia such as long QT syndrome or hypertrophic cardiomyopathy; or
 3. Either documented prior myocardial infarction or dilated cardiomyopathy and a measured left ventricular ejection fraction less than or equal to 0.35; or
 4. A previously implanted defibrillator now requires explantation

Other policies

1) BCBS 2014

- a. Medically Necessary: The wearable cardioverter defibrillator (WCD) is considered medically necessary for individuals at high-risk of sudden cardiac arrest, who meet the following criteria:
 - i. Individuals must meet the medical necessity criteria for an implantable cardioverter defibrillator (ICD); AND
 - ii. Individuals must have ONE of the following documented medical contraindications to ICD implantation:
 1. Those awaiting a heart transplantation - on waiting list and meet medical necessity criteria for heart transplantation; or
 2. Those with a previously implanted ICD that requires explantation due to infection with waiting period before ICD reinsertion; or
 3. Those with an infectious process or other temporary condition that precludes initial implantation of an ICD.

Wearable Cardiac Defibrillator Vests

HERC Staff Assessment

There is no evidence that wearable cardiac defibrillators (WCDs) reduce mortality based on the current peer reviewed literature. There is no evidence that they improve outcomes when used during the waiting period for implantable cardiac defibrillator (ICD) placement or in other situations in which an ICD is not indicated. Current major carriers generally limit coverage of WCDs to those limited situations in which an ICD is indicated but placement cannot be done due to infection or placement on a cardiac transplant waiting list.

HERC Staff Recommendations (October 1, 2014 PL/January 1, 2015 PL):

- 1) Adopt the following new ancillary guideline regarding wearable cardiac defibrillators
- 2) Alternative: place on the Excluded List due to lack of evidence of effectiveness

ANCILLARY GUIDELINE AXX WEARABLE CARDIAC DEFIBRILLATORS

Wearable cardiac defibrillators (CPT 93745, HCPCS K0606-K0609) is a covered benefit for patients who would otherwise qualify for implantable cardioverter defibrillator (ICD) placement but for whom ICD placement is contraindicated due to

- 1) Placement on heart transplant waiting list
- 2) A previous ICD requiring explantation due to infection with a waiting period before ICD re-insertion
- 3) An infectious process or other temporary condition (not including waiting period after acute MI, CABG or PCI or NICM) that precludes initial implantation of an ICD.

TITLE: **Wearable Cardioverter Defibrillator for Patients at
Risk for Sudden Cardiac Arrest**

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WEARABLE CARDIOVERTER DEFIBRILLATOR FOR PATIENTS AT RISK FOR SUDDEN CARDIAC ARREST

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) is asked to review the scientific evidence for the use of a wearable cardioverter defibrillator (WCD) for patients at risk for sudden cardiac arrest and who are not candidates for or refuse an implantable cardioverter defibrillator (ICD). This assessment reviews the peer reviewed, published trials of the only FDA approved WCD (the Zoll Lifecor LifeVest, www.zoll.com).

BACKGROUND

Sudden cardiac death (SCD), defined as deaths attributable to a cardiac etiology occurring less than one hour from a sudden, terminal event in a previously stable patient, is a significant public health problem accounting for 50% of all cardiac mortality in the United States^{1, 2}. Two-thirds of these deaths are in persons with no known cardiac history or with a history of heart disease but considered to be low risk. It is estimated that SCD is responsible for 200,000 to 450,000 deaths per year in the United States³ or one new event every two minutes⁴. Most SCD occurs outside of the hospital (in fact, most commonly in the home)⁴ and despite the fact that most of these persons have potentially reversible arrhythmias, very few (1% to 5%) survive to hospital discharge^{5, 6}. Prior studies have suggested that there is a direct correlation between time to defibrillation and survival³. Experts estimate that for each minute of ventricular fibrillation survival is reduced by ten percent⁷.

Ventricular fibrillation (VF) is the most common underlying electrophysiological (EP) disturbance in persons with SCD, but rapid ventricular tachycardia (VT) and bradyarrhythmias such as electromechanical dissociation have also been described¹. Coronary artery disease is the most common underlying medical condition leading to SCD, in addition to acquired or inherited cardiomyopathies, diseases of the aorta, primary electrophysiological processes and other conditions such as toxic ingestions or electrolyte disturbances. Other risk factors include history of diabetes mellitus, smoking, sedentary life-style and male gender. Patients are at increased

risk of SCD following an acute myocardial infarction (MI), with the greatest risk being six to 18 months following the acute event. Risk of SCD increases with the extent of damage to the myocardium as can be assessed through measurement of the ejection fraction.

Approaches to prevention of SCD include standard pharmacotherapy such as ACE inhibitors, beta blockers and statins; anti-arrhythmic therapy; and placement of an ICD in selected patients. Two large studies have shown a reduction in mortality with use of an ICD in primary prevention for patients with congestive heart failure (CHF)^{8, 9}. Although both studies had large relative risk reductions, they had much smaller absolute risk reductions and experts have attempted to identify which at-risk patients would most benefit from ICD placement. Various risk factors have been identified, such as ischemic heart disease, decreased left ventricular ejection fraction, and structural heart disease, and various risk stratification testing procedures have been proposed, such as standard and signal average electrocardiogram (EKG) and EP testing with programmed electrical stimulation in the EP lab. However, these tests may fail to identify a substantial portion of high-risk patients, as well as falsely predict increased risk in patients who never experience SCD. In a meta-analysis, no single method appeared to perform better than the others; however, a stepwise use of non-invasive methods, followed by an invasive EP study was able to stratify the majority (92%) of the patients¹⁰.

Lifecor LifeVest™

According to the manufacturer, the current LifeVest™ system is the third generation wearable defibrillator (www.lifecor.com). Unlike an ICD, the LifeVest™ is worn outside the body and consists of several main components: a lightweight garment worn under the patient's clothing to hold the device components; an electrode belt with sensing electrodes to continuously monitor the patient's heart and therapy electrodes for delivering a shock; a monitor and alarm module. If a life-threatening ventricular tachyarrhythmia is detected, the device alerts the patient with visual, audible and tactile alarms prior to delivering a shock, and thus allows a conscious patient to disarm the device so that a shock is not delivered to a conscious patient. If the patient is unconscious, the device releases a gel over the therapy electrodes and delivers a biphasic electrical shock (calibrated to the patient's rhythm disturbance) to restore normal rhythm. It generally takes 20 seconds for the monitor to detect a serious arrhythmia and up to 60 seconds

to deliver a shock of 75 to 150 joules. Up to five shocks can be delivered for each dysrhythmia. A web based data storage and retrieval system allows physicians to access patient data stored in the database.

Potential patient groups who may benefit from the LifeVest™ technology are those at high risk for SCD but who are not candidates for or refuse an ICD; this may include: post- MI patients with complications, cardiac surgery patients with complications, heart-transplant waiting list patients, advanced heart-failure patients, patients undergoing drug loading with potentially pro-arrhythmic medications, patients who need an ICD but have a condition that prevents or delays surgery (such as an infected ICD pocket), and patients who do not want to undergo surgery or have an implant (www.lifecor.com). In the Food and Drug Administration (FDA) pivotal trial, the two patient populations included for study were: 1) patients waiting for a heart transplant or with equivalent cardiac status (New York Heart Association Class III or IV heart failure and an ejection fraction (EF) below 30 percent; and 2) acute MI patients and those immediately following a coronary artery bypass graft procedure who had experienced ventricular fibrillation or tachycardia within the first 48 hours or a left ventricular EF of less than 30 percent. Contraindications to use of the WCD include: 1) patient already has an ICD implanted and operating; 2) has a vision or hearing problem that interferes with hearing or reading the WCD messages; 3) takes medication that interferes with reacting to the WCD alarm; 4) unable or not willing to continuously wear the WCD; 5) childbearing age and not attempting to prevent pregnancy (www.lifecor.com).

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The LIFECOR Wearable Cardioverter Defibrillator (WCD®) 2000 System (Zoll Lifecor, Inc., Pittsburgh, PA) received FDA premarket approval through the PMA process on December 18, 2001. The device is indicated for adult patients who are at risk for sudden cardiac arrest and are not candidates for or refuse an implantable defibrillator.

TA criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, EMBASE, Cochrane clinical trials and reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “wearable cardioverter defibrillator”, “wearable defibrillator”, “wearable automated defibrillator”, and “LifeVest™” from 1966 to December 2008. The bibliographies of systematic reviews and key articles were manually searched for additional references. Abstracts of citations were reviewed and all relevant articles reviewed in full.

The published, peer reviewed literature of the wearable cardioverter defibrillator consists of uncontrolled case series and case reports and one multicenter prospective trial (Feldman 2004) that served as the pivotal clinical trial for FDA approval of the device in 2001. The main outcomes assessed included ability of the LifeVest to successfully detect and treat potentially lethal ventricular arrhythmias in various groups of high-risk ambulatory patients, the ability of the LifeVest to deliver biphasic rather than monophasic shocks, and the ability of the LifeVest to accurately identify VF. Secondary outcomes included the rate of unnecessary shocks, the acceptability and comfort of the LifeVest and adverse reactions associated with the vest.

Overall, the limited scientific evidence does not permit conclusions concerning the effectiveness of the WCD regarding health outcomes for persons at risk of SCD. The current evidence is limited to one combined pivotal trial¹¹ with a precursor device and a small number of events. A confirmatory multi-center cohort study examining the impact of the WCD on mortality and quality of life in patients who meet criteria for but are unable (or perhaps unwilling) to have an ICD is needed before definitive conclusions can be made regarding its safety and effectiveness in the general population. In this population of patients who clearly meet current criteria for ICD it would not be appropriate to demand level 1 evidence (i.e. from a randomized clinical trial (RCT) before a determination can be made regarding efficacy and safety of the device. However, for patients who do not meet current criteria for an ICD but are considered to be at



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

risk for SCD (for example, patients s/p acute MI with reduced EF) a RCT of WCD compared with AED or no treatment with mortality outcome data is recommended before the safety and efficacy of the device can be evaluated for use in clinical practice.

41 additional references were reviewed, but did not meet criteria for inclusion in this assessment. (References 23 -63).

Level of evidence: 4, 5

TA Criterion 2 *is not* met.

TA Criterion 3: The technology must improve net health outcomes.

Auricchio (1998) report on a small study in Germany in which 15 survivors of sudden cardiac arrest (SCA) due to VT/VF were fitted with a monophasic first generation WCD and then underwent EP testing prior to hospital discharge¹². Five patients already had an ICD that was inactivated during the study. An episode of VF was successfully induced in ten of the 15 patients and the WCD correctly identified and successfully terminated the induced VT/VF in nine of the ten arrhythmias with a single 230-joule shock. In the one unsuccessful attempt, the electrodes had been inadvertently disconnected.

Reek (2003) report on a study conducted in Germany in 12 patients undergoing EPS testing for VF¹³. The study aim was to determine whether the LifeVest could effectively deliver a biphasic rather than monophasic shock. They found that induced VF was successfully terminated in 22 episodes with a single 70 or 100 joule biphasic shock. They conclude however, that the WCD should be programmed to deliver the maximum output of 150 joules when used in ambulatory patients.

Feldman (2004) report on a prospective, non-randomized multi-center trial (the WEARIT and BIROAD studies) designed to assess the safety and efficacy of a WCD in treating ventricular tachyarrhythmias in patients between 18 and 75 years of age at high risk for SCA but not eligible for an ICD or receipt of an ICD would be delayed for several months¹¹. Historical

controls of emergency medical services and SCA survivorship and reports of ICD unnecessary shock frequency were used to establish outcome criterion. These studies began as separate studies at 18 centers in the US and one cite in Germany but were combined at the request of the FDA. The WEARIT study enrolled patients with New York Heart Association (NYHA) functional Class III or IV heart failure and EF of < 0.30 , including patients on a heart transplant list. The BIROAD study enrolled patients with a recent MI complicated by VT within 48 hours of the event, and/or an EF of 0.30 three days after the infarct or an episode of syncope or SCA at least 48 hours after an MI but not candidates for an ICD. Other patients enrolled in BIROAD included: 1) patients with VT/VF, SCA or syncope within 48 hours of coronary artery bypass grafting (CABG) but unable to receive an ICD; 2) EF < 0.30 at least three days after CABG; 3) ICD candidates not expected to receive a device for at least four months and 5) met criteria for ICD but refused implantation. Patients were excluded from both studies if they were unable to use or wear the device, were DNR, participating in another clinical trial, were not seen daily by a caregiver or had a non-cardiac terminal illness. The study device used a monophasic wave form with a maximum output of 285 joules. The primary study endpoint was successful resuscitation in at least 25% of events at a confidence level of 90% and power of at least 50%. The comparison rate of 25% success was obtained by comparison to historical controls of patients who called 911 after SCA. All data were reviewed by an independent monitoring board. A total of 298 patients were enrolled (177 in WEARIT and 112 in BIROAD) when the study was terminated upon meeting the safety and efficacy endpoints. The participants were 82% male with an average age of 55 years and average EF or 23%. Overall, six successful defibrillations were observed in eight attempts for an estimated success rate of 69%.¹ Of the two unsuccessful attempts, the patients had inadvertently reversed the leads in both cases; one patient and the other were successfully resuscitated with an external defibrillator.² Two successful defibrillations occurred in the WEARIT patients (both in the same patient) and four successful defibrillations were reported in the BIROAD patients (two of these four were also in the same patient). They reported that six unnecessary shocks were delivered over a total of 901 months of use for a rate of 0.67% per month or eight percent per year of patient use. Five

¹ The FDA Summary of Safety and Effectiveness Data states that the device successfully treated 5 of 7 correctly diagnosed SCA events.

² The device has been redesigned so that lead reversal is no longer possible.

sudden deaths occurred in study participants who were not wearing the device at the time. Overall, 65 of the 289 subjects withdrew due to “comfort or lifestyle issues”, three additional withdrew due to adverse reactions and 46 patients received an ICD during the course of the study (most commonly as a result of increased ventricular arrhythmias). Seventeen patients complained of skin rash and itching associated with the device. One of 17 patients enrolled who met criteria for ICD use received an appropriate and successful shock from the WCD. The authors point out that the indications for ICD implantation have since expanded so that some of these patients would have been offered an ICD initially.

Patient Safety

In the FDA pivotal trial, 12 deaths were reported in the 289 patients enrolled. One death was considered device related. In this instance, the patient experienced a ventricular arrhythmia that was detected by the device but the device failed to deliver a shock due to incorrect placement of the front therapy electrode. (The device has been modified to prevent incorrect electrode placement).

Seven patients died at home while not wearing the device and four died in the hospital. Other device related adverse events in this trial included skin rashes in 5.9% (17 patients), inappropriate defibrillation in two percent, and pacemaker interaction in one patient.

Lapage (2008) report on a fatal device to device interaction between a WCD and a unipolar ventricular pacemaker in an 18 year old patient on a cardiac transplantation list for a failing Fontan circulation¹⁴. The patient had refused ICD placement and presented with cardiac arrest when the WCD failed to discharge due to artifacts from the unipolar ventricular pacemaker. Such interactions have also been reported between pacemakers and ICDs¹⁵.

In sum, the published peer reviewed literature of the WCD in clinical practice is limited to a single combined pivotal trial. This study (Feldman 2004) suggests that the WCD appears to be effective and safe as a cardioverter for resolving VT/VF in appropriate patients; however the overall number of events in this trial was small and the generalizability of the findings limited. Misuse of the device can lead to death and a subset of patients (22%) withdrew from the study

citing comfort and lifestyle” issues. Another large multi-center confirmatory study is needed to evaluate the WCD for use in select populations in the context of FDA and current clinical indications with careful ascertainment of appropriate outcomes of safety, morbidity and mortality and quality of life.

Ongoing Clinical Trials of WCD

One RCT, the “Vest Prevention of Early Sudden Death and PREDiction of ICD Therapies” (www.clinicaltrials.gov), is currently enrolling patients at more than 20 centers in the United States to evaluate the effectiveness of the LifeVest in preventing death from arrhythmia in patients in the two months after an MI. Patients will be randomized to receive the LifeVest or usual care with the primary outcome being all cause mortality at two to three months; non fatal cardiovascular events, VF/VT, compliance, quality of life, and cost will also be assessed. In the second part of the study, participants will be followed for up to eight years after receiving an ICD or Reveal monitor with the primary outcome being the occurrence of ventricular arrhythmias to improve the methods for predicting which patients will most benefit from an ICD.

TA criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The main potential alternatives to the Wearable Cardioverter Defibrillator are the automatic external defibrillator (AED), the ICD, antiarrhythmic drugs, surgical or transcatheter ablation and sudden cardiac arrest treatment by emergency medical services (EMS - generally activated by calling 911). Cardiac transplantation may be the ultimate alternative for some patients. Implantable cardioverter defibrillators (ICDs) were first implanted in humans in 1980. Since that time, scores of devices have been implanted, and the indications for the use of ICDs continue to be defined and expanded by clinical trials. The main indications for ICDs currently are for secondary prevention in patients with prior episodes of resuscitated VT or VF and with sustained hemodynamically unstable VT (not within 48 hours of an acute MI); for patients with

sustained VT and structural heart disease; for primary prevention in patients with prior MI and impaired EF and for patients with cardiomyopathy and impaired EF. Two large studies, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have shown a reduction in mortality with use of ICD in primary prevention for patients with CHF^{8, 9}. Although both studies had large relative risk reductions, they had much smaller absolute risk reductions and experts have attempted to identify which at-risk patients would most benefit from ICD placement. Having an ICD is not risk-free. Initial implantation requires anesthesia and a dye load, carrying risks with both of these as well as the risk of a wound infection¹⁶. In addition, inappropriate shocks may and can negatively impact quality of life. It has been estimated that for every 100 patients receiving an ICD approximately seven to eight will be saved by the device, the rest will experience an inappropriate shock or other complications or will not have the ICD fire at all¹⁷.

Several studies have found improved patient outcomes with use of the AED in public locations such as airports and casinos¹⁸⁻²¹. A clinical review concluded that use of AEDs by first responders and lay-persons reduces time to defibrillation and improves survival in persons with SCA⁶. It is estimated, however, that 70% of sudden cardiac arrests occur at home. AEDs are available for home use but this requires that someone be available to witness the event and are capable of using the AED rapidly and accurately. A recent study found that in survivors of MI at risk for SCA but who were not candidates for ICD, a home AED did not significantly improve survival²². Whether the WCD can improve outcomes in these patients is the major aim of an ongoing RCT.

Cardiac ablation involves localizing and selectively ablating abnormal conduction pathways percutaneously via catheter or less commonly during surgery. If successful, this procedure generally obviates the need for a WCD or ICD. While an important option for some patients with known or at risk for malignant VT/VF, this procedure will rarely be used as a potential alternative to WCD.

In sum, the ICD is the gold standard treatment for patients at risk for SCA/SCD who meet the current, evidence based guidelines for use. The WCD has been approved by the FDA for

patients who are not candidates for an ICD because of medical contraindications or who refuse an ICD. To date, the WCD has not been shown to be as effective as the ICD in treatment of patients who would have otherwise qualified for one. While a head to head trial of WCD and ICD is not the appropriate standard, the current literature is insufficient to conclude if the WCD should be offered to patients as an alternative to the ICD when use of an ICD is not feasible.

TA criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

The peer reviewed, published data are not sufficient to conclude that the efficacy and safety of the WCD has been established in the investigational setting, let alone under conditions of usual medical practice.

TA criterion 5 is not met.

CONCLUSION

SCA and death is a significant public health issue that is not adequately addressed by current medical, pharmacological or technological treatments. More than 160,000 out of hospital cardiac arrests occur in the US every year²². The WCD is a promising new technology that has the potential to ameliorate the risk of SCD in two major types of patients; 1) those who qualify for a permanent ICD but are unable or unwilling to have one implanted immediately (i.e. as a bridge to a permanent device), and 2) those felt to be at risk for SCA/SCD but who do not currently qualify for a permanent ICD or for whom the ICD may not be needed long term (e.g. patients immediately s/p acute MI or as a bridge to transplantation for patients awaiting cardiac transplant). Current FDA approval states that the Lifecor LifeVest (WCD) is indicated for adult patients at risk for sudden cardiac arrest and are not candidates for or refuse an ICD.

The existing peer reviewed literature consists of a single study (Feldman 2004) that found that use of the WCD was feasible in a heterogeneous population of patients in detecting and treating

VT/VF¹¹. It found that in patients with a variety of indications including as a bridge to cardiac transplant and in patients temporarily at risk for malignant ventricular arrhythmias (e.g. after MI or CABG) and who used the device for up to four months or until implantation of a permanent ICD, the WCD detected and successfully treated six of eight episodes of VT/VF. There were six unnecessary shocks delivered. This pivotal trial reported only short-term outcomes and did not examine the impact of the WCD on overall mortality compared with the current gold standard ICD or other alternatives such as the AED. Prior studies of ICDs have proven their effectiveness in reducing mortality for patients with life threatening ventricular arrhythmias and for those who previously survived SCA. Future studies of the WCD must examine the device's impact on overall mortality in selected patient populations.

It is unknown how many patients at risk for SCD refuse a permanent ICD and how compliant these patients would be with a WCD. In addition, the number of patients who are unable to receive an ICD or had the ICD removed because of infection or any other medical contraindication to ICD implantation is presumed to be small. And most patients felt to be too sick to receive an ICD would be unlikely to benefit from long term use of a WCD. It is difficult to draw definitive conclusions about the efficacy and safety of the WCD in these patient populations from the current peer reviewed literature.

The FDA indications state that the WCD is an appropriate alternative for patients at risk for SCD but who are unable or unwilling to have an ICD. Since it is known that most SCA/SCD that occur outside of the hospital take place at home⁴, this would suggest that the AED would be an effective intervention for patients at risk for SCD and a reasonable alternative to the WCD for these indications. To date, no trial has compared outcomes of the WCD with the AED

While overall the WCD appears to be safe, two patients died due to improper device set-up in the pivotal trial and almost one fourth of patients withdrew from the study due to discomfort or other lifestyle reasons. The WCD has since been redesigned to avoid improper use and to ease discomfort; whether this newest generation of the LifeVest can improve on these outcomes has not been studied in a clinical trial.

The WCD appears to be a potentially useful device for those patients who are at risk for sudden cardiac death but who are unable to receive an ICD or may not require a permanent ICD. Limited data from existing peer-reviewed literature is not adequate to address this question. Data from the ongoing RCT will help address some of the gaps in the current evidence.

RECOMMENDATION

It is recommended that the use of a wearable cardioverter defibrillator (WCD) for patients at risk for sudden cardiac arrest and who are not candidates for or refuse an implantable cardioverter defibrillator (ICD) *does not* meet CTAF TA criteria 2-5 for efficacy and improvement in health outcomes.

March 11, 2009

This is the first CTAF assessment of this technology.

The California Technology Assessment Forum panel voted to accept the recommendation.

RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)

The BCBSA Technology Evaluation Center (TEC) has not conducted a formal assessment of this technology.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

In the absence of a CMS NCD, policy decisions for the Wearable Defibrillator are determined by local carriers. Noridian Administrative Services provides access to this technology in California and several other states when patients meet specific criteria.

AMERICAN COLLEGE OF CARDIOLOGY, CALIFORNIA CHAPTER (CA ACC)

A CA ACC representative provided an opinion regarding the use of this technology.

ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death was published in the Journal of the American College of Cardiology in 2006. The report was developed in Collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. The Wearable Automatic Defibrillator is mentioned on page e271 6.5.3. Wearable Automatic Defibrillator. The guidelines are not specific as to the use of this device.

ABBREVIATIONS USED

CTAF	California Technology Assessment Forum
WCD	Wearable cardioverter defibrillator
ICD	Implantable cardioverter defibrillator
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia
MI	Myocardial infarction
EP	Electrophysiologic
CHF	Congestive heart failure
EKG	Electrocardiogram
FDA	Food and Drug Administration
DARE	Database of Abstracts of Reviews of Effects
RCT	Randomized clinical trial
SCA	Sudden cardiac arrest
NYHA	New York Heart Association
EF	Ejection fraction
CABG	Coronary artery bypass grafting
AED	Automatic external defibrillator
EMS	Emergency medical services
MADIT-II	Multicenter Automatic Defibrillator Implantation Trial II
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial

REFERENCES

1. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. Nov 24 1998;98(21):2334-2351.
2. Myerburg RJ, Castellanos A. Chapter 267: Cardiovascular collapse, cardiac arrest and sudden cardiac death. In: Fauci AS, Braunwald E, Kasper DL, et al., eds. *Harrison's Online-Harrison's Principles of Internal Medicine 17th edition*: McGraw-Hill; 2009.
3. Chan PS, Krumholz HM, Nichol G, Nallamothu BK. Delayed time to defibrillation after in-hospital cardiac arrest. *N Engl J Med*. Jan 3 2008;358(1):9-17.
4. Bardy GH, Lee KL, Mark DB, et al. Rationale and design of the Home Automatic External Defibrillator Trial (HAT). *Am Heart J*. Mar 2008;155(3):445-454.
5. Mosesso VN, Jr., Newman MM, Ornato JP, et al. Law Enforcement Agency Defibrillation (LEAD): proceedings of the National Center for Early Defibrillation Police AED Issues Forum. *Prehosp Emerg Care*. Jul-Sep 2002;6(3):273-282.
6. Marengo JP, Wang PJ, Link MS, Homoud MK, Estes NA, 3rd. Improving survival from sudden cardiac arrest: the role of the automated external defibrillator. *Jama*. Mar 7 2001;285(9):1193-1200.
7. Weaver WD, Peberdy MA. Defibrillators in public places--one step closer to home. *N Engl J Med*. Oct 17 2002;347(16):1223-1224.
8. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. Mar 21 2002;346(12):877-883.
9. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. Jan 20 2005;352(3):225-237.
10. Bailey JJ, Berson AS, Handelsman H, Hodges M. Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. *J Am Coll Cardiol*. Dec 2001;38(7):1902-1911.
11. Feldman AM, Klein H, Tchou P, et al. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. *Pacing Clin Electrophysiol*. Jan 2004;27(1):4-9.
12. Auricchio A, Klein H, Geller CJ, Reek S, Heilman MS, Szymkiewicz SJ. Clinical efficacy of the wearable cardioverter-defibrillator in acutely terminating episodes of ventricular fibrillation. *Am J Cardiol*. May 15 1998;81(10):1253-1256.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

13. Reek S, Geller JC, Meltendorf U, Wollbrueck A, Szymkiewicz SJ, Klein HU. Clinical efficacy of a wearable defibrillator in acutely terminating episodes of ventricular fibrillation using biphasic shocks. *Pacing Clin Electrophysiol.* Oct 2003;26(10):2016-2022.
14. LaPage MJ, Canter CE, Rhee EK. A fatal device-device interaction between a wearable automated defibrillator and a unipolar ventricular pacemaker. *Pacing Clin Electrophysiol.* Jul 2008;31(7):912-915.
15. Cohen AI, Wish MH, Fletcher RD, et al. The use and interaction of permanent pacemakers and the automatic implantable cardioverter defibrillator. *Pacing Clin Electrophysiol.* Jun 1988;11(6 Pt 1):704-711.
16. Gould PA, Krahn AD. Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories. *Jama.* Apr 26 2006;295(16):1907-1911.
17. Stevenson LW, Desai AS. Selecting patients for discussion of the ICD as primary prevention for sudden death in heart failure. *J Card Fail.* Aug 2006;12(6):407-412.
18. Caffrey SL, Willoughby PJ, Pepe PE, Becker LB. Public use of automated external defibrillators. *N Engl J Med.* Oct 17 2002;347(16):1242-1247.
19. Page RL, Joglar JA, Kowal RC, et al. Use of automated external defibrillators by a U.S. airline. *N Engl J Med.* Oct 26 2000;343(17):1210-1216.
20. Valenzuela TD, Roe DJ, Nichol G, Clark LL, Spaite DW, Hardman RG. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. *N Engl J Med.* Oct 26 2000;343(17):1206-1209.
21. Sanna T, La Torre G, de Waure C, et al. Cardiopulmonary resuscitation alone vs. cardiopulmonary resuscitation plus automated external defibrillator use by non-healthcare professionals: a meta-analysis on 1583 cases of out-of-hospital cardiac arrest. *Resuscitation.* Feb 2008;76(2):226-232.
22. Bardy GH, Lee KL, Mark DB, et al. Home use of automated external defibrillators for sudden cardiac arrest. *N Engl J Med.* Apr 24 2008;358(17):1793-1804.
23. *Summary of Safety and Effectiveness Data P010030 Lifecor, Inc. WCD 2000 System:* U.S. Food and Drug Administration; 2001.
24. *Wearable External Cardioverter Defibrillator for Ventricular Arrhythmia:* Kaiser-Interregional New Technologies Committee; October 21 2002.
25. *Wearable Cardioverter-Defibrillators:* Aetna; 2006.
26. *Cigna HealthCare Coverage Position Wearable Cardioverter Defibrillator and Automatic External Defibrillator:* Cigna; May 15, 2007.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

27. Abrahamson SD, Canzian S, Brunet F. Using simulation for training and to change protocol during the outbreak of severe acute respiratory syndrome. *Crit Care*. Feb 2006;10(1):R3.
28. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation*. Mar 26 2002;105(12):1453-1458.
29. Beauregard LA. Personal security: Clinical applications of the wearable defibrillator. *Pacing Clin Electrophysiol*. Jan 2004;27(1):1-3.
30. Capucci A, Villani GG, Rusticali G. Cost-effective use of a new wearable cardioverter defibrillator to protect patients at risk of SCA. *Europace Supplements*. 2003;4:A44-A45.
31. Chung MK, Szymkiewicz SJ, Joseph GK, Wilkoff BL. Robust Long-Term Cardiac Monitoring Using Dry, Nonadhesive Capacitive Electrodes. *JACC*. March 3 2004;43(5, Suppl A):141A.
32. Fetter JG, Benditt DG, Stanton MS. Electromagnetic interference from welding and motors on implantable cardioverter-defibrillators as tested in the electrically hostile work site. *J Am Coll Cardiol*. Aug 1996;28(2):423-427.
33. Gasparini G, Raviele A. A new wearable defibrillator: Initial single center experience. *Europace Supplements*. October 2003;4:A45.
34. Gronda E, Bourge RC, Costanzo MR, et al. Heart rhythm considerations in heart transplant candidates and considerations for ventricular assist devices: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. *J Heart Lung Transplant*. Sep 2006;25(9):1043-1056.
35. Gronefeld G, Hohnloser SH. What do implantable cardioverter/defibrillators teach us about the mechanisms of sudden cardiac death? *Cardiovasc Res*. May 2001;50(2):232-241.
36. Irnich W. A serious case of radiofrequency EMI, when an ICD wearer manipulated a remote control of a toy car. *Pacing Clin Electrophysiol*. Apr 1994;17(4 Pt 1):685.
37. Joseph GK, Szymkiewicz SJ, Wilkoff BL, Chung MK. Compliance and Effectiveness of the Wearable Cardioverter Defibrillator Vest. *JACC*. 2004;43(5 Suppl A):300A.
38. Krasteva VT, Papazov SP. Estimation of current density distribution under electrodes for external defibrillation. *Biomed Eng Online*. Dec 16 2002;1:7.
39. Krasteva VT, Papazov SP. Estimation of current density distribution under electrodes for external defibrillation. *Biomed Eng Online*. Dec 16 2002;1:7.
40. Lang CC, Hankins S, Hauff H, Maybaum S, Edwards N, Mancini DM. Morbidity and mortality of UNOS status 1B cardiac transplant candidates at home. *J Heart Lung Transplant*. Apr 2003;22(4):419-426.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

41. Lee KL, Hafley G, Fisher JD, et al. Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. *Circulation*. Jul 9 2002;106(2):233-238.
42. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation*. Jun 26 2007;115(25):3165-3172.
43. MacDonald RD, LeBlanc V, McArthur B, Dubrowski A. Performance of resuscitation skills by paramedic personnel in chemical protective suits. *Prehosp Emerg Care*. Apr-Jun 2006;10(2):254-259.
44. Maisel WH. Pacemaker and ICD generator reliability: meta-analysis of device registries. *Jama*. Apr 26 2006;295(16):1929-1934.
45. Maisel WH, Moynahan M, Zuckerman BD, et al. Pacemaker and ICD generator malfunctions: analysis of Food and Drug Administration annual reports. *Jama*. Apr 26 2006;295(16):1901-1906.
46. Maron BJ, Gohman TE, Kyle SB, Estes NA, 3rd, Link MS. Clinical profile and spectrum of commotio cordis. *Jama*. Mar 6 2002;287(9):1142-1146.
47. Meltendorf U. Using the Wearable Cardioverter Defibrillator-A Strategy for Bridging High Risk Patients After CABG. *Hearth Rhythm*. 2005;2(5, Suppl):S32.
48. Meltendorf U, Wollbruck A, Auricchio A, Reek S, Geller CJ, Klein H. The Wearable Defibrillator-a new Method to prevent Sudden Death. *PACE*. April 2000;23(4, Part II):606.
49. Mosesso VN, Jr., Newman MM, Ornato JP, Paris PM. Law enforcement agency defibrillation (LEA-D): proceedings of the National Center for Early Defibrillation Police AED Issues Forum. *Resuscitation*. Jul 2002;54(1):15-26.
50. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. Dec 26 1996;335(26):1933-1940.
51. Murray CL, Steffensen I. *Automated external defibrillators for home use*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2005.
52. Myers GE, Crick WF, King SW, et al. Latex versus iodinated contrast media anaphylaxis in the cardiac cath lab. *Cathet Cardiovasc Diagn*. Jul 1995;35(3):228-231.
53. Nilsson G, Wiberg S, Band S, Jonasson T. Postpausal ventricular fibrillation analyzed by Holter-ECG: a case report. *Pacing Clin Electrophysiol*. Dec 1992;15(12):2339-2343.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

54. Pignatelli G, Lolli G, Bottoni C, Tomasi C, Menozzi C. Use of a new wearable cardioverter defibrillator to reduce the risk of sudden cardiac death. *Europace Supplements*. October 2003;4:A45.
55. Reek S, Meltendorf U, Geller JC, Wollbruck A, Grund S, Klein HU. [The Wearable Cardioverter Defibrillator (WCD) for the prevention of sudden cardiac death -- a single center experience]. *Z Kardiol*. Dec 2002;91(12):1044-1052.
56. Reek S, Meltendorf U, Klein HU. [A wearable defibrillator for patients with an intermittent risk of arrhythmia]. *Dtsch Med Wochenschr*. Oct 11 2002;127(41):2127-2130.
57. Reek S, Meltendorf U, Wollbruck A, Szymkiewicz SJ, Klein H, Geller CJ. Clinical Efficacy of the Wearable Defibrillator in Acutely Terminating Episodes of Ventricular Fibrillation Using Biphasic Shocks. *PACE*. 2002;25(4 Part II):577.
58. Ricci R, Pignalberi C, Disertori M, et al. Efficacy of a dual chamber defibrillator with atrial antitachycardia functions in treating spontaneous atrial tachyarrhythmias in patients with life-threatening ventricular tachyarrhythmias. *Eur Heart J*. Sep 2002;23(18):1471-1479.
59. Schott R. Wearable defibrillator. *J Cardiovasc Nurs*. Apr 2002;16(3):44-52.
60. Suzzani P, Szymkiewicz SJ. The Lifecor Lifevest wearable cardioverter defibrillator. *Europace Supplements*. October 2003;4:A45.
61. Szymkiewicz SJ, Meltendorf U, Heilman MS, Klein H. Abstract 1771: Analysis of Sudden Cardiac Arrests During Wearable Defibrillator Use. *Circulation*. 2005;114(18, Suppl II):S32.
62. Traub D, Alpert B, Donahue B, Ganz L. Sudden cardiac arrest aborted by a wearable cardioverter-defibrillator in newly diagnosed non-ischemic cardiomyopathy. *Heath Rhythm*. 2007;4(5 Suppl):S101.
63. Wase A, Wilson A. Wearable Defibrillators: A New Tool in the Management of Ventricular Tachycardia/Ventricular Fibrillation. *EP Lab Digest*. 2005;12:22-24.



Medical Policy

Subject: Wearable Cardioverter Defibrillators

Policy #: MED.00055

Current Effective Date: 01/14/2014

Status: Reviewed

Last Review Date: 11/14/2013

Description/Scope

This document addresses the wearable cardioverter defibrillator, an external vest-like garment device that is intended to perform the same tasks as an implantable cardioverter defibrillator (ICD), without requiring any invasive procedures.

Position Statement

Medically Necessary:

The wearable cardioverter defibrillator (WCD) is considered **medically necessary** for individuals at high-risk of sudden cardiac arrest, who meet the following criteria:

1. Individuals must meet the medical necessity criteria for an implantable cardioverter defibrillator* (ICD); **AND**
2. Individuals must have ONE of the following documented medical contraindications to ICD implantation:
 - a. Those awaiting a heart transplantation - on waiting list and meet medical necessity criteria for heart transplantation;** **or**
 - b. Those with a previously implanted ICD that requires explantation due to infection with waiting period before ICD reinsertion; **or**
 - c. Those with an infectious process or other temporary condition that precludes initial implantation of an ICD.

* Refer to [SURG.00033 Implantable Cardioverter-Defibrillator \(ICD\)](#)

**Refer to [TRANS.00033 Heart Transplantation](#)

Investigational and Not Medically Necessary:

The wearable cardioverter defibrillator (WCD) is considered **investigational and not medically necessary** for all other indications, including but not limited to, the following:

- Individuals with a history of an acute myocardial infarction (MI) within the last 40 days;
- Individuals with drug-refractory class IV congestive heart failure (CHF) who are not candidates for heart transplantation;
- Individuals with a history of psychiatric disorders that interfere with the necessary care and follow-up;
- Individuals in whom a reversible triggering factor for ventricular tachycardia/ventricular fibrillation (VT/VF) can be definitely identified, such as ventricular tachyarrhythmias in evolving acute myocardial infarction or electrolyte abnormalities;
- Individuals with terminal illnesses.

Rationale

The U.S. Food and Drug Administration (FDA) granted clearance for the Lifecor Wearable Cardioverter Defibrillator (WCD[®]) 2000 system via premarket application approval in December 2001, based on clinical data submitted to the FDA by the manufacturer, which has subsequently been published in the peer-reviewed literature, and referred to as the BIROAD and WEARIT studies (Feldman, 2004). The trials consisted of prospective, non-randomized studies, which compared the outcomes of the WCD with historical controls of subjects suffering sudden cardiac arrest (SCD) who called 911 emergency services. While this study demonstrated that the WCD could detect arrhythmias and appropriately deliver a counter shock, its long-term efficacy will depend on user compliance, and from a practical perspective, the WCD cannot be continuously worn. For example, the BIROAD and WEARIT studies included 289 subjects; there were 12 deaths reported, and 50% occurred in those who were either not wearing the device or wearing it inappropriately. Additionally, 68 of the 289 subjects discontinued wearing the device due to comfort issues or adverse reactions. Therefore, an implantable cardiac defibrillator (ICD) is considered the gold standard and, as such, a WCD would be considered an alternative to an ICD only in the small subset that have co-morbidities or other contraindications for an ICD. For example, individuals with an infected ICD requiring removal may benefit from a WCD worn during the limited interim period until an ICD can be reimplanted. Additionally, a small subset awaiting heart transplantation may be considered at high risk for arrhythmia, but are not candidates for an ICD due to co-morbidities. A WCD may be considered an alternative to an ICD in these individuals while they are on the heart transplant waiting list.

There has been interest in offering WCDs to individuals in the immediate post myocardial infarction (MI) period, when they are considered at high risk of arrhythmia. However, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) demonstrated that an ICD is not indicated during this period (Hohnloser, 2004). The DINAMIT trial randomized 674 subjects to receive either an ICD or no ICD within 40 days of an MI. All participants had reduced ejection fractions (LVEF less than or equal to 35%) and impaired cardiac autonomic function. The primary outcome was mortality from any cause, and the secondary outcome was death from arrhythmia.

During a mean follow-up of 30 ± 13 months, there was no difference in overall mortality between the two groups. Of 120 subjects who died, 62 were in the ICD group, and 58 were in the control group. There were 12 deaths due to arrhythmia in the ICD group and 29 in the control group.

There were 50 deaths from nonarrhythmic causes in the ICD group, however, and 29 in the control group. The authors concluded that ICD therapy does not reduce overall mortality in high-risk subjects who have recently had an MI. Although ICD therapy was associated with a reduction in arrhythmia-related death, this was offset by an increase in nonarrhythmic-related death. While the nonrandomized BIROAD study investigated subjects treated with a WCD in the immediate post MI period, the results of the large randomized DINAMIT study provide a higher level of evidence, which may be extrapolated to WCD.

Two prospective, randomized, controlled trials compared the use of ICDs to that of conventional therapy: the Multi-Center Automatic Defibrillator Implantation Trial (MADIT; $n = 196$) and the Multi-Center Automatic Defibrillator Implantation Trial II (MADIT II; $n = 1,232$). Both trials were conducted on subjects with coronary artery disease (CAD) who had experienced MIs and who had reduced LVEFs. Both trials were well designed and of good quality. The observed all-cause mortality rate in the conventionally treated group was somewhat lower in MADIT II (19.8%, with average follow-up at 20 months) than in MADIT (38.6%, with average follow-up at 27 months), suggesting some differences in the baseline mortality risk between these two populations.

Both trials reported that ICD treatment resulted in more statistically significant reductions in all-cause mortality (primary endpoint) than conventional therapy did. The MADIT and MADIT II trials provide consistent evidence that individuals with CAD, prior MI and reduced LVEF who meet selection criteria for either trial have significantly reduced mortality when treated with ICDs than when given conventional therapy (Moss, 1996). However, results of the MADIT II trial concluded that risk of SCD in those with LVEF less than or equal to 30% increases as a function of

time from MI. The survival benefit associated with ICD placement appears to be greater for remote MI and remains substantial for up to (greater than or equal to) 15 years after MI. "There appeared to be a trend toward increasing survival benefit associated with ICD therapy as time from MI increased." These findings can also be extrapolated to use of the WCD device (Wilber, 2004).

To date, there have been few additional studies of the WCD. Rao evaluated the short- and long-term outcomes of individuals with congenital structural heart disease (CSHD) and those with inherited arrhythmias (IA) who received a WCD for the prevention of SCD. The study population included 162 subjects with CSHD (n = 43) and IA (n = 119) who were prospectively followed up in a nationwide registry from 2005 to 2010. The mortality rates were compared using Kaplan-Meier survival analysis. It was noted that subjects with CSHD had a greater frequency of left ventricular dysfunction (ejection fraction < 30%) than did those with IA (37% vs. 5%, respectively; p = 0.002). The predominant indication for WCD was pending genetic testing in the IA group and transplant listing in the CSHD group. Compliance with the WCD was similar in the 2 groups (91%). WCD shocks successfully terminated three ventricular tachyarrhythmias in the subjects with IA during a median follow-up of 29 days of therapy (corresponding to 23 appropriate WCD shocks per 100 subject-years). No arrhythmias occurred in the subjects with CSHD during a median follow-up of 27 days, and no subjects died while actively wearing the WCD. At 1 year of follow-up, the survival rates were significantly lower among the subjects with CSHD (87%) than among those with IA (97%, p = 0.02). The authors concluded that the data suggested the WCD can be safely used in high-risk adult individuals with IA and CSHD, although the subjects with IA showed a greater rate of ventricular tachyarrhythmias during therapy but significantly lower long-term mortality rates (Rao, 2011).

Background/Overview

The implantable cardioverter defibrillator (ICD) has been proven to be effective in reducing mortality in individuals with episodes of ventricular arrhythmias or in survivors of SCD, often seen in those with coronary artery disease (CAD). More recently, randomized studies, (i.e., MADIT I and MADIT II trials) have demonstrated that ICDs are effective prophylactic therapy in those who are considered at high risk for lethal arrhythmias, such as those with prior MI and reduced LVEF. ICDs consist of implantable leads in the heart that connect to a pulse generator implanted beneath the skin of the chest or abdomen. In the past, ICD placement required a thoracotomy, but current technology allows implantation with only a minor surgical procedure, with the cardiac leads placed percutaneously. Potential adverse effects of ICD placement are bleeding, infection, pneumothorax, and delivery of unnecessary countershocks.

The wearable cardioverter defibrillator (WCD) is an external device that is intended to perform the same tasks as an ICD, without requiring any invasive procedures. It consists of a vest that is worn continuously underneath the clothing. Part of this vest is the 'electrode belt' that contains the cardiac monitoring electrodes and the therapy electrodes that deliver a countershock. The vest is connected to a monitor with a battery pack and alarm module that is worn on the belt. The monitor contains the electronics that interpret the cardiac rhythm and determine when a countershock is necessary. The alarm module alerts the wearer to certain conditions by lights or voice messages. The U.S. Food and Drug Administration (FDA) gave clearance to the Lifecor WCD® 2000 system via premarket application approval in December 2001 for "Adult patients who are at risk for sudden cardiac arrest and are either not candidates for or refuse an implantable defibrillator." The trade name of the WCD 2000 System was changed to LifeVest™ in 2002, and the LIFECOR business was acquired by ZOLL Medical Corporation (Philadelphia, PA) in 2006.

Definitions

Cardiac arrhythmia: A disturbance in the electrical activity of the heart that manifests as an

abnormality in the heart rate or heart rhythm. Individuals with arrhythmias may experience a wide variety of symptoms ranging from palpitations to fainting.

Coronary artery: A pair of vessels that supply blood to the myocardium (middle layer of the walls of the heart).

Coronary artery disease: This condition involves narrowing of the coronary arteries that is sufficient enough to prevent adequate blood supply to the myocardium.

Defibrillation: A treatment in which an electronic device sends an electric shock to the heart to stop an extremely rapid, irregular heartbeat, in order to restore the normal heart rhythm.

Ejection fraction: A measure of ventricular contractility.

Electrophysiologic study of the heart: This is a test of the electrical conduction system of the heart (the system that generates the heart beat).

Fibrillation: This term refers to very rapid contractions or twitching of small muscle fibers in the heart.

Tachycardia: An abnormally rapid heart beat.

Ventricle: One of two lower chambers of the heart.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

93745	Initial set-up and programming by a physician or other qualified health care professional of wearable cardioverter-defibrillator, includes initial programming of system, establishing baseline electronic ECG, transmission of data to data repository, patient instruction in wearing system and patient reporting of problems or events

HCPCS

K0606	Automatic external defibrillator, with integrated electrocardiogram analysis, garment type

ICD-9 Diagnosis *[For dates of service prior to 10/01/2014]*
All diagnoses

ICD-10 Diagnosis *[For dates of service on or after 10/01/2014]*
All diagnoses

When services are Investigational and Not Medically Necessary:

For the procedure codes listed above when criteria are not met; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

References

Peer Reviewed Publications:

1. Auricchio A, Klein H, Geller CJ, et al. Clinical efficacy of the wearable cardioverter defibrillator in acutely terminating episodes of ventricular fibrillation. *Am J Cardiol.* 1998; 81(10):1253-1256.
2. Beauregard LA. Personal security: clinical applications of the wearable defibrillator. *Pacing Clin Electrophysiol.* 2004; 27(1):1-3.
3. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass surgery. The CABG-PATCH Trial Investigators. *N Engl J Med.* 1997; 337(22):1569-1575.
4. Boehmer JP. Device therapy for heart failure. *Am J Cardiol.* 2003; 91(suppl):53D-59D.
5. Chung MK, Szymkiewicz SJ, Shao M, et al. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. *J Am Coll Cardiol.* 2010; 56(3):194-203. Available at: <http://content.onlinejacc.org/article.aspx?articleid=1142987>. Accessed on October 21, 2013.
6. Epstein AE, Abraham WT, Bianco N, et al. Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post myocardial infarction. *Am Coll Cardiol.* 2013; (epub ahead of print).
7. Feldman AM, Klein H, Tchou P, et al. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: Results of the WEARIT/BIROAD. *Pacing Clin Electrophysiol.* 2004; 27(1):4-9.
8. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* 2004; 351(24):2481-2488.
9. Kao AC, Krause SW, Handa R, et al; Wearable defibrillator use In heart Failure (WIF) Investigators. Wearable defibrillator use in heart failure (WIF): Results of a prospective registry. *BioMed Cardiovas Disorders.* 2012; 12:123.
10. Klein HU, Meltendorf U, Reek S, et al. Bridging a temporary high risk of sudden arrhythmic death. Experience with the wearable cardioverter defibrillator (WCD). *Pacing Clin Electrophysiol.* 2010; 33(3):353-367.
11. Pouleur AC, Barkoudah E, Uno H, VALIANT Investigators, et al. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *Circ.* 2010; 122(6):597-602.
12. Rao M, Goldenberg I, Moss AJ, et al. Wearable Defibrillator in Congenital Structural Heart Disease and Inherited Arrhythmias. *Am J Cardiol.* 2011; 108(11):1632-1638.
13. Reek S, Geller JC, Meltendorf U, et al. Clinical efficacy of a wearable defibrillator in acutely terminating episodes of ventricular fibrillation using biphasic shocks. *Pacing Clin Electrophysiol.* 2003; 26(10):2016-2022.
14. Reek S, Meltendorf U, Geller JC, et al. The wearable cardioverter defibrillator (WCD) for the prevention of sudden cardiac death – a single center experience. *Z Kardiol.* 2002; 91(12):1044-1052 (abstract available in English; article in German).
15. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med.* 2005; 352(25):2581-2588.
16. Steinbeck G, Andresen D, Seidl K, et al; IRIS Investigators. Defibrillator implantation early after myocardial infarction. *N Engl J Med.* 2009; 361(15):1427-1436.
17. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation.* 2004; 109(9):1082-1084.
18. Zishiri ET, Williams S, Cronin EM, et al. Early risk of mortality after coronary artery revascularization in patients with left ventricular dysfunction and potential role of the wearable cardioverter defibrillator. *Circ Arrhythm Electrophysiol.* 2013; 6(1):117-128.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Blue Cross Blue Shield Association. Wearable cardioverter-defibrillator as a bridge to implantable cardioverter-defibrillator treatment. TEC Assessment, 2010; 25(2).
2. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008; 51:1-62. Available at: <http://circ.ahajournals.org/content/117/21/2820.full.pdf>. Accessed on October 21, 2013.
3. Feldman MD. Wearable Cardioverter Defibrillator for Patients at risk for Sudden Cardiac Arrest: A Technology Assessment. California Technology Assessment Forum™. San Francisco, CA. March 11, 2009. Available at: <http://www.ctaf.org/assessments/wearable-cardioverter-defibrillator-patients-risk-sudden-cardiac-arrest>. Accessed on October 21, 2013.
4. Goldberger JJ, Cain ME, Kadish AH, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A Scientific Statement From the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. J Am Coll Cardiol. 2008; 52:1179-1199. Available at: <http://content.onlinejacc.org/article.aspx?articleid=1139251>. Accessed on October 21, 2013.
5. Gronda E, Bourge RC, Costanzo MR, et al. Heart Rhythm Considerations in Heart Transplant Candidates and Considerations for Ventricular Assist Devices: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006. J Heart Lung Trans. 2006; 25:1043-1056. Available at: <http://www.jhltonline.org/article/PIIS1053249806004578/fulltext>. Accessed on October 21, 2013.
6. Jessup M, Abraham WT, Casey DE, et al. writing on behalf of the 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult Writing Committee. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009; 53:1343-1382. Available at: <http://circ.ahajournals.org/content/119/14/1977.full>. Accessed on October 21, 2013.
7. Kushner FG, Hand M, Smith SC, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009; 54(23):2205-2241. Available at: <http://content.onlinejacc.org/article.aspx?articleid=1140245>. Accessed on October 21, 2013.
8. National Heart, Lung and Blood Institute (NHLBI) for the PREDICTS portion only, Medtronic, ZOLL Lifecor, General Electric. Evaluating the Effectiveness of the LifeVest Defibrillator and Improving Methods for Determining the Use of Implantable Cardioverter Defibrillators (VEST/PREDICTS). NCT00628966. Last updated April 29, 2013. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00628966?term=Vest+Prevention+of+Early+Sudden+Death+and+PREDiCtion+of+ICD&rank=1>. Accessed on October 21, 2013.
9. U.S. Food and Drug Administration. Center for Devices and Radiological Health (CDRH) 510(k) Premarket Notification Database. Lifecor WCD® 2000 System Summary of Safety and Effectiveness. No. P010030. Rockville, MD: FDA. December 18, 2001. Available at:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p010030>.

Accessed on October 21, 2013.

10. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006; 48:e247-e346. Available at: <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-VASCD-ES.pdf>. Accessed on October 21, 2013.
11. Zoll Medical Corporation. Study of the Wearable Defibrillator in Heart-Failure Patients (SWIFT). NCT01326624. Last updated April 1, 2013. Available at: <http://clinicaltrials.gov/ct2/show/NCT01326624>. Accessed on October 21, 2013.

Web Sites for Additional Information

1. American Heart Association information. Available at: <http://www.americanheart.org/>
Accessed on October 21, 2013.

Index

Cardioverter Defibrillators
Lifecor WCD 2000 System
LifeVest
Sudden Cardiac Arrest
Wearable Cardioverter Defibrillators

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/14/2013	Medical Policy & Technology Assessment Committee (MPTAC) review. No change to criteria. References were updated.
Reviewed	11/08/2012	MPTAC review. No change to criteria. References were updated. Updated Coding section to include 01/01/2013 CPT descriptor change.
Reviewed	11/17/2011	MPTAC review. No change to criteria. The Rationale and References were updated.
Reviewed	11/18/2010	MPTAC review. No change to criteria. References and Coding were updated.
Reviewed	11/19/2009	MPTAC review. No change to criteria. References were updated.
Reviewed	11/20/2008	MPTAC review. No change to criteria. Consideration was given to expansion of medically necessary indications/criteria to add the immediate post-acute MI recovery period (first 40 days) in response to specialty society recommendation but no revision to existing criteria was approved by MPTAC. Annual Review research was also performed. The Rationale and Reference sections were updated. Updated Coding section with 01/01/2009 CPT changes.
Revised	11/29/2007	MPTAC review. The criteria considered investigational and not medically necessary regarding: "History of an acute myocardial infarction within thirty days" has been revised from 30 to 40 days

post-MI for consistency with SURG.00033 (ICD criteria regarding no history of MI in the last *forty* days). Also, the phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." References were also updated.

Reviewed	12/07/2006	MPTAC review. No change to criteria. References and coding were updated.
Revised	12/01/2005	MPTAC revised. Added additional indication for WCD i.e., patients with an infectious process or other temporary condition that precludes initial implantation of an ICD.
Revised	09/22/2005	MPTAC review. Position Statement: Provided clarification that candidates must have a documented medical contraindication to ICD placement with either of the following: those awaiting a heart transplantation - on waiting list and meets medical necessity criteria for heart transplantation, or those with a previously implanted ICD that requires explantation due to infection with waiting period before ICD reinsertion.
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	07/28/2005	MED.00049	Automatic External Defibrillators and Wearable Cardioverter Defibrillators
WellPoint, Inc.	04/28/2005	9.04.04	Wearable Cardioverter Defibrillators for Prevention of Sudden Cardiac Death

Fibromyalgia Related Diagnoses

Question: Should diagnoses similar to fibromyalgia be placed on the new fibromyalgia line?

Question source: HERC staff

Issue: A new fibromyalgia line was created during the 2014 biennial review for fibromyalgia. HERC staff have identified several related diagnoses which could be appropriately added to this new line.

Line XXX Fibromyalgia

Treatment: Medical Therapy

ICD-9 729.1 Myalgia and myositis, unspecified

ICD-10: M79.7 Fibromyalgia

CPT: CBT (90785, 90832-90853), medical office visits (98966-99215, 99441-99449, 99487-99489), medical team conference (99366-99368), preventive medicine visit (99381-99429)

Proposed additional diagnoses:

ICD-9 Code	ICD-10 Code	Code Description	Current Line(s)	Recommended Placement
359.89	G72.89	Other myopathies	75,297,349,381 (Dysfunction Lines)	75,297,349,381
359.9	G72.9	Myopathy, unspecified	75,297,349,381 G72.9--Excluded	Fibromyalgia line
729.0	M79.0	Rheumatism, unspecified and fibrositis	612 DISORDERS OF SOFT TISSUE	Fibromyalgia line
729.4		Fasciitis, unspecified	612	Fibromyalgia line

HERC Staff Recommendation:

- 1) Add the above ICD-9/ICD-10 codes to the new fibromyalgia line and remove from current lines/lists
- 2) Change line name to "Fibromyalgia, [Chronic Fatigue Syndrome, and Related Disorders](#)"
 - a. See related issue on Chronic Fatigue Syndrome

Chronic Fatigue Syndrome

Question: Where should chronic fatigue syndrome (CFS) be prioritized?

Question source: HERC staff

Issue: CFS is currently on the Excluded List. It was reviewed by the HSC in 1998. It is more appropriately placed on a line on the Prioritized List, where the treatment of this condition can be prioritized against other conditions on the List.

Chronic fatigue syndrome is characterized by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. The cause of CFS is unknown. There is no specific diagnostic test for this condition. Few adult patients with chronic fatigue syndrome recover to their previous level of functioning (6-10%). Due to the unclear etiology, diagnostic uncertainty, and the heterogeneity of these populations, there are also no firmly established treatment recommendations. Treatment options that are used in clinical practice are directed toward relieving symptoms and improving function, and include pharmacological, immunological and antiviral agents, cognitive/behavioral therapies and physical therapies. Few clinical studies have been published for any of these options. CFS is associated with considerable disability and public health burden. The impact of these conditions is not only physical in nature but extends to psychological, social, emotional, and economic dimensions as well. Approximately 37% CFS patients are unable to work. There is no increased mortality from this condition.

Evidence

1) NICE 2007

- a. Cognitive behavioural therapy and/or graded exercise therapy should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.
- b. Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered for people with CFS/ME who have poor sleep or pain.
- c. Relaxation techniques appropriate to the person with CFS/ME should be offered for the management of pain, sleep problems and comorbid stress or anxiety.
- d. The following drugs should not be used for the treatment of CFS/ME:
 - i. monoamine oxidase inhibitors
 - ii. glucocorticoids (such as hydrocortisone)
 - iii. mineralocorticoids (such as fludrocortisone)
 - iv. dexamphetamine
 - v. methylphenidate
 - vi. thyroxine
 - vii. antiviral agents.
- e. The following strategies should not be offered to people with CFS/ME:
 - i. Advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply 'go to the gym' or 'exercise more') because this may worsen symptoms.
 - ii. Specialist management programmes delivered by practitioners with no experience in the condition.
- f. There is insufficient evidence that complementary therapies are effective treatments for CFS/ME and therefore their use is not recommended.

Chronic Fatigue Syndrome

- g. There is insufficient evidence for the use of supplements – such as vitamin B₁₂, vitamin C, co-enzyme Q10, magnesium, NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals
- 2) **Adams 2009**, Cochrane review of traditional Chinese medicine approaches to CFS
 - a. No studies that met all inclusion criteria were identified.
 - b. **Authors' conclusions** Although studies examining the use of TCM herbal products for chronic fatigue were located, methodologic limitations resulted in the exclusion of all studies.
- 3) **Price 2008**, Cochrane review of cognitive behavioral therapy for CFS
 - a. **N=15 studies (1043 patients)**
 - b. When comparing CBT with usual care (six studies, 373 participants), the difference in fatigue mean scores at post-treatment was highly significant in favour of CBT (SMD -0.39, 95% CI -0.60 to -0.19), with 40% of CBT participants (four studies, 371 participants) showing clinical response in contrast with 26% in usual care (OR 0.47, 95% CI 0.29 to 0.76). Findings at follow-up were inconsistent. For CBT versus other psychological therapies, comprising relaxation, counselling and education/support (four studies, 313 participants), the difference in fatigue mean scores at post-treatment favoured CBT (SMD -0.43, 95% CI -0.65 to -0.20). Findings at follow-up were heterogeneous and inconsistent. Only two studies compared CBT against other interventions and one study compared CBT in combination with other interventions against usual care.
 - c. **Authors' conclusions** CBT is effective in reducing the symptoms of fatigue at post-treatment compared with usual care, and may be more effective in reducing fatigue symptoms compared with other psychological therapies. The evidence base at follow-up is limited to a small group of studies with inconsistent findings. There is a lack of evidence on the comparative effectiveness of CBT alone or in combination with other treatments, and further studies are required to inform the development of effective treatment programmes for people with CFS.
- 4) **Edmonds 2004**, Cochrane review of exercise for CFS
 - a. N=5 studies (number of patients not given)
 - b. Compared to control patients, patient receiving exercise therapy were less fatigued at 12 weeks (SMD -0.77, 95% CIs -1.26 to -0.28), but no difference was found at 24 weeks. Physical functioning was significantly improved with exercise therapy group vs control (SMD -0.64, CIs -0.96 to -0.33) but there were more dropouts with exercise therapy (RR 1.73, CIs 0.92 to 3.24). Depression did not significantly vary between exercise or control groups at 12 weeks. There were no significant differences between participants receiving exercise therapy compared to the antidepressant fluoxetine for fatigue or depression or quality of life. Participants receiving the combination of the two interventions, exercise + fluoxetine, had no significant differences in fatigue, depression or quality of life compared to participants receiving exercise therapy alone. When exercise therapy was combined with patient education, those receiving the combination were less fatigued than those receiving exercise therapy alone at 12 weeks (WMD 0.70, 95% CIs -1.48 to 2.88).
 - a. **Authors' conclusions** There is encouraging evidence that some patients may benefit from exercise therapy and no evidence that exercise therapy may worsen outcomes on average. However the treatment may be less acceptable to patients than other management approaches, such as rest or pacing. Patients with CFS who are similar to those in these trials should be offered exercise therapy, and their progress monitored. Further high quality randomised studies are needed.

Chronic Fatigue Syndrome

- 5) **Reid 2000**, review of treatments for CFS
 - a. Beneficial:
 - i. Exercise
 - ii. Cognitive behavioural therapy
 - b. Unknown effectiveness:
 - i. Corticosteroids
 - ii. Antidepressants
 - iii. Dietary supplements
 - iv. Oral nicotinamide adenine dinucleotide (NADH)
 - c. Unlikely to be beneficial:
 - i. Immunotherapy
 - d. Likely to be ineffective or harmful:
 - i. Prolonged rest

Summary: Exercise therapy and CBT appear to be beneficial for treatment of CFS. The effect size for CBT appears small, with an improvement over placebo of about 15%. Exercise therapy was shown to have short term decreases in fatigue and increases in physical functioning compared to control, but overall the effect of exercise was small. No medications were shown to have significant impact on CFS symptoms or outcomes.

Prioritization: CFS treatments with evidence of effectiveness appear similar to fibromyalgia treatments (exercise, CBT).

Scoring (fibromyalgia line scores in parentheses)

Category: 7 (7)

HL: 4 (4)

Suffering: 3 (3)

Population effects: 0 (0)

Vulnerable population: 0 (0)

Tertiary prevention: 0 (0)

Effectiveness: 1 (1)

Need for service: 0.8 (0.8)

Net cost: 2 (2)

Score: 112

Approximate line placement: 534

HERC staff recommendations:

- 1) Add chronic fatigue syndrome (ICD-9 780.71/ICD-10 R53.82) to the new fibromyalgia line
 - a. Prioritization scores are similar, CBT included on this line
- 2) Advise DMAP to remove CFS from the Excluded List
- 3) Change line name to "Fibromyalgia, [Chronic Fatigue Syndrome, and Related Disorders](#)"

Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy)

Diagnosis and management of CFS/ME in adults and children

Issued: August 2007

NICE clinical guideline 53

guidance.nice.org.uk/cg53

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Introduction

Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (or encephalopathy) (ME) is a relatively common illness. The physical symptoms can be as disabling as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, congestive heart failure and other chronic conditions. CFS/ME places a substantial burden on people with the condition, their families and carers, and hence on society.

There is a lack of epidemiological data for the UK, so population estimates are based on extrapolations from other countries. Overall, evidence suggests a population prevalence of at least 0.2–0.4%. This means that a general practice with 10,000 patients is likely to include up to 40 people with CFS/ME; half of these people will need input from specialist services.

Many different potential aetiologies for CFS/ME – including neurological, endocrine, immunological, genetic, psychiatric and infectious – have been investigated, but the diverse nature of the symptoms can not yet be fully explained. The World Health Organization (WHO) classifies CFS/ME as a neurological illness (G93.3), and some members of the Guideline Development Group (GDG) felt that, until research further identifies its aetiology and pathogenesis, the guideline should recognise this classification. Others felt that to do so did not reflect the nature of the illness, and risked restricting research into the causes, mechanisms and future treatments for CFS/ME.

CFS/ME comprises a range of symptoms that includes fatigue, malaise, headaches, sleep disturbances, difficulties with concentration and muscle pain. A person's symptoms may fluctuate in intensity and severity, and there is also great variability in the symptoms different people experience. CFS/ME is characterised by debilitating fatigue that is unlike everyday fatigue and can be triggered by minimal activity. This raises especially complex issues in adults and children with severe CFS/ME.

CFS/ME, like other chronic conditions for which the causes and disease processes are not yet fully understood, poses significant problems for healthcare professionals. It can cause profound, prolonged illness and disability, which has a substantial impact on people with CFS/ME and their carers. Uncertainties about diagnosis and management, and a lack of clinical guidance for healthcare professionals, have exacerbated this impact.

The recommendations in this guideline emphasise the importance of early symptom management, making an accurate diagnosis, ensuring that significant clinical features are investigated, and working in partnership with people with CFS/ME to manage the condition. Different combinations of approaches will be helpful for different people.

Definitions used in this guideline are provided in Appendix D.

Patient-centred care

This guideline offers best practice advice on the care of people with CFS/ME.

Treatment and care should take into account patients' individual needs and preferences.

People with CFS/ME should have the opportunity to make informed decisions about their care and treatment. For children and young people with CFS/ME, this will depend on their age and capacity to make decisions. It is good practice for healthcare professionals to involve the young person's parent(s) or guardian(s) in the decision-making process.

If patients do not have the capacity to make decisions, healthcare professionals should follow the [Department of Health's advice on consent](#) and the [code of practice that accompanies the Mental Capacity Act](#). In Wales, healthcare professionals should follow [advice on consent from the Welsh Government](#).

Good communication between healthcare professionals and people with CFS/ME is essential. All healthcare professionals should have a high standard^[1] of consultation and communication skills and use a consulting style that enables people with CFS/ME (and their families and/or carers as appropriate) to participate as partners in all decisions about their healthcare, taking fully into account their socioeconomic status, culture, cognitive ability and any specific needs.

Communication should be supported by evidence-based written information tailored to the person's needs. Treatment and care, and the information people with CFS/ME (and their families and carers as appropriate) are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

Carers and relatives should have the opportunity to be involved in decisions about the patient's care and treatment, unless the patient specifically excludes them.

Carers and relatives should also be given the information and support they need.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with CFS/ME. As part of the transition process from paediatric to adult services,

diagnosis and management should be reviewed and, throughout, there should be clarity about who is the lead clinician to ensure continuity of care.

Transitional care should be planned and managed according to the best practice guidance described in [Transition: getting it right for young people](#).

^[4] The standards detailed in the video workbook 'Summative assessment for general practice training: assessment of consulting skills – the MRCGP/summative assessment single route' are a good example of standards for consulting skills.

Key priorities for implementation

General principles of care

- Shared decision-making between the person with CFS/ME and healthcare professionals should take place during diagnosis and all phases of care. The healthcare professional should:
 - Acknowledge the reality and impact of the condition and the symptoms.
 - Provide information about the range of interventions and management strategies as detailed in this guideline (such as the benefits, risks and likely side effects).
 - Provide information on the possible causes, nature and course of CFS/ME.
 - Provide information on returning to work or education.
 - Take account of the person's age (particularly for children younger than 12 years), the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s).
 - Offer information about local and national self-help groups and support groups for people with CFS/ME and their carers (see also the NHS Expert Patients Programme^[2]).
- Healthcare professionals should be aware that – like all people receiving care in the NHS – people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care.
- To facilitate effective management of the condition, healthcare professionals should aim to establish a supportive and collaborative relationship with the person with CFS/ME and their carers. Engagement with the family is particularly important for children and young people, and for people with severe CFS/ME.
- Healthcare professionals should provide diagnostic and therapeutic options to people with CFS/ME in ways that are suitable for the individual person. This may include providing domiciliary services (including specialist assessment) or using methods such as telephone or email.

Diagnosis and initial management

- Advice on symptom management should not be delayed until a diagnosis is established. This advice should be tailored to the specific symptoms the person has and be aimed at minimising their impact on daily life and activities.
- A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for:
 - 4 months in an adult
 - 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician.
- Healthcare professionals should proactively advise about fitness for work and education, and recommend flexible adjustments or adaptations to work or studies to help people with CFS/ME to return to them when they are ready and fit enough. This may include, with the informed consent of the person with CFS/ME, liaising with employers, education providers and support services, such as:
 - occupational health services
 - disability services through Jobcentre Plus
 - schools, home education services and local education authorities
 - disability advisers in universities and colleges.

Specialist CFS/ME care

- Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their symptoms, and the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional.
- An individualised, person-centred programme should be offered to people with CFS/ME. The objectives of the programme should be to:
 - sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity
 - manage the physical and emotional impact of their symptoms.

-
- Cognitive behavioural therapy and/or graded exercise therapy should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.

^[2] For more information see [Expert Patients Programme](#) or [Education Programme for Patients Wales](#)

1 Guidance

The following guidance is based on the best available evidence. The [full guideline](#) ('CFS/ME: diagnosis and management of adults and children') gives details of the methods and the evidence used to develop the guidance (see [section 5](#) for details).

1.1 *General principles of care*

1.1.1 Shared decision-making

1.1.1.1 Shared decision-making between the person with CFS/ME and healthcare professionals should take place during diagnosis and all phases of care. The healthcare professional should:

- Acknowledge the reality and impact of the condition and the symptoms.
- Provide information about the range of interventions and management strategies as detailed in this guideline (such as the benefits, risks and likely side effects).
- Provide information on the possible causes, nature and course of CFS/ME.
- Provide information on returning to work or education.
- Take account of the person's age (particularly for children younger than 12 years), the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s).
- Offer information about local and national self-help groups and support groups for people with CFS/ME and their carers (see also the NHS Expert Patients Programme^[3]).

1.1.1.2 When providing care for children and young people, healthcare professionals should follow best practice as described in the national service frameworks for children for England or for Wales^[4].

1.1.1.3 Healthcare professionals should be aware that – like all people receiving care in the NHS – people with CFS/ME have the right to refuse or withdraw from

any component of their care plan without this affecting other aspects of their care, or future choices about care.

- 1.1.1.4 Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims and goals of the overall management plan. The pace of progression throughout the course of any intervention should be mutually agreed.
- 1.1.1.5 Healthcare professionals should provide diagnostic and therapeutic options to people with CFS/ME in ways that are suitable for the individual person. This may include providing domiciliary services (including specialist assessment) or using methods such as telephone or email.

1.1.2 Support and information

- 1.1.2.1 To facilitate effective management of the condition, healthcare professionals should aim to establish a supportive and collaborative relationship with the person with CFS/ME and their carers. Engagement with the family is particularly important for children and young people, and for people with severe CFS/ME.
- 1.1.2.2 A named healthcare professional should be responsible for coordinating care for each person with CFS/ME.
- 1.1.2.3 Healthcare professionals should provide accurate information to people at all stages of CFS/ME, starting from when a diagnosis is first being considered. This should be tailored to the person's circumstances, including the stage and duration of the condition, symptoms experienced and relevant personal and social factors.
- 1.1.2.4 Information should be available in a variety of formats if appropriate (printed copy, electronic and audio), which people with CFS/ME and their carers can refer to at home and in the clinical setting.

1.1.3 Provision of care

1.1.3.1 Healthcare professionals responsible for caring for people with CFS/ME should have appropriate skills and expertise in the condition.

1.1.3.2 Every person diagnosed with CFS/ME should be offered:

- information about the illness (see [section 1.1.2](#))
- acceptance and understanding
- assistance negotiating the healthcare, benefits and social care systems
- assistance with occupational activities including work and education if appropriate (see [section 1.4.5](#)).

1.1.3.3 An individualised management plan should be developed with the person with CFS/ME, and their carers if appropriate. The plan should be reviewed and changes documented at each contact. It should include:

- relevant symptoms and history
- plans for care and treatment, including managing setbacks/relapses
- information and support needs
- any education, training or employment support needs
- details of the healthcare professionals involved in care and their contact details.

1.2 Presentation

1.2.1 Presenting symptoms suspicious of CFS/ME

1.2.1.1 CFS/ME is recognised on clinical grounds alone. Primary healthcare professionals should be familiar with and be able to identify the characteristic features of CFS/ME.

1.2.1.2 Healthcare professionals should consider the possibility of CFS/ME if a person has:

- fatigue with all of the following features:
 - new or had a specific onset (that is, it is not lifelong)
 - persistent and/or recurrent
 - unexplained by other conditions
 - has resulted in a substantial reduction in activity level
 - characterised by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days)

and

- one or more of the following symptoms:
 - difficulty with sleeping, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep–wake cycle
 - muscle and/or joint pain that is multi-site and without evidence of inflammation
 - headaches
 - painful lymph nodes without pathological enlargement
 - sore throat
 - cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding, planning/organising thoughts and information processing
 - physical or mental exertion makes symptoms worse
 - general malaise or 'flu-like' symptoms
 - dizziness and/or nausea
 - palpitations in the absence of identified cardiac pathology.

1.2.1.3 Healthcare professionals should be aware that the symptoms of CFS/ME fluctuate in severity and may change in nature over time.

1.2.1.4 Signs and symptoms that can be caused by other serious conditions ('red flags') should not be attributed to CFS/ME without consideration of alternative diagnoses or comorbidities. In particular, the following features should be investigated^[5]:

- localising/focal neurological signs
- signs and symptoms of inflammatory arthritis or connective tissue disease
- signs and symptoms of cardiorespiratory disease
- significant weight loss
- sleep apnoea
- clinically significant lymphadenopathy.

1.2.2 History, examinations and investigations

1.2.2.1 A full history (including exacerbating and alleviating factors, sleep disturbance and intercurrent stressors) should be taken, and a physical examination and assessment of psychological wellbeing should be carried out.

1.2.2.2 A child or young person who has symptoms suggestive of CFS/ME should be referred to a paediatrician for assessment to exclude other diagnoses within 6 weeks of presentation.

1.2.2.3 The following tests should usually be done:

- urinalysis for protein, blood and glucose
- full blood count
- urea and electrolytes
- liver function

- thyroid function
- erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- random blood glucose
- serum creatinine
- screening blood tests for gluten sensitivity
- serum calcium
- creatine kinase
- assessment of serum ferritin levels (children and young people only).

Clinical judgement should be used when deciding on additional investigations to exclude other diagnoses.

1.2.2.4 Tests for serum ferritin in adults should not be carried out unless a full blood count and other haematological indices suggest iron deficiency.

1.2.2.5 Tests for vitamin B₁₂ deficiency and folate levels should not be carried out unless a full blood count and mean cell volume show a macrocytosis.

1.2.2.6 The following tests should not be done routinely to aid diagnosis:

- the head-up tilt test
- auditory brainstem responses
- electrodermal conductivity.

1.2.2.7 Serological testing should not be carried out unless the history is indicative of an infection. Depending on the history, tests for the following infections may be appropriate:

- chronic bacterial infections, such as borreliosis

- chronic viral infections, such as HIV or hepatitis B or C
- acute viral infections, such as infectious mononucleosis (use heterophile antibody tests)
- latent infections, such as toxoplasmosis, Epstein–Barr virus or cytomegalovirus.

1.2.3 Advice on symptom management before diagnosis

1.2.3.1 Advice on symptom management should not be delayed until a diagnosis is established. This advice should be tailored to the specific symptoms the person has, and be aimed at minimising their impact on daily life and activities.

1.2.4 Re-assessment before diagnosis

1.2.4.1 If symptoms do not resolve as expected in a person initially suspected of having a self-limiting condition, primary healthcare professionals should listen carefully to the person's and their family and/or carers' concerns and be prepared to reassess their initial opinion.

1.2.4.2 If considering the possibility of CFS/ME or another serious alternative condition, primary healthcare professionals should consider discussion with a specialist if there is uncertainty about the interpretation of signs and symptoms and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals if symptoms are unusual.

1.3 Diagnosis

1.3.1 Making a diagnosis

1.3.1.1 A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for:

- 4 months in an adult
- 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician.

1.3.1.2 When a diagnosis of CFS/ME is made, healthcare professionals should provide honest, realistic information about CFS/ME and encourage cautious optimism.

- Most people with CFS/ME will improve over time and some people will recover and be able to resume work and normal activities.
- However, others will continue to experience symptoms or relapse and some people with severe CFS/ME may remain housebound.
- The prognosis in children and young people is more optimistic.

1.3.1.3 The diagnosis of CFS/ME should be reconsidered if none of the following key features are present:

- post-exertional fatigue or malaise
- cognitive difficulties
- sleep disturbance
- chronic pain.

1.4 General management strategies after diagnosis

1.4.1 Symptom management

1.4.1.1 There is no known pharmacological treatment or cure for CFS/ME. However, symptoms of CFS/ME should be managed as in usual clinical practice.

1.4.1.2 No research evidence was found to support the experience of some people with CFS/ME that they are more intolerant of drug treatment and have more severe adverse/side effects. However, if people with CFS/ME have concerns, healthcare professionals may consider starting drug treatment for CFS/ME symptoms at a lower dose than in usual clinical practice. The dose may be increased gradually, in agreement with the patient.

1.4.1.3 Specific drug treatment for children and young people with CFS/ME should be started by a paediatrician. However, prescribing may be continued in primary

care, depending on the preferences of the patient and their carers, and local circumstances.

- 1.4.1.4 If a person experiences nausea as part of CFS/ME, this should be managed conventionally, including giving advice on eating little and often, snacking on dry starchy foods and sipping fluids. The use of anti-emetic drugs should be considered only if the nausea is severe.
- 1.4.1.5 Although exclusion diets are not generally recommended for managing CFS/ME, many people find them helpful in managing symptoms, including bowel symptoms. If a person with CFS/ME undertakes an exclusion diet or dietary manipulation, healthcare professionals should seek advice from a dietitian because of the risk of malnutrition.

1.4.2 Function and quality-of-life management

Sleep management

- 1.4.2.1 Healthcare professionals should provide tailored sleep management advice that includes:
- Explaining the role and effect of disordered sleep or sleep dysfunction in CFS/ME.
 - Identifying the common changes in sleep patterns seen in CFS/ME that may exacerbate fatigue symptoms (such as insomnia, hypersomnia, sleep reversal, altered sleep–wake cycle and non-refreshing sleep).
 - Providing general advice on good sleep hygiene^[6].
 - Introducing changes to sleep patterns gradually.
 - Regular review.
- 1.4.2.2 If sleep management strategies do not improve the person's sleep and rest, the possibility of an underlying sleep disorder or dysfunction should be considered, and interventions provided if needed.

- 1.4.2.3 Sleep management strategies should not include encouraging daytime sleeping and naps. People with CFS/ME should be advised that excessive sleep does not generally improve physical or mental functioning, and excessive periods of daytime sleep or frequent napping may further disrupt the sleep–wake cycle.

Rest periods

- 1.4.2.4 Rest periods are a component of all management strategies for CFS/ME. Healthcare professionals should advise people with CFS/ME on the role of rest, how to introduce rest periods into their daily routine, and the frequency and length appropriate for each person. This may include:
- Limiting the length of rest periods to 30 minutes at a time.
 - Introducing 'low level' physical and cognitive activities (depending on the severity of symptoms).
 - Using relaxation techniques (see recommendation 1.4.2.6).
- 1.4.2.5 Healthcare professionals should review the use of rest periods regularly as part of the patient's management plan.

Relaxation

- 1.4.2.6 Relaxation techniques appropriate to the person with CFS/ME should be offered for the management of pain, sleep problems and comorbid stress or anxiety. There are a number of different relaxation techniques (such as guided visualisation or breathing techniques) that can be incorporated into rest periods.

Pacing

- 1.4.2.7 People with CFS/ME have reported pacing to be helpful in self-managing CFS/ME. However, healthcare professionals should advise people with CFS/ME that, at present, there is insufficient research evidence on the benefits or harm of pacing.

1.4.3 Diet

See also recommendations on managing nausea (1.4.1.4) and bowel symptoms (1.4.1.5), and use of supplements (1.4.7.2–4).

1.4.3.1 Healthcare professionals should emphasise the importance of a well-balanced diet in line with 'The balance of good health'^[7]. They should work with the person with CFS/ME to develop strategies to minimise complications that may be caused by nausea, swallowing problems, sore throat or difficulties with buying, preparing and eating food.

1.4.3.2 Healthcare professionals should emphasise the importance of eating regularly, and including slow-release starchy foods in meals and snacks. The physiological consequences of not doing so should be explained to the person with CFS/ME.

1.4.4 Equipment to maintain independence

1.4.4.1 For people with moderate or severe CFS/ME, providing or recommending equipment and adaptations (such as a wheelchair, blue badge or stairlift) should be considered as part of an overall management plan, taking into account the risks and benefits for the individual patient. This may help them to maintain their independence and improve their quality of life.

1.4.5 Education and employment

1.4.5.1 Having to stop their work or education is generally detrimental to people's health and well-being. Therefore, the ability of a person with CFS/ME to continue in education or work should be addressed early and reviewed regularly.

1.4.5.2 Healthcare professionals should proactively advise about fitness for work and education, and recommend flexible adjustments or adaptations to work or studies to help people with CFS/ME to return to them when they are ready and fit enough. This may include, with the informed consent of the person with CFS/ME, liaising with employers, education providers and support services, such as:

- occupational health services
- disability services through Jobcentre Plus
- schools, home education services and local education authorities
- disability advisers in universities and colleges.

1.4.5.3 For people with CFS/ME who are able to continue in or return to education or employment, healthcare professionals should ensure, with the person's informed consent, that employers, occupational health or education institutions have information on the condition and the agreed management plan.

Education

1.4.5.4 Healthcare professionals should follow the guidance from the Department for Children, Schools and Families^[9] on education for children and young people with medical needs, or equivalent statutory guidance.

1.4.5.5 Healthcare professionals should work closely with social care and education services to ensure a common understanding of the goals of the person with CFS/ME. The use of a flexible approach should be discussed, including home tuition and use of equipment that allows a gradual reintegration into education.

1.4.5.6 Time in education should not be used as a sole marker of progress of CFS/ME, and education should not be the only activity a person undertakes. There should be a balance between time spent attending school or college and doing homework, and time spent on home and social activities.

Employment

1.4.5.7 If possible, and with the informed consent of the person with CFS/ME, healthcare professionals should discuss employment issues with occupational health professionals, who will communicate with the person's manager or human resources representative. If there is no access to occupational health services, the responsible clinician should liaise with the employer directly^[9].

1.4.6 Strategies that should not be used for CFS/ME

1.4.6.1 The following drugs should not be used for the treatment of CFS/ME:

- monoamine oxidase inhibitors
- glucocorticoids (such as hydrocortisone)
- mineralocorticoids (such as fludrocortisone)
- dexamphetamine
- methylphenidate
- thyroxine
- antiviral agents.

1.4.6.2 The following strategies should not be offered to people with CFS/ME:

- Advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply 'go to the gym' or 'exercise more') because this may worsen symptoms.
- Specialist management programmes (see [section 1.6](#)) delivered by practitioners with no experience in the condition.

1.4.6.3 Although there is considerable support from patients (particularly people with severe CFS/ME) for the following strategies, healthcare professionals should be aware that there is no controlled trial evidence of benefit:

- Encouraging maintenance of activity levels at substantially less than full capacity to reserve energy for the body to heal itself (sometimes known as the envelope theory).
- Encouraging complete rest (cognitive, physical and emotional) during a setback/relapse.

1.4.6.4 Strategies for managing CFS/ME should not include:

- Prolonged or complete rest or extended periods of daytime rest in response to a slight increase in symptoms.
- An imposed rigid schedule of activity and rest.

1.4.7 Complementary and supplementary therapies

- 1.4.7.1 There is insufficient evidence that complementary therapies are effective treatments for CFS/ME and therefore their use is not recommended. However, some people with CFS/ME choose to use some of these therapies for symptom control, and find them helpful.
- 1.4.7.2 There is insufficient evidence for the use of supplements – such as vitamin B₁₂, vitamin C, co-enzyme Q10, magnesium, NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals – for people with CFS/ME, and therefore they should not be prescribed for treating the symptoms of the condition. However, some people with CFS/ME have reported finding these helpful as a part of a self-management strategy for their symptoms.
- 1.4.7.3 People with CFS/ME who are using supplements should be advised not to exceed the safe levels recommended by the Food Standards Agency^[10].
- 1.4.7.4 Some people with CFS/ME need supplements because of a restricted dietary intake or nutritional deficiencies. Healthcare professionals should seek advice from a dietitian about any concerns.

1.5 Referral to specialist CFS/ME care

- 1.5.1.1 Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their symptoms, and the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional.
- 1.5.1.2 Referral to specialist CFS/ME care should be offered:
- within 6 months of presentation to people with mild CFS/ME

- within 3–4 months of presentation to people with moderate CFS/ME symptoms
- immediately to people with severe CFS/ME symptoms.

1.6 Specialist CFS/ME care

1.6.1.1 After a patient is referred to specialist care, an initial assessment should be done to confirm the diagnosis.

1.6.1.2 If general management strategies (see [section 1.4](#)) are helpful for a person with CFS/ME, these should be continued after referral to specialist CFS/ME care.

1.6.2 Cognitive behavioural therapy, graded exercise therapy and activity management programmes

Choosing and planning treatment

1.6.2.1 An individualised, person-centred programme should be offered to people with CFS/ME. The objectives of the programme should be to:

- sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity
- manage the physical and emotional impact of their symptoms.

1.6.2.2 The rationale and content of the different programmes, including their potential benefits and risks, should be fully explained to the person with CFS/ME. Healthcare professionals should explain that no single strategy will be successful for all patients, or during all stages of the condition.

1.6.2.3 Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims of the programme. The choice of the programme, its components, and progression throughout the programme should be mutually agreed and based on:

- the person's age, preferences and needs

- the person's skills and abilities in managing their condition, and their goals (such as improvement or treatment of deterioration of symptoms, prevention of relapse or maintenance)
- the severity and complexity of symptoms
- physical and cognitive functioning.

1.6.2.4 Cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.

1.6.2.5 If a full CBT or GET programme is inappropriate or not available, components of CBT or GET should be offered, either individually or more effectively in combination with:

- activity management strategies (see 1.6.2.22)
- sleep management (see [1.4.2.1–3](#))
- relaxation techniques (see [1.4.2.6](#)).

1.6.2.6 The choice of programme, its components and progression through it should be reviewed regularly, taking into account the goals and abilities of the person with CFS/ME, and other approaches agreed as necessary.

1.6.2.7 Healthcare professionals should advise people with CFS/ME to contact them if they experience an increase in symptoms that lasts for longer than a few days after starting the specialist programme, or if symptoms are severe or distressing.

Cognitive behavioural therapy (CBT)

1.6.2.8 A course of CBT should be delivered only by a healthcare professional with appropriate training in CBT and experience in CFS/ME, under clinical supervision. The therapist should adhere closely to empirically grounded therapy protocols.

1.6.2.9 CBT should be offered on a one-to-one basis if possible.

1.6.2.10 CBT for a person with CFS/ME should be planned according to the usual principles of CBT, and should include:

- Acknowledging and validating the person's symptoms and condition.
- Explaining the CBT approach in CFS/ME, such as the relationship between thoughts, feelings, behaviours and symptoms, and the distinction between causal and perpetuating factors.
- Discussing the person's attitudes and expectations.
- Developing a supportive and collaborative therapeutic relationship.
- Developing a shared formulation and understanding of factors that affect CFS/ME symptoms.
- Agreeing therapeutic goals.
- Tailoring treatment to the person's needs and level of functioning.
- Recording and analysing patterns of activity and rest, and thoughts, feelings and behaviours (self-monitoring).
- Establishing a stable and maintainable activity level (baseline) followed by a gradual and mutually agreed increase in activity.
- Challenging thoughts and expectations that may affect symptom improvement and outcomes.
- Addressing complex adjustment to diagnosis and acceptance of current functional limitations.
- Developing awareness of thoughts, expectations or beliefs and defining fatigue-related cognitions and behaviour.
- Identifying perpetuating factors that may maintain or exacerbate CFS/ME symptoms to increase the person's self-efficacy (sense of control over symptoms).

- Addressing any over-vigilance to symptoms and related checking or reassurance-seeking behaviours by providing physiological explanations of symptoms and using refocusing/distraction techniques.
- Problem solving using activity management and homework tasks to test out alternative thoughts or beliefs, such as undertaking pleasure and mastery tasks (tasks that are enjoyable and give a sense of accomplishment).
- Building on existing assertion and communication skills to set appropriate limits on activity.
- Managing sleep problems, for example by addressing any unhelpful beliefs about sleep, behavioural approaches to sleep disturbance, stress management, and/or relaxation training (see recommendations [1.4.2.1–6](#)).
- Treating any associated or comorbid anxiety, depression or mood disorder according to NICE clinical guidelines on these conditions (see [section 6](#)).
- Offering information on managing setbacks/relapses (see [section 1.7](#)).

Graded exercise therapy (GET)

1.6.2.11 GET should be delivered only by a suitably trained GET therapist with experience in CFS/ME, under appropriate clinical supervision.

1.6.2.12 GET should be offered on a one-to-one basis if possible.

1.6.2.13 People with mild or moderate CFS/ME should be offered GET that includes planned increases in the duration of physical activity. The intensity should then be increased when appropriate, leading to aerobic exercise (that is, exercise that increases the pulse rate).

1.6.2.14 GET should be based on the person's current level of activities (such as physical activity, daily routines, sleep patterns and frequency of setbacks/relapses) and emotional factors, vocational or educational factors and individual goals (details of these may be obtained from an activity diary). The programme should also include sleep and relaxation strategies (see recommendations [1.4.2.1–6](#)).

1.6.2.15 When planning GET, the healthcare professional should:

- Undertake an activity analysis to ensure that the person with CFS/ME is not in a 'boom and bust' cycle before they increase the time spent in exercise.
- Discuss with the person the ultimate goals that are important and relevant to them. This might be, for example, a twice-daily short walk to the shops, a return to a previous active hobby such as cycling or gardening, or, for people with severe CFS/ME, sitting up in bed to eat a meal.
- Recognise that it can take weeks, months or even years to achieve goals, and ensure that this is taken into account in the therapy structure (for example, by setting short- and medium-term goals).
- Explain symptoms and the benefits of exercise in a physiological context.

1.6.2.16 When starting GET, the healthcare professional should:

- Assess the person's current daily activities to determine their baseline.
- Agree with them a level of additional low-intensity exercise that is sustainable, independent of daily fluctuations in symptoms, and does not lead to 'boom and bust' cycles. This may be sitting up in bed or brushing hair, for example, for people with severe CFS/ME, or gentle stretches or a slow walk.
- Encourage them to undertake this exercise for at least 5 days out of 7, or build up to this level if and when possible.
- Advise them that this level of exercise may mildly increase symptoms for a few days (for example, a mild to moderate increase in stiffness and fatigue), explain why this may occur and discuss strategies to mitigate it.
- Offer information on the management of setbacks/relapses (see [section 1.7](#)).

Progressing with GET

1.6.2.17 When the low-intensity exercise can be sustained for 5 days out of 7 (usually accompanied by a reduction in perceived exertion), the duration should be reviewed and increased, if appropriate, by up to 20%. For example, a 5-minute

walk becomes 6 minutes, or a person with severe CFS/ME sits up in bed for a longer period, or walks to another room more often. The aim is to reach 30 minutes of low-intensity exercise.

1.6.2.18 When the duration of low-intensity exercise has reached 30 minutes, the intensity of the exercise may be increased gradually up to an aerobic heart rate zone, as assessed individually by a healthcare professional. A rate of 50–70% maximum heart rate is recommended.

1.6.2.19 Exercise intensity should be measured using a heart rate monitor, so that the person knows they are within their target heart rate zone.

1.6.2.20 If agreed GET goals are met, exercise duration and intensity may be increased further if appropriate, if other daily activities can also be sustained, and in agreement with the person with CFS/ME.

Maintaining exercise

1.6.2.21 After completing a GET programme, the healthcare professional and the person with CFS/ME should continue working together to develop and build on strategies to maintain exercise. Support should be available, if needed, to enable the person to reinforce the learning and lifestyle changes made and continue GET beyond discharge.

Activity management

1.6.2.22 Activity management is a goal-oriented and person-centred approach tailored to the needs of the person with CFS/ME. It should include:

- Understanding that activities have physical, emotional and cognitive components, and identifying these components.
- Keeping a diary that records cognitive and physical activity, daytime rest and sleep. This will help to set baseline levels of activity (a stable and sustainable range of functioning), identify patterns of over- and underactivity, and develop an activity/exercise strategy.

- Establishing a baseline; specific activities may need to be increased or decreased while this is happening.
- Gradually increasing activity above the baseline in agreement with the person.
- Planning daily activities to allow for a balance and variety of different types of activity, rest and sleep. This may include making a weekly activity schedule.
- Spreading out difficult or demanding tasks over the day or week.
- Splitting activities into small achievable tasks according to the person's level of ability/functioning, followed by gradual increases in the complexity of the tasks.
- Monitoring, regulating and planning activities to avoid a 'boom and bust' cycle.
- Goal setting, planning and prioritising activities.
- Explaining the role of rest in CFS/ME and helping the person work out how to build in rest periods and achieve a productive day (see recommendations [1.4.2.1–6](#)).
- Regularly reviewing activity levels and goals.
- Offering information on the management of setbacks/relapses (see [section 1.7](#)).

1.6.3 Pharmacological interventions for symptom control

- 1.6.3.1 If chronic pain is a predominant feature, healthcare professionals should consider referral to a pain management clinic.
- 1.6.3.2 Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered for people with CFS/ME who have poor sleep or pain. Tricyclic antidepressants should not be offered to people who are already taking selective serotonin reuptake inhibitors (SSRIs) because of the potential for serious adverse interactions.
- 1.6.3.3 Melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because it is not licensed in the UK.

1.7 Management of setbacks/relapses

1.7.1 Preparing for a setback/relapse

- 1.7.1.1 People with CFS/ME should be advised that setbacks/relapses are to be expected as part of CFS/ME.
- 1.7.1.2 Healthcare professionals and people with CFS/ME should develop a plan for managing setbacks/relapses, so that skills, strategies, resources and support are readily available and accessible when needed. This plan may be shared with the person's carers, if they agree.

1.7.2 During a setback/relapse

- 1.7.2.1 Setbacks/relapses may be triggered by factors such as unexpected/unplanned activities, poor sleep, infection or stress. Healthcare professionals, in discussion with the person with CFS/ME, should try to identify the cause(s) of a setback/relapse, but it should be recognised that this may not always be possible.
- 1.7.2.2 When managing a setback/relapse, the management plan should be reviewed. Healthcare professionals should discuss and agree an appropriate course of action with the person with CFS/ME, taking into account:
- the person's experience
 - possible causes of the setback/relapse, if known
 - the nature of the symptoms
 - the severity and duration of the setback/relapse
 - the current management plan.
- 1.7.2.3 When managing setbacks, healthcare professionals should put strategies in place that:
- Include relaxation and breathing techniques.

- Maintain activity and exercise levels if possible, by alternating activities with breaks and pacing activities, as appropriate.
- Involve talking to families and carers, if appropriate.
- Recognise distressing thoughts about setbacks/relapses such as 'this means I'll never get better', but encourage optimism.
- Involve reconsidering and revising the levels and types of symptom control.

1.7.2.4 In some setbacks/relapses, it may be necessary to reduce, or even stop some activities and increase the frequency and/or duration of rest periods to stabilise symptoms and re-establish a baseline activity level. This should be discussed and agreed with the person with CFS/ME.

1.7.2.5 People with CFS/ME should be advised to minimise daytime sleep periods. However, healthcare professionals should recognise that this is not always possible, depending on the severity of a person's symptoms and the setback.

1.7.3 After a setback/relapse

1.7.3.1 After a setback/relapse, healthcare professionals should review the person's activity levels to re-establish a baseline and review the management plan. A gradual return, when possible, to previous exercise and functional routines should be encouraged. Activity should be increased gradually.

1.7.3.2 Healthcare professionals should advise on:

- Slowly decreasing the frequency and duration of rest periods.
- Continuing the use of relaxation techniques, even when the person with CFS/ME is beginning to feel better.

1.7.3.3 After a setback, healthcare professionals and people with CFS/ME should review the experience to determine, if possible, whether triggers can be managed in the future, and put strategies in place to do this.

1.8 Review and ongoing management

1.8.1.1 Regular, structured review should be undertaken for all people with CFS/ME.

The review should include, if appropriate:

- Assessing improvement or deterioration in symptoms.
- Assessing any adverse or unwanted effects of therapy.
- Ongoing investigations.
- Considering the need to repeat investigations (for children and young people, repeating investigations should be considered if there is no improvement after 1 year).
- Reviewing the diagnosis, especially if signs and symptoms change (see recommendation [1.2.1.4](#)).
- Considering referral to specialist CFS/ME care.
- Reviewing equipment needs.
- Assessing any additional support needs (see sections [1.1](#) and [1.4](#)).

1.8.1.2 The timing of the reviews should depend on the severity and complexity of symptoms, the effectiveness of any interventions, and the needs of the person with CFS/ME.

1.9 Key principles of care for people with severe CFS/ME

1.9.1 General principles of care

1.9.1.1 Management of severe CFS/ME is difficult and complex and healthcare professionals should recognise that specialist expertise is needed when planning and providing care for people with severe CFS/ME.

1.9.1.2 Diagnosis, investigations, management and follow-up care for people with severe CFS/ME should be supervised or supported by a specialist in CFS/ME.

- 1.9.1.3 People with severe CFS/ME may need to use community services at times. These services may include nursing, occupational therapy, dietetics, respite care, psychology and physiotherapy (see the 'National service framework for long-term conditions'^[1]). The input of different professionals should be coordinated by a named professional.
- 1.9.1.4 People with severe CFS/ME should be offered a summary record of every consultation because of their cognitive difficulties.
- 1.9.1.5 Most people with CFS/ME will not need hospital admission. However, there may be circumstances when a planned admission should be considered. The decision to admit should be made with the person with CFS/ME and their family, and be based on an informed consideration of the benefits and disadvantages. For example, a planned admission may be useful if assessment of a management plan and investigations would require frequent visits to the hospital.

1.9.2 Rest

- 1.9.2.1 When making decisions about prolonged bed rest, healthcare professionals should seek advice from a specialist experienced in the care of people with severe CFS/ME. The significant physical and psychological risks associated with prolonged bed rest should be taken into account.
- 1.9.2.2 Healthcare professionals working with people with severe CFS/ME who are in bed most (or all) of the time, should explain the associated risks (such as postural hypotension, deep venous thrombosis, osteoporosis, pressure sores and deconditioning) and monitor these.

1.9.3 Management approaches

- 1.9.3.1 People with severe CFS/ME should be offered an individually tailored activity management programme (see recommendation [1.6.2.22](#)) as the core therapeutic strategy, which may:

- be delivered at home, or using telephone or email if appropriate

- incorporate the elements of recommendation [1.6.2.22](#) and draw on the principles of CBT and GET (see recommendations [1.6.2.1–21](#)).

1.9.3.2 An activity management programme should be reviewed regularly and frequently.

^[3] For more information see [Expert Patients Programme](#) or [Education Programme for Patients Wales](#)

^[4] Available from the [Department of Health](#) (England; this framework includes an exemplar pathway for CFS/ME) and [NHS Wales](#).

^[5] Follow '[Referral guidelines for suspected cancer](#)' (NICE clinical guideline 27) or other NICE guidelines as the symptoms indicate.

^[6] For general advice on sleep hygiene, see the [NHS Direct website](#).

^[7] Food Standards Agency (2006) '[The balance of good health](#)'. London: Foods Standards Agency.

^[8] See [Department for Education](#)

^[9] [NHS Plus](#) has produced guidance on the occupational aspects of the management of CFS/ME (search for 'chronic fatigue syndrome').

^[10] See [Food Standards Agency](#)

^[11] Available from the [Department of Health](#).

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a [scope](#) that defines what the guideline will and will not cover.

This guideline addresses the diagnosis, treatment and management of CFS/ME in adults and in children aged 5 years and older, in primary and secondary care and in specialist centres and teams. The guideline is also relevant to the work of occupational health services, social services, educational services and the voluntary sector, although it does not make recommendations for them directly.

The guideline does not cover the management of comorbidities, highly specialised procedures, service provision or models of care.

How this guideline was developed

NICE commissioned the National Collaborating Centre for Primary Care to develop this guideline. The Centre established a Guideline Development Group (see [appendix A](#)), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see [appendix B](#)).

There is more information about [how NICE clinical guidelines are developed](#) on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is [available](#).

3 Implementation

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health', issued in July 2004. Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed [tools](#) to help organisations implement this guidance (listed below). These are available on our [website](#).

- Slides highlighting key messages for local discussion.
- Costing tools:
 - costing report to estimate the national savings and costs associated with implementation
 - costing template to estimate the local costs and savings involved.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- Audit criteria to monitor local practice.

4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the [full guideline](#).

The aetiology of CFS/ME was outside the scope of the guideline and therefore a systematic search of the area was not carried out. For that reason, the GDG has not made a research recommendation about the causes of CFS/ME, but it recognises that research in this area would be very helpful.

4.1 Extrapolating use of intervention strategies

Are intervention strategies that have been shown to be effective in mildly to moderately affected adults also effective in children and in people (adults and children) with severe CFS/ME?

Why this is important

There is limited evidence for the use or effectiveness of strategies recommended in this guideline in these two patient groups. Population data suggest that these groups constitute a significant percentage of the population with CFS/ME. Some patient experience suggests that some of these interventions may be harmful and/or not effective.

4.2 Delivery of standard methods of care

Are there more efficient ways of delivering standard methods of care? For example, what is the most efficient way of delivering domiciliary care for people with CFS/ME?

Why this is important

Randomised controlled trials, with adequate power, are needed to compare different methods of delivering standard methods of care, and whether outcomes differ depending on whether they are delivered in primary or secondary care. Subgroup analysis may clarify which approach is most efficient (that is, cost effective without decreasing efficacy) in different groups of people with CFS/ME (for example, people who are severely affected).

4.3 Prevalence and course of the illness

What is the prevalence and incidence of CFS/ME in different populations? What is the natural course of the illness?

Why this is important

Reliable information on the prevalence and incidence of this condition is needed to plan services. This will require well-constructed epidemiological studies across different populations to collect longitudinal data to predict outcome, and to calculate the economic impact of loss of work or education.

We recommend that these questions are answered using a mixture of:

- cross-sectional population studies, including people with different levels of disease severity from all ethnic groups and social classes
- longitudinal cohorts of people with CFS/ME, and population cohorts to assess the incidence and prognosis of CFS/ME in a previously normal cohort.

4.4 Measuring outcome

What is the best way of measuring outcome in research studies?

Why this is important

There is a lack of studies in this area. Knowing what is important to people with CFS/ME is crucial for designing future studies. It is not known how best to measure improvement scientifically for people with CFS/ME, and how much of an improvement is significant. More information is needed on functional outcomes such as return to work or education, return to normal family life or social activities, or increased self-esteem, to inform future estimates of the cost effectiveness of treatment.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, [Chronic fatigue syndrome/myalgic encephalomyelitis \(or encephalopathy\): diagnosis and management of CFS/ME in adults and children](#) contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Primary Care.

5.2 Information for the public

NICE has produced [information for the public](#) explaining this guideline.

We encourage NHS and voluntary sector organisations to use text from this information in their own materials.

6 Related NICE guidance

Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition [NICE clinical guideline 32](#) (2006).

Referral guidelines for suspected cancer. [NICE clinical guideline 27](#) (2005).

Depression in children and young people: identification and management in primary, community and secondary care. [NICE clinical guideline 28](#) (2005).

Depression: management of depression in primary and secondary care. NICE clinical guideline 23 (2004, amended 2007). [Replaced by [NICE clinical guideline 90](#)]

Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. NICE clinical guideline 22 (2004, amended 2007). [Replaced by [NICE clinical guideline 113](#)]

Irritable bowel syndrome. [NICE clinical guideline 61](#) (2008).

Management of long-term sickness and incapacity. [NICE public health programme guidance 19](#) (2009).

7 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

Appendix A: The Guideline Development Group

Chair: Professor Richard Baker

Head of Department, Department of Health Sciences, University of Leicester

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Patient Representative, Nottingham

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Patient Representative, Sheffield

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Miss Nicola Costin

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Health Economist (from December 2006), NCC-PC

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Mrs Karina Ramos

Administrator (from March 2007), NCC-PC

Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The Panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

Professor Mike Drummond (Chair)

Professor of Health Economics, Centre for Health Economics, University of York

Ms Karen Cowley

Practice Development Nurse, York Health Services NHS Trust

Mr Barry Stables

Patient/Lay Representative

Dr John Harley

Clinical Governance and Prescribing Lead, North Tees PCT

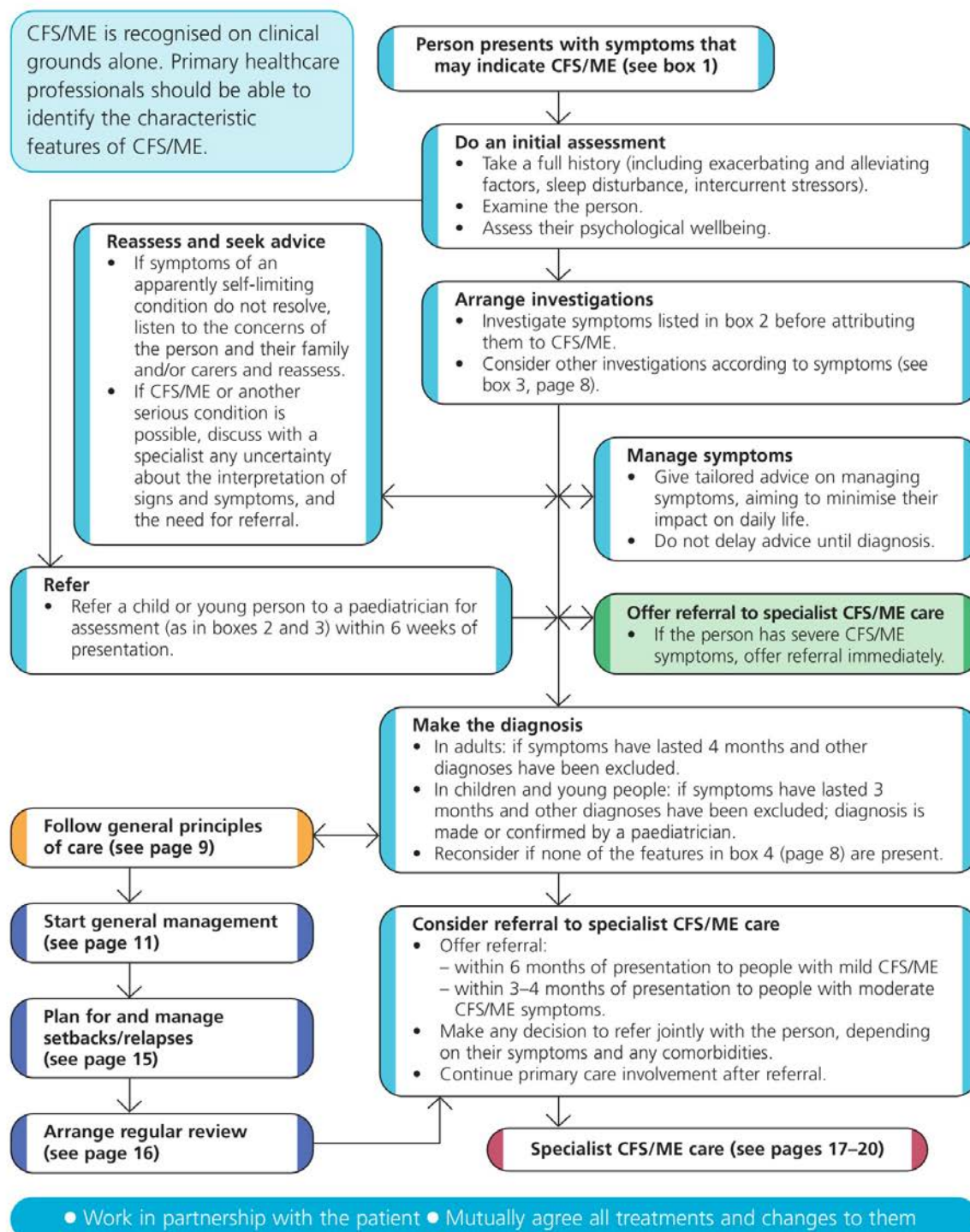
Dr David Gillen

Medical Director, Pfizer Ltd

Appendix C: The algorithms

Care pathway

Presentation, diagnosis and pathway of care



Appendix D: Definitions used in this guideline

Activity

Any task or series of tasks that a person performs. A task may have physical, emotional, cognitive and social components.

Activity management

A person-centred approach to managing a person's symptoms by using activity. It is goal-directed and uses activity analysis and graded activity to enable people to improve, evaluate, restore and/or maintain their function and well-being in self-care, work and leisure.

Age

- Adult: aged 18 years and older.
- Young person: aged between 12 and 17 years.
- Child: aged between 5 and 11 years.

The age at which care is transferred between child and adult health services varies between 16 and 19 years, depending on the young person and their family's preferences and local circumstances.

'Boom and bust' cycles

Cycles of fluctuating activity levels and symptoms, which are a common feature of CFS/ME. Boom and bust cycles can happen when a person with CFS/ME is overactive when they are feeling better, which may lead to an increase in symptoms and a decrease in function.

Cognitive behavioural therapy (CBT)

An evidence-based psychological therapy that is used in many health settings, including cardiac rehabilitation and diabetes management. It is a collaborative treatment approach. When it is used for CFS/ME, the aim is to reduce the levels of symptoms, disability and distress associated

with the condition. A course of CBT is usually 12–16 sessions. The use of CBT does not assume or imply that symptoms are psychological or 'made up'.

Deconditioning

Loss of physical fitness as the general physiological response to, for example, a prolonged period of inactivity.

Graded exercise therapy (GET)

An evidence-based approach to CFS/ME that involves physical assessment, mutually negotiated goal-setting and education. The first step is to set a sustainable baseline of physical activity, then the duration of the activity is gradually increased in a planned way that is tailored to the person. This is followed by an increase in intensity, when the person is able, taking into account their preferences and objectives, current activity and sleep patterns, setbacks/relapses and emotional factors. The objective is to improve the person's CFS/ME symptoms and functioning, aiming towards recovery.

Pacing

The report of the Chief Medical Officer's working group^[12] defined the principles of pacing, and these are supported by people with CFS/ME and patient groups. Many of the principles are included in this guideline's recommendations on CBT, GET and activity management. Examples include spreading activities over the week, breaking tasks down into small manageable parts, interspersing activity with rest and setting appropriate, realistic goals for increasing activity.

In this guideline, pacing is defined as energy management, with the aim of maximising cognitive and physical activity, while avoiding setbacks/relapses due to overexertion. The keys to pacing are knowing when to stop and rest by listening to and understanding one's own body, taking a flexible approach and staying within one's limits; different people use different techniques to do this.

However, in practice, the term pacing is used differently by different groups of people. One understanding of its meaning is as adaptive pacing therapy, which is facilitated by healthcare professionals, in which people with CFS/ME use an energy management strategy to monitor and

plan their activity, with the aim of balancing rest and activity to avoid exacerbations of fatigue and other symptoms.

Another understanding is that pacing is a self-management strategy, without specific intervention from a healthcare professional. People with CFS/ME generally support this approach.

Rest periods

Short periods when a person is neither sleeping nor engaged in physical or mental activity. Rest periods are a core component of all management approaches for CFS/ME.

Setback/relapse

An increase in symptoms above the usual daily fluctuations, which may result in a reduction in function for a time.

Severity

The degree to which CFS/ME affects a person's functioning and daily life^[13].

- People with **mild CFS/ME** are mobile, can care for themselves and can do light domestic tasks with difficulty. Most are still working or in education, but to do this they have probably stopped all leisure and social pursuits. They often take days off, or use the weekend to cope with the rest of the week.
- People with **moderate CFS/ME** have reduced mobility and are restricted in all activities of daily living, although they may have peaks and troughs in their level of symptoms and ability to do activities. They have usually stopped work, school or college and need rest periods, often sleeping in the afternoon for 1 or 2 hours. Their sleep at night is generally poor quality and disturbed.
- People with **severe CFS/ME** are unable to do any activity for themselves, or can carry out minimal daily tasks only (such as face washing, cleaning teeth). They have severe cognitive difficulties and depend on a wheelchair for mobility. They are often unable to leave the house, or have a severe and prolonged after-effect if they do so. They may also spend most of their time in bed, and are often extremely sensitive to light and noise.

Specialist CFS/ME care

A service providing expertise in assessing, diagnosing and advising on the clinical management of CFS/ME, including symptom control and specific interventions. Ideally this is provided by a multidisciplinary team, which may include GPs with a special interest in the condition, neurologists, immunologists, specialists in infectious disease, paediatricians, nurses, clinical psychologists, liaison psychiatrists, dietitians, physiotherapists and occupational therapists.

Stage

There are different stages in the natural course of CFS/ME: acute illness, maintenance or stabilisation, and recovery.

^[12] [Department of Health](#) (2002) *A report of the CFS/ME working group: report to the Chief Medical Officer of an independent working group*. London: Department of Health.

^[13] These definitions were agreed by the GDG and have been derived from definitions in:

- Royal College of Paediatrics and Child Health (2004) [Evidence-based guideline for the management of CFS/ME \(chronic fatigue syndrome/myalgic encephalopathy\) in children and young people](#).

- [Department of Health](#) (2002) *A report of the CFS/ME working group: report to the Chief Medical Officer of an independent working group*. London: Department of Health.

- Cox DL, Findley L (1998) Management of chronic fatigue syndrome in an inpatient setting: presentation of an approach and perceived outcome. *British Journal of Occupational Therapy* 61: 405–9 (this approach was adopted in the CFS/ME working group's report to the Chief Medical Officer, see footnote 12).

About this guideline

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

The guideline was developed by the National Collaborating Centre for Primary Care. The Collaborating Centre worked with a group of healthcare professionals (including consultants, GPs and nurses), patients and carers, and technical staff, who reviewed the evidence and drafted the recommendations. The recommendations were finalised after public consultation.

The methods and processes for developing NICE clinical guidelines are described in [The guidelines manual](#).

We have produced [information for the public](#) explaining this guideline. Tools to help you put the guideline into practice and information about the evidence it is based on are also [available](#).

Changes after publication

January 2012: minor maintenance

November 2013: minor maintenance

Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome (Review)

Adams D, Wu T, Yang X, Tai S, Vohra S



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[Intervention Review]

Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome

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ABSTRACT

Background

Chronic fatigue is increasingly common. Conventional medical care is limited in treating chronic fatigue, leading some patients to use traditional Chinese medicine therapies, including herbal medicine.

Objectives

To assess the effectiveness of traditional Chinese medicine herbal products in treating idiopathic chronic fatigue and chronic fatigue syndrome.

Search strategy

The following databases were searched for terms related to traditional Chinese medicine, chronic fatigue, and clinical trials: CCDAN Controlled Trials Register (July 2009), MEDLINE (1966-2008), EMBASE (1980-2008), AMED (1985-2008), CINAHL (1982-2008), PSYCHINFO (1985-2008), CENTRAL (Issue 2 2008), the Chalmers Research Group PedCAM Database (2004), VIP Information (1989-2008), CNKI (1976-2008), OCLC Proceedings First (1992-2008), Conference Papers Index (1982-2008), and Dissertation Abstracts (1980-2008). Reference lists of included studies and review articles were examined and experts in the field were contacted for knowledge of additional studies.

Selection criteria

Selection criteria included published or unpublished randomized controlled trials (RCTs) of participants diagnosed with idiopathic chronic fatigue or chronic fatigue syndrome comparing traditional Chinese medicinal herbs with placebo, conventional standard of care (SOC), or no treatment/wait lists. The outcome of interest was fatigue.

Data collection and analysis

13 databases were searched for RCTs investigating TCM herbal products for the treatment of chronic fatigue. Over 2400 references were located. Studies were screened and assessed for inclusion criteria by two authors.

Main results

No studies that met all inclusion criteria were identified.

Authors' conclusions

Although studies examining the use of TCM herbal products for chronic fatigue were located, methodologic limitations resulted in the exclusion of all studies. Of note, many of the studies labelled as RCTs and conducted in China did not utilize rigorous randomization procedures. Improvements in methodology in future studies is required for meaningful synthesis of data.

PLAIN LANGUAGE SUMMARY

Traditional Chinese medicinal herbs for chronic fatigue

Treatment options for idiopathic chronic fatigue are limited. This review attempted to examine the use of traditional Chinese herbal remedies for this condition. Although some studies investigating traditional Chinese herbs for were found for chronic fatigue syndrome, no studies met the inclusion criteria. Choice of inclusion criteria was intended to narrow inclusion to methodologically rigorous and meaningful studies. Methodological limitations in the studies identified, such as type of control used and study design, limited the usefulness of the data

BACKGROUND

Description of the condition

Fatigue may be described as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion. Fatigue may result from behavioral problems such as excess physical or mental activity, sleep deprivation, and poor diet or a range of medical conditions including infection, and cardiovascular, metabolic, connective tissue and endocrine disorders (De Merlier 2003). Fatigue may be of known or unknown aetiology and ranges in duration from short-term to chronic. The more severe forms of fatigue include idiopathic chronic fatigue (ICF) and chronic fatigue syndrome (CFS) (Fukuda 1994). The aetiology of ICF/CFS is as yet unexplained, although numerous theories have been proposed and investigated. ICF/CFS has been identified by many names throughout its documented history; current terminology also varies depending on global region and diagnostic criteria. Some of the names that may be used to describe ICF/CFS or its subtypes include neurasthenia, post-viral fatigue syndrome (PVFS), myalgic encephalomyelitis (ME), and chronic fatigue immune deficiency syndrome (CFIDS) (Wessely 1998).

CFS is characterised by severe disabling fatigue and a combination of four additional symptoms that may include impairments in cognitive or neurological function, sleep dysfunction, musculoskeletal

pain, and endocrine or immune dysfunction. Additionally, alternative medical and psychiatric causes must have been ruled out, and the condition must have been present for at least six months (Fukuda 1994). ICF meets all of the criteria for CFS except for the need for four additional symptoms (Fukuda 1994). The prognosis of ICF and CFS is often poor. Longitudinal studies have reported that less than 30% of ICF and 10% of CFS patients fully recover (Joyce 1997). The prevalence of ICF and CFS in primary care has been reported at 9% and 2.6% respectively (Wessely 1997). ICF/CFS is associated with considerable disability and public health burden. The impact of these conditions is not only physical in nature but extends to psychological, social, emotional, and economic dimensions as well. Approximately 26% of ICF and 37% CFS patients are unable to work (Bombardier 1996). Cost estimates in Britain have determined that each case of ICF/CFS in adults cost an average of £1906 over three months in informal health care and lost productivity (McCrone 2003). Similar estimates in the US reported annual individual and national losses of \$20 000 and \$9.1 billion (USD) respectively (Reynolds 2004). There is no definitive cure for ICF/CFS. Due to the unclear etiology, diagnostic uncertainty, and the heterogeneity of these populations, there are also no firmly established treatment recommendations (Afari 2003), although treatment guidelines are available in some countries (Carruthers 2003, Turnbull 2007). Treatment

Cognitive behaviour therapy for chronic fatigue syndrome in adults (Review)

Price JR, Mitchell E, Tidy E, Hunot V



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[Intervention Review]

Cognitive behaviour therapy for chronic fatigue syndrome in adults

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ABSTRACT

Background

Chronic fatigue syndrome (CFS) is a common, debilitating and serious health problem. Cognitive behaviour therapy (CBT) may help to alleviate the symptoms of CFS.

Objectives

To examine the effectiveness and acceptability of CBT for CFS, alone and in combination with other interventions, compared with usual care and other interventions.

Search strategy

CCDANCTR-Studies and CCDANCTR-References were searched on 28/3/2008. We conducted supplementary searches of other bibliographic databases. We searched reference lists of retrieved articles and contacted trial authors and experts in the field for information on ongoing/completed trials.

Selection criteria

Randomised controlled trials involving adults with a primary diagnosis of CFS, assigned to a CBT condition compared with usual care or another intervention, alone or in combination.

Data collection and analysis

Data on patients, interventions and outcomes were extracted by two review authors independently, and risk of bias was assessed for each study. The primary outcome was reduction in fatigue severity, based on a continuous measure of symptom reduction, using the standardised mean difference (SMD), or a dichotomous measure of clinical response, using odds ratios (OR), with 95% confidence intervals (CI).

Main results

Fifteen studies (1043 CFS participants) were included in the review. When comparing CBT with usual care (six studies, 373 participants), the difference in fatigue mean scores at post-treatment was highly significant in favour of CBT (SMD -0.39, 95% CI -0.60 to -0.19), with 40% of CBT participants (four studies, 371 participants) showing clinical response in contrast with 26% in usual care (OR 0.47, 95% CI 0.29 to 0.76). Findings at follow-up were inconsistent. For CBT versus other psychological therapies, comprising relaxation, counselling and education/support (four studies, 313 participants), the difference in fatigue mean scores at post-treatment favoured CBT (SMD -0.43, 95% CI -0.65 to -0.20). Findings at follow-up were heterogeneous and inconsistent. Only two studies compared CBT against other interventions and one study compared CBT in combination with other interventions against usual care.

Authors' conclusions

CBT is effective in reducing the symptoms of fatigue at post-treatment compared with usual care, and may be more effective in reducing fatigue symptoms compared with other psychological therapies. The evidence base at follow-up is limited to a small group of studies with inconsistent findings. There is a lack of evidence on the comparative effectiveness of CBT alone or in combination with other treatments, and further studies are required to inform the development of effective treatment programmes for people with CFS.

PLAIN LANGUAGE SUMMARY

Cognitive behaviour therapy for chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a very common and disabling condition, in which people suffer from persistent symptoms of fatigue that are unexplained. Cognitive behaviour therapy is a psychological therapy model that is commonly used to treat a range of psychological and chronic pain conditions. This review aimed to find out whether CBT is effective for CBT, both as a standalone treatment and in combination with other treatments, and whether it is more effective than other treatments used for CFS. The review included 15 studies, with a total of 1043 CFS participants. The review showed that people attending for CBT were more likely to have reduced fatigue symptoms at the end of treatment than people who received usual care or were on a waiting list for therapy, with 40% of people in the CBT group showing clinical improvement, in contrast with 26% in usual care. At follow-up, 1-7 months after treatment ended, people who had completed their course of CBT continued to have lower fatigue levels, but when including people who had dropped out of treatment, there was no difference between CBT and usual care. The review also compared CBT against other types of psychological therapy, including relaxation techniques, counselling and support/education, and found that people attending for CBT was more likely to have reduced fatigue symptoms at the end of treatment than those attending for other psychological therapies. Physical functioning, depression, anxiety and psychological distress symptoms were also more reduced when compared with other psychological therapies. However at follow-up, the results were inconsistent and the studies did not fit well together, making it difficult to draw any conclusions. Very few studies reported on the acceptability of CBT and no studies examined side effects. Only two studies compared the effectiveness of CBT against other treatments, both exercise therapy, and just one study compared a combination of CBT and other treatments with usual care. More studies should be carried out to establish whether CBT is more helpful than other treatments for CFS, and whether CBT in combination with other treatments is more helpful than single treatment approaches.

BACKGROUND

Description of the condition

Chronic fatigue syndrome (CFS) is a condition characterised by persistent fatigue and significant associated disability, but without evident physical or psychological disorder to explain the problem. Sufferers endure fatigue which may cause considerable and per-

sisting debility. They may also experience a lack of understanding from others, including health professionals. This may be exacerbated by normal or equivocal findings on physical examination or investigation despite the sufferer's experience of illness. It is an important health care issue, presenting major problems for both its sufferers and for health services.

Whilst fatigue is so common as to be almost a normal consequence

Exercise therapy for chronic fatigue syndrome (Review)

Edmonds M, McGuire H, Price JR



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WILEY

Exercise therapy for chronic fatigue syndrome

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ABSTRACT

Background

Chronic fatigue syndrome (CFS) is an illness characterised by persistent medically unexplained fatigue. CFS is a serious health-care problem with a prevalence of up to 3%. Treatment strategies for CFS include psychological, physical and pharmacological interventions.

Objectives

To investigate the relative effectiveness of exercise therapy and control treatments for CFS.

Search methods

CCDANCTR-Studies and CENTRAL were searched using "Chronic Fatigue" and Exercise. The Journal of Chronic Fatigue Syndrome and CFS conferences were handsearched. Experts in the field were contacted. Clinicaltrials.gov and controlled-trials.com were searched.

Selection criteria

Only Randomised Controlled Trials (RCT) including participants with a clinical diagnosis of CFS and of any age were included.

Data collection and analysis

The full articles of studies identified were inspected by two reviewers (ME and HMG). Continuous measures of outcome were combined using standardised mean differences. An overall effect size was calculated for each outcome with 95% confidence intervals. One sensitivity analysis was undertaken to test the robustness of the results.

Main results

Nine studies were identified for possible inclusion in this review, and five of those studies were included. At 12 weeks, those receiving exercise therapy were less fatigued than the control participants (SMD -0.77, 95% CIs -1.26 to -0.28). Physical functioning was significantly improved with exercise therapy group (SMD -0.64, CIs -0.96 to -0.33) but there were more dropouts with exercise therapy (RR 1.73, CIs 0.92 to 3.24). Depression was non-significantly improved in the exercise therapy group compared to the control group at 12 weeks (WMD -0.58, 95% CIs -2.08 to 0.92).

Participants receiving exercise therapy were less fatigued than those receiving the antidepressant fluoxetine at 12 weeks (WMD -1.24, 95% CIs -5.31 to 2.83). Participants receiving the combination of the two interventions, exercise + fluoxetine, were less fatigued than

those receiving exercise therapy alone at 12 weeks, although again the difference did not reach significance (WMD 3.74, 95% CIs -2.16 to 9.64).

When exercise therapy was combined with patient education, those receiving the combination were less fatigued than those receiving exercise therapy alone at 12 weeks (WMD 0.70, 95% CIs -1.48 to 2.88).

Authors' conclusions

There is encouraging evidence that some patients may benefit from exercise therapy and no evidence that exercise therapy may worsen outcomes on average. However the treatment may be less acceptable to patients than other management approaches, such as rest or pacing. Patients with CFS who are similar to those in these trials should be offered exercise therapy, and their progress monitored. Further high quality randomised studies are needed.

PLAIN LANGUAGE SUMMARY

Exercise for chronic fatigue syndrome

Based on five included studies, this systematic review cautiously concludes that exercise therapy is a promising treatment for chronic fatigue syndrome. However, studies of higher quality are needed that involve different patient groups and settings, and that measure additional outcomes such as adverse effects, quality of life and cost effectiveness over longer periods of time.

BACKGROUND

Chronic fatigue syndrome (CFS) is an illness characterised by persistent medically unexplained fatigue of more than six months duration. Sufferers experience significant disability and distress, which may be further exacerbated by a lack of understanding from others, including health professionals. CFS is a serious problem thought to affect up to 1% of the general population ([Wessely 1995](#)) though the reported prevalence ranges from 0.006% to 3% depending on the setting and criteria used ([Afari 2003](#)). It has also been known as Royal Free disease, Iceland disease, neurasthenia, myalgic encephalomyelitis ('ME'), and post-viral fatigue syndrome. However, CFS is the term that has been adopted and clearly defined for the purpose of research in this area.

Non-persistent medically unexplained fatigue (fatigue of more than 3 months but less than 6 months) is more common but 75% of these patients have fatigue that do not meet CFS ([Ridsdale 2001](#)). With usual medical care typically in a general practice setting 70-75% of these patients report that their fatigue symptoms become chronic ([Ridsdale 1993](#)).

Many sufferers in the community attend their local general practitioners for assessment. However, diagnosis is poor due to normal or equivocal findings on physical examination or investigation. As a result some attend alternative practitioners, whilst others are referred to out-patient clinics for assessment. Referrals are made to a variety of specialist clinics including general medicine,

endocrinology, infectious disease, neurology, and psychiatry. This reflects the uncertainty, and often disagreement between doctors and sufferers regarding the causes of CFS, which in turn may lead to unsatisfactory patient-professional relationships, and ultimately dissatisfied patients.

Opinions regarding the causes of CFS have generally focused on either physical or psychological explanations, although more recently there has been an increasing awareness of the potential interaction of physical and psychological factors in the development and maintenance of the disorder. Psychosocial factors appear to be important. While there is some evidence for abnormalities in the hypothalamic-pituitary-adrenal axis similar to those evident in post-traumatic stress disorder, it is uncertain whether these changes are causal or a result of the disorder. The current scientific consensus is that CFS involves the neuro-endocrine system, but not in a manner identical to depression.

Treatment strategies for CFS include psychological, physical and pharmacological interventions. Randomised controlled trials have been carried out to assess the effectiveness of treatments as diverse as exercise therapy ([Fulcher 1997](#); [Wearden 1998](#)), self-help treatment ([Chalder 1997](#)), antidepressants ([Behan 1995](#); [Vercoulen 1996](#); [Wearden 1998](#)), and dietary supplementation with fatty acids ([Warren 1999](#)) and folic acid ([Kaslow 1989](#)). A recent systematic review found that cognitive behaviour therapy was effective for CFS in adults ([Price 2000](#)).

Clinical review

Extracts from “Clinical Evidence”

Chronic fatigue syndrome

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BMJ 2000;320:292–6

Interventions

Beneficial:

Exercise
Cognitive behavioural therapy

Unknown effectiveness:

Corticosteroids
Antidepressants
Dietary supplements
Oral nicotinamide adenine dinucleotide (NADH)

Unlikely to be beneficial:

Immunotherapy

Likely to be ineffective or harmful:

Prolonged rest

used definitions of chronic fatigue syndrome (from the US Centers for Disease Control and Prevention¹ and from Oxford²—see table) were developed as operational criteria for research. There are two important differences between these definitions. The British criteria insist on the presence of mental fatigue; the American criteria include a requirement for several physical symptoms, reflecting the belief that chronic fatigue syndrome has an underlying immunological or infective pathology.

Incidence/prevalence Community and primary care based studies have reported the prevalence of chronic fatigue syndrome to be 0.2–2.6%, depending on the criteria used.^{3–4} Systematic population surveys have found similar rates of the syndrome in people of different socioeconomic status, and in all ethnic groups.^{4–5} Female sex is the only demographic risk factor (relative risk 1.3 to 1.7 depending on diagnostic criteria used).⁶

Aetiology The cause of chronic fatigue syndrome is poorly understood.

Prognosis Studies of prognosis in chronic fatigue syndrome have focused on people attending specialist clinics, who are likely to have had the condition for longer and to have a poorer outlook. Children with

Background

Definition Chronic fatigue syndrome is characterised by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. Two widely

Diagnostic criteria for chronic fatigue syndrome

Centers for Disease Control, 1994¹

Diagnostic criteria

Clinically evaluated, medically unexplained fatigue of at least six months' duration that is:

- of new onset
- not a result of ongoing exertion
- not substantially alleviated by rest
- a substantial reduction in previous levels of activity

The occurrence of four or more of the following symptoms:

- subjective memory impairment
- tender lymph nodes
- muscle pain
- joint pain
- headache
- unrefreshing sleep
- postexertional malaise (>24 hours)

Exclusion criteria

Active, unresolved, or suspected disease likely to cause fatigue

Psychotic, melancholic or bipolar depression (but not uncomplicated major depression)

Psychotic disorders

Dementia

Anorexia or bulimia nervosa

Alcohol misuse or other substance misuse

Severe obesity

Oxford²

Severe, disabling fatigue of at least six months' duration that:

- affects both physical and mental functioning
- was present for more than 50% of the time

Other symptoms, particularly myalgia and sleep and mood disturbance, may be present

Active, unresolved, or suspected disease likely to cause fatigue

Psychotic, melancholic or bipolar depression (but not uncomplicated major depression)

Psychotic disorders

Dementia

Anorexia or bulimia nervosa



This review is one of 87 chapters from the second issue of *Clinical Evidence*

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Section 5.0

Coverage Guidances

Hyperbaric Oxygen

Question: How should the HTAS Coverage Guidance regarding hyperbaric oxygen treatment be applied to the Prioritized List?

Question source: Health Technology Assessment Subcommittee

Issue: HTAS approved a new Coverage Guidance at their July, 2014 meeting. This CG needs final approval by HERC at the August, 2014 meeting. The summary of the coverage guidance is shown below. In addition, the OHP Medical Directors have requested consideration for some types of limits on hyperbaric oxygen therapy, such as a limit on visit numbers, a requirement for re-evaluation showing progress every 30 days, or other limit.

HERC COVERAGE GUIDANCE

Hyperbaric oxygen therapy is recommended for coverage (*strong recommendation*) for diabetic wounds of the lower extremities in patients who meet the all of the following criteria:

- Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, and
- Patient has a wound classified as Wagner grade III or higher, and
- Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days.

Hyperbaric oxygen therapy is recommended for coverage for late radiation tissue injury, and gas gangrene (*strong recommendation*).

Hyperbaric oxygen therapy is recommended for coverage for compromised surgical flaps and grafts, and for crush injuries (*weak recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for cerebral palsy, multiple sclerosis or chronic sensorineural hearing loss (*strong recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for the following conditions (*weak recommendation*):

- Venous ulcers,
- Surgical reconstruction without flaps and grafts,
- Refractory osteomyelitis,
- acute traumatic brain injury
- Brain injuries other than acute traumatic brain injury,
- Migraines and cluster headaches,
- Acute sensorineural hearing loss,
- Delayed or non-healing fractures,
- Bell's Palsy,
- Malignant otitis externa,
- Vascular dementia,
- Thermal burns, or
- Acute coronary syndrome.

Hyperbaric Oxygen

The following indications are presumed to be appropriate for coverage but are excluded from these coverage guidance recommendations: air or gas embolism, acute carbon monoxide poisoning, decompression illness and cyanide poisoning.

In addition to the Coverage Guidance, HTAS found the following indications to be considered appropriate/standard for treatment and/or life-saving and not requiring review:

- Necrotizing fasciitis
- Non-clostridial myonecrosis
- Crepitant anaerobic cellulitis
- Progressive bacterial gangrene
- Zygomycotic gangrenous cellulitis
- Decompressive illness ("Caisson disease")
- CO intoxication
- Cyanide poisoning
- Gas embolism
- Gas gangrene
- Progressive necrotizing infections

Current Prioritized List status:

CPT 99183 (Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session) is currently on lines 336 ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN Treatment: HYPERBARIC OXYGEN and 373 TOXIC EFFECT OF GASES, FUMES, AND VAPORS REQUIRING HYPERBARIC OXYGEN Treatment: HYPERBARIC OXYGEN. There is a guideline associated with these lines which restricts coverage in certain cases.

Line: 336

Condition: ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN (See Guideline Note 107)

Treatment: HYPERBARIC OXYGEN

ICD-9: 040.0,526.4,526.89,639.0,639.6,670.02-670.04,673.00-673.04,686.00-686.09,709.3,728.0,730.91-730.99,785.4,958.0,990,996.52,996.70-996.79,999.

ICD-10: I70.361-I70.369,I70.461-I70.469,I70.561-I70.569,I70.661-I70.669,I70.761-I70.769,I96,M27.8,M46.20-M46.39,M60.000-M60.005,M60.011-M60.09,M72.6,M86.9,O08.0,O88.011-O88.03,S47.1xxA-S47.1xxD,S47.2xxA-S47.2xxD,S47.9xxA-S47.9xxD,T66.xxxA-T66.xxxD,T79.0xxA-T79.0xxD,T80.0xxA-T80.0xxD,T82.898A-T82.898D,T82.9xxA-T82.9xxD,T83.89xA-T83.89xD,T83.9xxA-T83.9xxD,T84.89xA-T84.89xD,T84.9xxA-T84.9xxD,T85.89xA-T85.89xD,T85.9xxA-T85.9xxD,T86.820-T86.829

CPT: 98966-98969,99051,99060,99070,99078,99183,99201-99215,99281-99285,99341-99355,99358-99378,99381-99404,99408-99412,99429-99449,99487-99496,99605-99607

HCPCS: G0396,G0397,G0463

Line: 373

Condition: TOXIC EFFECT OF GASES, FUMES, AND VAPORS REQUIRING HYPERBARIC OXYGEN (See Guideline Note 107)

Treatment: HYPERBARIC OXYGEN

ICD-9: 986,987.0-987.9,993.3

ICD-10: T58.01xA-T58.01xD,T58.02xA-T58.02xD,T58.03xA-T58.03xD,T58.04xA-T58.04xD,T58.11xA-T58.11xD,T58.12xA-T58.12xD,T58.13xA-T58.13xD,T58.14xA-T58.14xD,T58.2x1A-T58.2x1D,T58.2x2A-T58.2x2D,T58.2x3A-T58.2x3D,T58.2x4A-T58.2x4D,T58.8x1A-T58.8x1D,T58.8x2A-T58.8x2D,T58.8x3A-T58.8x3D,T58.8x4A-T58.8x4D,T58.91xA-T58.91xD,T58.92xA-T58.92xD,T58.93xA-T58.93xD,T58.94xA-T58.94xD,T59.4x4A-T59.4x4D,T59.93xA-T59.93xD,T70.3xxA-T70.3xxD

CPT: 98966-98969,99051,99060,99070,99078,99183,99201-99239,99281-99285,99291-99404,99408-99412,99429-99449,99471-99476,99487-99496,99605-99607

HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463

Hyperbaric Oxygen

GUIDELINE NOTE 107, HYPERBARIC OXYGEN (Current List)

Lines 358,399

Hyperbaric oxygen is a covered service only under the following circumstances:

- when paired with ICD-9-CM code 526.4 for osteomyelitis of the jaw only
- when paired with ICD-9-CM codes 526.89 for osteoradionecrosis of the jaw only
- when paired with ICD-9-CM codes 639.0, 670.02, and 670.04 only if the infection is a necrotizing soft-tissue infection
- when paired with ICD-9-CM codes 730.10-730.99 only for chronic refractory osteomyelitis unresponsive to conventional medical and surgical management
- when paired with ICD-9-CM codes 927-929 only for posttraumatic crush injury of Gustilo type III B and C
- when paired with ICD-9-CM codes 990 only for osteoradionecrosis
- when paired with ICD-9-CM codes 996.7 only for compromised myocutaneous flaps

GUIDELINE NOTE 107, HYPERBARIC OXYGEN (January 1, 2015 ICD-10 List)

Lines 336,373

Hyperbaric oxygen is a covered service only under the following circumstances:

- when paired with ICD-10-CM code M27.2 for osteomyelitis of the jaw only
- when paired with ICD-10-CM codes M27.8 for osteoradionecrosis of the jaw only
- when paired with ICD-10-CM codes O08.0, M60.000-M60.09 only if the infection is a necrotizing soft-tissue infection;
- when paired with ICD-10-CM codes M46.20-M46.39, M86.9 only for chronic refractory osteomyelitis unresponsive to conventional medical and surgical management;
- when paired with ICD-10-CM codes S47.9, S57.0, S57.8, S67, S77, S87, S97 only for posttraumatic crush injury of Gustilo type III B and C;
- when paired with ICD-10-CM codes T66.xxxA only for osteoradionecrosis;
- when paired with ICD-10-CM codes T82.898A, T82.898D, T82.9xxA, T82.9xxD, T83.89xA, T83.89xD, T83.9xxA, T83.9xxD, T84.89xA, T84.89xD, T84.9xxA, T84.9xxD, T85.89xA, T85.89xD, T859xxA, T859xxD only for compromised myocutaneous flaps

Hyperbaric Oxygen

Codes currently on lines 336/373 or reviewed in HTAS report

ICD-9 code	Code description	Current Placement	Staff recommendation
040.0	Gas gangrene	239,336	No change
250.7	Diabetes with peripheral circulatory disorders	8,30,169,239	Add to line 336 with guideline Includes gangrene
250.8	Diabetes with other specified manifestations	30,75,297,349,381	Add to line 336 with guideline Includes diabetic ulcers
290.40	Vascular dementia	75,205,297,349,381	Do not add
340	Multiple sclerosis	75,255,297,349,381	Do not add
343	Cerebral palsy	75,297,349,381,(498)	Do not add
346.9	Migraine headache	414	Do not add
351.0	Bell's palsy	491	Do not add
380.14	Malignant otitis externa	209	Do not add
389.1	Sensorineural hearing loss	317,450	Do not add
339.0	Cluster headache	414	Do not add
410	Acute myocardial infarction	73	Do not add
411.81	Acute coronary occlusion without infarction	73	Do not add
526.4	Inflammatory conditions of jaw	188,270,336	Osteomyelitis of the jaw Remove from 336
526.89	Other specified diseases of the jaws	336, 533	Guideline restricting to osteoradionecrosis of the jaw No change
639.0	Genital tract and pelvic infection following abortion or ectopic and molar pregnancies	39,336	Guideline restricting to necrotizing soft-tissue infection No change
639.6	Embolism following abortion or ectopic and molar pregnancies	39,336	No change
670.02	Major puerperal infection, delivered, with mention of postpartum complication	1,336	Guideline restricting to necrotizing soft-tissue infection No change
670.04	Major puerperal infection, postpartum condition or complication	1,336	Guideline restricting to necrotizing soft-tissue infection No change
673.0x	Obstetrical air embolism	1,336	No change
686.00	Pyoderma, unspecified	209,336(D)	Scheduled for removal from line 336
686.01/ L88,	Pyoderma gangrenosum	336	Scheduled for removal from line 336 with ICD-10
686.09/ L08.89,	Other pyoderma	336	Scheduled for removal from line 336 with ICD-10
709.3	Degenerative skin disorders	336,633	Unclear what diagnosis this is related to. Remove from 336
728.0	Infective myositis	135,239,336	Form of gangrene. No change
730.0	Acute osteomyelitis	188	Do not add
730.1	Chronic osteomyelitis	258	Do not add
730.2	Unspecified osteomyelitis	Excluded	Do not add
730.9	Unspecified infection of bone	258,336	Remove from line 336
785.4	Gangrene	239,336	No change

Hyperbaric Oxygen

800-829	Fractures	Variable based on location	Do not add
854	Intracranial injury of other and unspecified nature	75,297,349,381	Do not add
870-897	Open wound, various locations	Variable based on location	Do not add—diabetic wounds and wounds with gangrene can be covered with other included codes
927-929	Crush injury	135	Add to 336 Note: some ICD-10 codes already added to line
940-949	Burns	61,76,200,613	Do not add
958.0	Air embolism	75,297,336,349,381	No change
986	Toxic effects of carbon monoxide	107,373	No change
987.x	Toxic effects of other gas	107,373	No change
990	Effects of radiation, unspecified	336,427	Current guideline limits to osteoradionecrosis—add soft tissue injury as an indication
993.3	Caisson disease	373	No change
996.52	Mechanical complication due to graft of other tissue, not elsewhere classified	336,427	No change in coding Add to guideline
996.7x	Other complications due to inserted device or prosthesis	290,336	No change
999.1	Air embolism as a complication of medical care, not elsewhere classified	290,336	No change
E868	Accidental poisoning by CO	Ancillary	No change
E952	Suicide by gases	Ancillary	No change
E962.2	Assault by gases	Ancillary	No change
E982.1	Poisoning by CO, undetermined	Ancillary	No change

Hyperbaric Oxygen

HERC staff recommendations:

- 1) For the October 1, 2014 and January 1, 2015 Prioritized Lists, add/delete diagnoses on line 358/336 as shown below
 - a. No changes required to line 399/373
 - b. Changes to line 358/336 as reviewed in table above
- 2) For the next biennial review List (October 1, 2015 or January 1, 2016 Prioritized List), combine lines 336 and 373, as shown below, with placement of the combined line at line 336.
 - a. Diagnoses included on new line as noted in the table above
 - b. CPT and HCPCS codes included from both lines
 - c. Keep Guideline Note 107 revisions from January 1, 2015 List
- 3) Modify GN 107 as shown below
 - a. Wording based on the HTAS coverage guidance, with added language from the CMS HBOT guideline regarding need for re-evaluation of diabetic wounds every 30 days and need for proof of progress. This addition addresses the OHP Medical Directors concerns.

For the October 1, 2014 PL and January 1, 2015 PL:

Line: 358/336

Condition: ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN (See Guideline Note 107)

Treatment: HYPERBARIC OXYGEN

ICD-9: 040.0, [250.7](#), [250.8](#), ~~526.4~~, 526.89, 639.0, 639.6, 670.02-670.04, 673.00-673.04, ~~686.00-686.09~~, ~~709.3~~, 728.0, 730.91-730.99, 785.4, [927-929](#), 958.0, 990, 996.52, 996.70-996.79, 999.

ICD-10: [E11.5x](#), [E11.621](#), [E11.622](#), [E11.628](#), I70.361-I70.369, I70.461-I70.469, I70.561-I70.569, I70.661-I70.669, I70.761-I70.769, I96, M27.8, ~~M46.20~~, ~~M46.39~~, M60.000-M60.005, M60.011-M60.09, M72.6, ~~M86.9~~, O08.0, O88.011-O88.03, [S07.xxx](#), [S17.xxx](#), [S38.xxx](#), S47.1xxA-S47.1xxD, S47.2xxA-S47.2xxD, S47.9xxA-S47.9xxD, [S57.xxx](#), [S67.xxx](#), [S77.xxx](#), [S87.xxx](#), [S97.xxx](#), T66.xxA-T66.xxD, T79.0xxA-T79.0xxD, [T79.Axx](#), T80.0xxA-T80.0xxD, T82.898A-T82.898D, T82.9xxA-T82.9xxD, T83.89xA-T83.89xD, T83.9xxA-T83.9xxD, T84.89xA-T84.89xD, T84.9xxA-T84.9xxD, T85.89xA-T85.89xD, T85.9xxA-T85.9xxD, T86.820-T86.829

CPT: 98966-98969, 99051, 99060, 99070, 99078, 99183, 99201-99215, 99281-99285, 99341-99355, 99358-99378, 99381-99404, 99408-99412, 99429-99449, 99487-99496, 99605-99607

HCPCS: G0396, G0397, G0463

Line: 399/373

Condition: TOXIC EFFECT OF GASES, FUMES, AND VAPORS REQUIRING HYPERBARIC OXYGEN (See Guideline Note 107)

Treatment: HYPERBARIC OXYGEN

ICD-9: 986, 987.0-987.9, 993.3

ICD-10: T58.01xA-T58.01xD, T58.02xA-T58.02xD, T58.03xA-T58.03xD, T58.04xA-T58.04xD, T58.11xA-T58.11xD, T58.12xA-T58.12xD, T58.13xA-T58.13xD, T58.14xA-T58.14xD, T58.2x1A-T58.2x1D, T58.2x2A-T58.2x2D, T58.2x3A-T58.2x3D, T58.2x4A-T58.2x4D, T58.8x1A-T58.8x1D, T58.8x2A-T58.8x2D, T58.8x3A-T58.8x3D, T58.8x4A-T58.8x4D, T58.91xA-T58.91xD, T58.92xA-T58.92xD, T58.93xA-T58.93xD, T58.94xA-T58.94xD, T59.4x4A-T59.4x4D, T59.93xA-T59.93xD, T70.3xxA-T70.3xxD

CPT: 98966-98969, 99051, 99060, 99070, 99078, 99183, 99201-99239, 99281-99285, 99291-99404, 99408-99412, 99429-99449, 99471-99476, 99487-99496, 99605-99607

HCPCS: G0396, G0397, G0406-G0408, G0425-G0427, G0463

Hyperbaric Oxygen

For the Biennial Review List:

Line: 336

Condition: ~~ANAEROBIC INFECTIONS~~ CONDITIONS REQUIRING HYPERBARIC OXYGEN THERAPY (See Guideline Note 107)

Treatment: HYPERBARIC OXYGEN

ICD-9: 040.0, 250.7, 250.8, 526.4, 526.89, 639.0, 639.6, 670.02-670.04, 673.00, 673.04, ~~686.00, 686.01, 686.09, 709.3~~, 728.0, ~~730.91-730.99~~, 785.4, 927-929, 958.0, 990, 996.52, 996.70-996.79, 986, 987.0-987.9, 993.3, 999.

ICD-10: E11.5x, E11.621, E11.622, E11.628, I70.361-I70.369, I70.461-I70.469, I70.561-I70.569, I70.661-I70.669, I70.761-I70.769, I96, M27.8, ~~M46.20-M46.39~~, M60.000-M60.005, M60.011-M60.09, M72.6, ~~M86.9~~, O08.0, O88.011-O88.03, S07.xxx, S17.xxx, S38.xxx, S47.1xxA-S47.1xxD, S47.2xxA-S47.2xxD, S47.9xxA-S47.9xxD, S57.xxx, S67.xxx, S77.xxx, S87.xxx, S97.xxx, T58.01xA-T58.01xD, T58.02xA-T58.02xD, T58.03xA-T58.03xD, T58.04xA-T58.04xD, T58.11xA-T58.11xD, T58.12xA-T58.12xD, T58.13xA-T58.13xD, T58.14xA-T58.14xD, T58.2x1A-T58.2x1D, T58.2x2A-T58.2x2D, T58.2x3A-T58.2x3D, T58.2x4A-T58.2x4D, T58.8x1A-T58.8x1D, T58.8x2A-T58.8x2D, T58.8x3A-T58.8x3D, T58.8x4A-T58.8x4D, T58.91xA-T58.91xD, T58.92xA-T58.92xD, T58.93xA-T58.93xD, T58.94xA-T58.94xD, T59.4x4A-T59.4x4D, T59.93xA-T59.93xD, T66.xxxA-T66.xxxD, T70.3xxA-T70.3xxD, T79.0xxA-T79.0xxD, T79.Axx, T80.0xxA-T80.0xxD, T82.898A-T82.898D, T82.9xxA-T82.9xxD, T83.89xA-T83.89xD, T83.9xxA-T83.9xxD, T84.89xA-T84.89xD, T84.9xxA-T84.9xxD, T85.89xA-T85.89xD, T85.9xxA-T85.9xxD, T86.820-T86.829

CPT: 98966-98969, 99051, 99060, 99070, 99078, 99183, 99201-99215, 99281-99285, 99291-99404, 99341-99355, 99358-99378, 99381-99404, 99408-99412, 99429-99449, 99471-99476, 99487-99496, 99605-99607

HCPCS: G0396, G0397, G0406-G0408, G0425-G0427, G0463

For all Lists:

GUIDELINE NOTE 107, HYPERBARIC OXYGEN

Lines 336, ~~373~~ (delete only for biennial review List)

Hyperbaric oxygen is a covered service only under the following circumstances:

- when paired with ICD-9-CM code ~~526.4~~ for osteomyelitis of the jaw only
- when paired with ICD-9-CM codes 250.7x and 250.8x/ICD-10-CM E11.5x and E11.621, E11.622, E11.623 for diabetic wounds with gangrene OR diabetic wounds of the lower extremities in patients who meet the all of the following criteria:
 - Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, AND
 - Patient has a wound classified as Wagner grade III or higher, AND
 - Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days, AND
 - Wounds must be evaluated at least every 30 days during administration of hyperbaric oxygen therapy. Continued treatment with hyperbaric oxygen therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.
- when paired with ICD-9-CM codes 526.89/ ICD-10--CM codes M27.8 for osteoradionecrosis of the jaw only
- when paired with ICD-9-CM codes 639.0, 670.02, and 670.04/ ICD-10--CM codes O08.0, M60.000-M60.09 only if the infection is a necrotizing soft-tissue infection
- when paired with ICD-9-CM codes ~~730.10-730.99/ICD-10-CM M46.20-M46.39, M86.9~~ only for chronic refractory osteomyelitis unresponsive to conventional medical and surgical management
- when paired with ICD-9-CM codes 927-929/ICD-10 CM codes S07.xxx, S17.xxx, S38.xxx, S47.1xxA-S47.1xxD, S47.2xxA-S47.2xxD, S47.9xxA-S47.9xxD, S57.xxx, S67.xxx, S77.xxx, S87.xxx, S97.xxx, T79.Axx, only for posttraumatic crush injury of Gustilo type III B and C
- when paired with ICD-9-CM codes 990/ ICD-10--CM codes T66.xxxA only for osteoradionecrosis and soft tissue radiation injury
- when paired with ICD-9-CM codes 996.52, 996.7/ ICD-10--CM codes ~~T86.820-T86.829~~, T82.898A, T82.898D, T82.9xxA, T82.9xxD, T83.89xA, T83.89xD, T83.9xxA, T83.9xxD, T84.89xA, T84.89xD, T84.9xxA, T84.9xxD, T85.89xA, T85.89xD, T85.9xxA, T85.9xxD, T85.9xxD only for compromised myocutaneous flaps

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: INDICATIONS FOR HYPERBARIC OXYGEN THERAPY

DRAFT for VbBS meeting materials 8/14/2014

HERC COVERAGE GUIDANCE

Hyperbaric oxygen therapy is recommended for coverage (*strong recommendation*) for diabetic wounds of the lower extremities in patients who meet all of the following criteria:

- Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, and
- Patient has a wound classified as Wagner grade III or higher, and
- Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days.

Hyperbaric oxygen therapy is recommended for coverage for late radiation tissue injury, and gas gangrene (*strong recommendation*).

Hyperbaric oxygen therapy is recommended for coverage for compromised surgical flaps and grafts, and for crush injuries (*weak recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for cerebral palsy, multiple sclerosis or chronic sensorineural hearing loss (*strong recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for the following conditions (*weak recommendation*):

- Venous ulcers,
- Surgical reconstruction without flaps and grafts,
- Refractory osteomyelitis,
- acute traumatic brain injury
- Brain injuries other than acute traumatic brain injury,
- Migraines and cluster headaches,
- Acute sensorineural hearing loss,
- Delayed or non-healing fractures,
- Bell's Palsy,
- Malignant otitis externa,
- Vascular dementia,
- Thermal burns, or
- Acute coronary syndrome.

The following indications are presumed to be appropriate for coverage but are excluded from these coverage guidance recommendations: air or gas embolism, acute carbon monoxide poisoning, decompression illness and cyanide poisoning.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted Sources

Bennett, M.H., Lehm, J.P., & Jepson, N. (2011). Hyperbaric oxygen therapy for acute coronary syndrome. *Cochrane Database of Systematic Reviews, Issue 8*. Art. No.: CD004818. DOI: 10.1002/14651858.CD004818.pub3. Retrieved from <http://summaries.cochrane.org/CD004818/hyperbaric-oxygen-may-reduce-the-risk-of-dying-the-time-to-pain-relief-and-the-chance-of-adverse-heart-events-in-people-with-heart-attack-and-unstable-angina>

Bennett, M.H., Stanford, R.E., & Turner, R. (2012a). Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union. *Cochrane Database of Systematic Reviews, Issue 11*. Art. No.: CD004712. DOI: 10.1002/14651858.CD004712.pub4. Retrieved from <http://summaries.cochrane.org/CD004712/using-oxygen-at-high-pressure-in-a-compression-chamber-for-the-treatment-of-broken-bones>

Bennett, M.H., Trytko, B., & Jonker, B. (2012b). Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. *Cochrane Database of Systematic Reviews, Issue 12*. Art. No.: CD004609. DOI: 10.1002/14651858.CD004609.pub3. Retrieved from <http://summaries.cochrane.org/CD004609/does-hyperbaric-oxygen-therapy-improve-the-survival-and-quality-of-life-in-patients-with-traumatic-brain-injury>

- Buckley, N.A., Juurlink, D.N., Isbister, G., Bennett, M.H. & Lavonas, E.J. (2011). Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database of Systematic Reviews, Issue 4*. Art. No.: CD002041. DOI: 10.1002/14651858.CD002041.pub3. Retrieved from <http://summaries.cochrane.org/CD002041/there-is-insufficient-evidence-to-support-the-use-of-hyperbaric-oxygen-for-treatment-of-patients-with-carbon-monoxide-poisoning>
- Holland, N.J., Bernstein, J.M., & Hamilton, J.W. (2012). Hyperbaric oxygen therapy for Bell's palsy. *Cochrane Database of Systematic Reviews, Issue 2*. Art. No.: CD007288. DOI: 10.1002/14651858.CD007288.pub2. Retrieved from <http://summaries.cochrane.org/CD007288/high-pressure-hyperbaric-oxygen-therapy-for-bells-palsy>
- Leof, A., Kriz, H., & King, V. (2012). *Hyperbaric oxygen therapy for treatment of gas gangrene*. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.
- National Institute for Health and Clinical Excellence (NICE). (2012). *Diabetic foot problems: Inpatient management of diabetic foot problems. NICE clinical guideline 119*. London: NICE. Retrieved from www.nice.org.uk/guidance/CG119
- Phillips, J.S., & Jones, S.E.M. (2013). Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa. *Cochrane Database of Systematic Reviews, Issue 5*. Art. No.: CD004617. DOI: 10.1002/14651858.CD004617.pub3. Retrieved from <http://summaries.cochrane.org/CD004617/hyperbaric-oxygen-as-an-additional-treatment-for-malignant-otitis-externa>
- Washington State Health Care Authority Health Technology Assessment Program (WA HTA). (2013). *Hyperbaric oxygen therapy (HBOT) for tissue damage, including wound care and treatment of central nervous system (CNS) conditions*. Olympia: WA HTA. Retrieved from <http://www.hca.wa.gov/hta/Pages/Hyperbaric%20Oxygen%20%28HBO2%29%20Treatment%20for%20Tissue%20Damage.aspx>
- Xiao, Y., Wang, J., Jiang, S., & Luo, H. (2012). Hyperbaric oxygen therapy for vascular dementia. *Cochrane Database of Systematic Reviews, Issue 7*. Art. No.: CD009425. DOI: 10.1002/14651858.CD009425.pub2. Retrieved from <http://summaries.cochrane.org/CD009425/hyperbaric-oxygen-therapy-for-vascular-dementia>

Additional Sources Provided by Expert

Murad, M.H., Altayar, O., Bennett, M., Wei, J.C., Claus, P.L., Asi, N., et al. (2013). Using GRADE for evaluating the quality of evidence in hyperbaric oxygen therapy clarifies evidence limitations. *Journal of Clinical Epidemiology*, 67(1), 65-72. doi: 10.1016/j.jclinepi.2013.08.004. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/24189086>

Undersea and Hyperbaric Medical Society (UHMS). (2014). *Hyperbaric oxygen therapy indications* (13th ed.). L.K. Weaver (Ed.). Durham, NC: UHMS. Retrieved from <http://membership.uhms.org/>

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

The following clinical background summary is extracted from the WA HTA report (2013, p. 2-3).

Hyperbaric oxygen therapy (HBOT) involves the systemic administration of 100% oxygen while the patient is inside a treatment chamber under pressures > 1 atmosphere absolute (ATA). Hyperbaric oxygen was introduced as a medical treatment more than 200 years ago and has been advocated as a treatment for a wide variety of conditions over the years. Despite a large body of published literature, it remains unclear as to the indications for which HBOT is most effective and safe. Among the indications for which questions still remain are diabetic non-healing wounds, including foot ulcers; other non-healing wounds, including skin and tissue grafts, thermal burns, and surgical wounds; refractory osteomyelitis; late radiation tissue injury (LRTI); brain injury; cerebral palsy; headache and migraine; multiple sclerosis; and sensorineural hearing loss.

Foot wounds are one of the most common complications of diabetes and are responsible for substantial morbidity. At any given time, lower extremity ulcers affect approximately 1 million diabetics. HBOT is used along with traditional systemic and topical therapies to promote diabetic wound healing. It is purported to reverse anaerobic infection, improve blood supply, and reduce ischemic nerve damage.

Chronic wounds other than those related to diabetes include venous and pressure sores, with causes that are related to venous insufficiency, pressure, trauma, vascular disease, and immobilization. Although the causes of chronic

wounds vary, in all cases, at least one of the phases of wound healing is compromised.

Surgical wounds present a medical problem if they are large in size, especially if bones and tendons are exposed and therefore are not amenable to primary closure. By increasing the oxygen tension in hypoxic wounds, HBOT is thought to restore the level of oxygenation required for compromised tissue to function efficiently. HBOT is also proposed as a means of preparing a base for skin grafts and flaps or preserving compromised grafts and flaps.

Thermal burns are the third largest cause of accidental death, with 300,000 serious burns and 6000 fatalities occurring annually in the United States. HBOT for thermal burns is directed at enhancing host defenses, preserving marginally viable tissue, protecting the microvasculature, augmenting neovascularization, and promoting wound closure.

Chronic osteomyelitis can develop when bacterial or fungal infection within bone deprives the bone of its blood supply, and the resulting ischemia causes bone tissue necrosis. It has been hypothesized that the additional oxygen delivered during HBOT may promote collagen synthesis and angiogenesis in patients with hypoxic osteomyelitic wounds.

More than 1.4 million Americans are diagnosed with cancer each year, and approximately half of these patients receive radiation therapy as part of their management. Radiation side effects can be categorized as either acute or delayed (chronic) complications; the latter may develop months or years after radiation treatment and collectively are known as late radiation tissue injury (LRTI) or late radiation side effects. Although any tissue may be affected, late radiation tissue injury occurs most commonly in the head and neck, chest wall, breast, and pelvis, reflecting the anatomical areas most commonly irradiated. Chronic radiation damage is called *osteoradionecrosis (ORN)* when bone is damaged and *soft tissue radionecrosis* when muscle, skin, or internal organs have been damaged. Evidence continues to emerge as to the effectiveness of HBOT for the treatment of LRTI, including ORN.

The use of HBOT for brain injuries is based on a theory that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically. Traumatic brain injury (TBI), accounts for more than 1.3 million emergency room visits, approximately 275,000 hospitalizations, and 52,000 deaths annually.

Cerebral palsy is a neuromuscular disorder that arises in children due to damage of the developing brain. This disorder occurs in 0.1% to 0.5% of live births and is

characterized by impairments of muscle control, the senses, and perception. There is no known cure for cerebral palsy; the usefulness of HBOT for the treatment of cerebral palsy relates to the possibility of restoring function in portions of the brain that have suffered damage due to lack of oxygenation or other trauma.

More than 45 million individuals in the United States suffer from chronic, recurring headaches. Approximately 90% of headaches are primary headaches, which do not arise from an underlying medical condition. Cluster headaches are quite rare and occur in only 0.1% of the population. Migraine headache affects more than 28 million individuals in the United States and more than 300 million individuals worldwide. The theory is that HBOT might favorably influence vascular headache resistant to conventional drug therapy.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that afflicts an estimated 400,000 individuals in the United States and more than 2.5 million worldwide. The use of HBOT as a treatment for MS was originally based on the demonstrated ability of HBOT to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy. For several years, there was a flurry of investigation into its effectiveness for the treatment of MS, which produced a number of randomized studies in the UK, U.S., and Europe.

Sudden sensorineural hearing loss (SSHL), or sudden deafness, is a rapid loss of hearing with onset over a period of less than 72 hours. The estimated incidence of SSHL ranges from 5 to 20 per 100,000 persons per year but may be as high as 300 per 100,000 persons per year. HBOT has been proposed for the treatment of SSHL, the rationale being that the hearing loss appears to be caused by a hypoxic event in the cochlear apparatus; therefore, HBOT may potentially reverse the oxygen deficit, increase oxygen pressures in the cochlea, and improve microcirculation. Proving the effectiveness of HBOT for SSHL is complicated given the fact that up to two thirds of SSHL cases resolve spontaneously.

Bell's palsy is an acute unilateral facial weakness without an identifiable cause. It is often associated with ear discomfort, noise sensitivity and decreased tear production. It is estimated that it affects one person in 60 during their lifetime. Corticosteroids improve rates of recovery, while antiviral agents do not. It is hypothesized that in Bell's palsy, hypoxic degeneration of the facial nerve can be reduced and functional recovery can be improved with use of HBOT.

Fractures of bone are common and typically heal within three to six months (Bennett, 2012a). However, the fracture healing process may be impaired leading to delayed or non-union of the fractured bone. Non-union is considered present when there has been no evidence of healing after six months. Rates vary widely, but range from 5% to 10% of fractures. In cases where there is a strong possibility of a delayed or non-union, extra interventions to promote healing are often appropriate. HBOT has been proposed as one of those interventions.

Malignant otitis externa is a potentially fatal infection of the external ear canal and surrounding soft tissue and bone (Phillips, 2013). It may be complicated by involvement of cranial nerves, principally the facial nerves and the contents of the jugular foramen. It is an uncommon condition mainly found in the elderly or in diabetics. Traditionally the mainstay of treatment has been prolonged antibiotic therapy, repeated debridement of necrotic tissue and sometimes aggressive surgical management. Hyperbaric oxygen has been proposed as a beneficial adjunctive therapy.

Carbon monoxide is a gas generated from incomplete combustion, and poisoning with CO is an important cause of injury worldwide (Buckley, 2011). In the United States alone, there are an estimated 50,000 annual incidences of CO poisoning. There are two syndromes that can occur after acute CO poisoning, persistent and delayed neurologic sequelae. Standard treatment for CO poisoning includes removal from the site of exposure, administration of supplemental oxygen, and general supportive care. The elimination of carboxyhemoglobin is shortened significantly by the administration of 100% oxygen at atmospheric pressure. The administration of HBOT further hastens this process.

Dementia is a condition characterized by loss of memory, confusion, problems with speech and comprehension, and changes in personality (Xiao, 2012). The number of dementia cases is projected to reach 81 million by the year 2040. Vascular dementia, the second most common form of dementia, is not a single disease but a group of syndromes based on a variety of vascular conditions. There are no current effective treatments, and possible benefits of HBOT have been proposed.

Cardiovascular disease (CVD) is the leading cause of death in the world (Bennett, 2011). Acute coronary syndrome (ACS) is defined as unstable or persistent angina with or without myocardial infarction (MI). A significant number of patients with acute MI will suffer major morbidity or mortality, despite interventions such as thrombolysis or angioplasty. Hyperbaric oxygen therapy has been proposed to improve outcomes following ACS.

Gas gangrene is a bacterial infection usually caused by *Clostridium perfringens* bacteria (Leof, 2012). Infection of this type is a medical emergency and can cause myonecrosis,

gas production and sepsis and, without immediate treatment, may progress to toxemia, shock and death. Treatment usually consists of wound debridement and excision and can frequently require amputation. HBOT therapy has also been frequently used.

Technology Description

The technology description is extracted from the WA HTA report (2013, p. 3-4).

HBOT involves the therapeutic administration of 100% oxygen at environmental pressures > 1 ATA, the atmospheric pressure at sea level. Administering oxygen at pressures greater than 1 ATA requires compression. This is achieved by placing the patient in an airtight chamber. The pressure is increased inside the chamber, and 100% oxygen is given for respiration, which delivers a greatly increased pressure of oxygen to the lungs, blood, and tissues.

There are 2 types of chambers used for administering HBOT: a monoplace chamber for a single patient; or a multiplace chamber used for multiple patients and medical personnel. No standard protocol has been identified for administering HBOT.

Costs for HBOT were reported in the WA HTA report for three different populations, public employees, Medicaid and labor and industry. Costs, average treatment days and the range of days of treatment are presented in the table below:

Population	Public Employee	Medicaid	Labor and Industry
Average allowed amount per patient	\$27,710	\$46,774	\$9,526
Average days of treatment	29	23	20
Range of days of treatment	1-101	1-93	1-120

Evidence Review

Effectiveness of HBOT

The majority of the evidence presented in this document that pertains to HBOT comes from the trusted sources listed at the beginning of this document. However, for several conditions, evidence was determined by HTAS to be insufficient for the committee to recommend policy, therefore they requested that additional evidence provided by the assigned expert be incorporated into this document. Two such evidence sources were utilized. One was the book, Hyperbaric Oxygen Therapy Indications, published by the Undersea and Hyperbaric Medical Society (UHMS) in 2014. The other, Murad 2013, is a systematic review of the literature on HBOT for all outcomes. The authors included 17

systematic reviews that included 44 RCTs and 131 observational studies, plus an additional 5 RCTs published after the dates of the SRs. The authors (three of whom are members of the GRADE working group) then rated the quality of the evidence using GRADE for all indications for which there was sufficient information, and compared that rating to an assessment using the American Heart Association (AHA) criteria that relies primarily on study type. This AHA evidence quality grading system is used by the UHMS, and in this framework, level A evidence is derived from multiple RCTs or meta-analyses, level B is derived from a single RCT or non-randomized studies, and level C is derived from expert opinion or case studies. When the evidence is from one of these two sources, it will be identified as such by *italics*.

Diabetic Nonhealing Wounds, Including Foot Ulcers

Moderate-quality evidence from three systematic reviews (1437 participants), including 16 peer-reviewed studies reporting on the effectiveness of HBOT for the treatment of diabetic foot ulcers, suggests that the addition of HBOT to standard wound care promotes wound healing and limb salvage in the short term (WA HTA, 2013). The results are clinically meaningful, with pooled data from three studies suggesting that eight patients would need to be treated with HBOT as an adjunct to standard wound care for an additional one person to have complete wound healing. In addition, the findings from two studies (one good quality, one fair quality) provide moderate quality evidence that the effectiveness of HBOT to heal remains significant at one-year follow-up. Incidence of healing and wound size reduction are clinically synonymous but are often measured as separate research outcomes. There was insufficient evidence to determine the effectiveness of HBOT to reduce wound size but given that the evidence supports HBOT for improved incidence of healing, it is reasonable to assume that further study into the effectiveness of HBOT to reduce wound size would find similar benefits. There is low-quality evidence suggesting no benefit from HBOT on quality of life (QOL) measures.

A NICE guideline on inpatient management of diabetic foot problems recommends that HBOT not be offered as a treatment unless part of a clinical trial (NICE, 2012). However, the evidence review that supports the guideline included six RCTs, and allowed authors to conclude that there was moderate evidence that HBOT resulted in fewer surgical interventions and low evidence that it resulted in fewer major amputations. On the other hand, there was moderate evidence that HBOT did not reduce the number of minor amputations, or improve complete wound healing at 4 to 6 weeks, and low evidence that it does not reduce ulcer surface area. A cost-effectiveness evaluation found that an incremental cost-effectiveness ratio of around £25,000.

Other Nonhealing Wounds, Including Skin and Tissue Grafts, Thermal Burns and Surgical Wounds

Overall, there is limited low-quality evidence from 12 peer-reviewed studies, suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, and surgical reconstruction (without grafts or flaps) (WA HTA, 2013). There is low confidence in the reported estimate of effects for these conditions and the reported benefits should be interpreted with caution.

Venous Ulcers

The evidence for venous wounds includes two small RCTs (total N=46) and one case series (n=35). One of the RCTs found a significant reduction in wound area after 6 weeks but no difference at 18 weeks, while the other found a 59% reduction in wound area in the HBOT group compared to a 26% increase in the control group after 30 days.

UHMS 2014 notes the existence of one RCT evaluating HBOT for treatment of leg ulcers of undefined etiology, but go on to state:

“HBOT treatment is not indicated in the primary management of venous stasis ulcers of the lower extremities.”

Murad 2013 states that for venous ulcers, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of the proportion of ulcers healed, the relative effect size is 5.00 (95% CI 0.28 to 90.18), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias and imprecision, and upgraded for a large treatment effect.

Surgical Reconstruction without Flaps and Grafts

For patients who have undergone surgical reconstruction without flaps or grafts, the evidence is limited to two poor quality prospective cohort studies (N=84). One found improved healing in more HBOT patients (89% vs. 83%), while the other found significantly more patients suffered infection and breakdown in the control group (78% vs. 17%). *This indication is not addressed in the UHMS 2014 book or by Murad 2013.*

Compromised Flaps and Grafts

For graft and flap survival, the evidence includes three RCTs (2 poor quality, 1 unknown quality), four case series and one additional study of unknown design. Total N=425. One of the RCTs found significantly better graft survival at 7 days in the HBOT group, while another found no significant benefit when compared to heparin and dexamethasone. The third RCT found improved healing of compromised skin grafts, while the study of unknown design reported significantly greater delay in wound healing in the control group (55% vs. 11%).

UHMS 2014 reported on a large number of animal studies. With regard to studies in humans, the authors report that there are no fewer than 16 studies supporting the effectiveness of HBOT for threatened grafts, which include a range of study types from RCTs to animal research. The only RCT discussed in detail (Perrins 1967) was included in the WA HTA report and was rated poor quality; it found that grafts survived in 64% of the HBOT arm compared to 17% of control ($p < 0.01$). The authors also reference one retrospective cohort study and 8 case series to support their assessment. They state:

“the use of HBOT for the salvage of compromised grafts and flaps should be considered as a class 1b intervention according to the American Heart Association Evidence-based Guidelines as it is both useful and effective based on evidence from a single randomized trial and non-randomized studies with the potential benefit far outweighing the risks.”

Murad 2013 states that for split skin grafting, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of complete graft survival at day 7, the relative effect size is 3.5 (95% CI 1.35 to 9.11), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias, imprecision and indirectness, and upgraded for a large treatment effect.

For flap grafting for limb skin defects, the quality of evidence is listed as class B using the AHA grading system. Murad et al. report that for the outcome of flap survival at day 7, the relative effect size is 1.18 (95% CI 1.02 to 1.35), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias and imprecision.

In addition, there is insufficient evidence from one study to determine the effectiveness of HBOT for crush injuries, insufficient evidence (primarily due to mixed results) from two studies to determine if HBOT is effective for the treatment of thermal burns, and insufficient evidence from one study to determine the effectiveness of HBOT for the treatment of acute traumatic peripheral ischemia.

Crush Injuries

For crush injuries, the evidence is limited to one fair quality RCT of 36 patients, which found significantly more complete healing in the HBOT group, but no difference in time to healing, number of amputations or length of hospital stay.

UHMS 2014 reports approximately 600 clinical cases of using HBOT for crush injuries, and of those, approximately 80% reported positive outcomes. Only one RCT is specifically discussed (Bouachour 1996), which was included as the only RCT in the WA HTA review and rated fair quality. UHMS states that complete wound healing

occurred in 94% of the HBOT group compared to 33% of controls ($p<0.01$), and that there was a need for additional surgeries in 6% of the HBOT group compared to 33% of controls ($p<0.05$). The description of this study in the WA HTA report adds additional information:

“...significantly more complete healing among the HBOT group (94% complete healing) compared with controls (56% complete healing) (RR, 1.7; 95% CI, 1.11-2.61; NNT, 3), no significant difference with regard to mean time to healing among the HBOT group (50.2 days) versus controls (55.8 days) (MD, 5.6 days; 95% CI, -19 to 7.8), no significant difference with regard to the number of amputations among the HBOT group (0) versus controls (2) (RR, 0.2; 95% CI, 0.01-3.89), and no significant difference in mean length of hospital stay among the HBOT group (22.4 days) versus controls (22.9 days) (MD, -5.0; 95% CI, -9.96 to 8.96).”

Murad 2013 states that for crush injuries, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of complete wound healing without necrosis requiring excision, the relative effect size is 1.70 (95% CI 1.11 to 2.61), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias and imprecision.

Thermal Burns

For patients with thermal burns, the evidence includes two fair quality RCTs (N=141). One found no significant difference in hospital length of stay, additional surgeries or mortality, while the other found better time to healing in the HBOT group (20 days vs. 44 days).

Acute Traumatic Peripheral Ischemia

For acute traumatic peripheral ischemia, the evidence is limited to one case series (n=23) that did not provide detailed data.

Refractory Osteomyelitis

Low-quality evidence from 23 primary data studies (one fair quality nonrandomized controlled trial, one poor quality nonrandomized controlled trial, 21 case series) suggests that HBOT may be effective as an adjunct treatment for refractory osteomyelitis but there is low confidence in the reported estimate of effects (WA HTA, 2013). There is some evidence from the one small, fair-quality, nonrandomized trial that HBOT may reduce the rates of relapse infection (0% vs. 33%), but this is contradicted by the other nonrandomized trial, which found no significant difference in relapse rate (14% for HBOT, 7% for control). The latter trial (n=28) also found no benefit from HBOT as an adjunct to surgery and antibiotics with regard to cure (79% cure for HBOT vs.

93% cure for control). Further good-quality studies are necessary to determine the effectiveness of HBOT for the treatment of refractory osteomyelitis.

UHMS 2014 reports that the evidence pertaining to the use of HBOT for refractory osteomyelitis consists of 26 reports, three of which utilized some kind of comparison group, although none were RCTs. The authors recommend the use of HBOT either before or after surgical debridement, depending on location of the infection, rationalizing that:

“The overwhelming majority of available studies supported the use of HBOT as a beneficial adjunct in the management of refractory osteomyelitis Treatment success rates generally exceeded that found in the literature for “standard of care” therapy using antibiotics and debridement alone....”

Murad 2013 states that for refractory osteomyelitis, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of infection cure, the relative effect size is 0.85 (95% CI 0.62 to 1.15), and using GRADE, has very low quality evidence; evidence from one prospective cohort study was downgraded for imprecision.

Late Radiation Tissue Injury

There is moderate-quality evidence from 35 primary data studies suggesting that HBOT improves outcomes of late radiation tissue injury affecting bone and soft tissues (WA HTA, 2013). There is no overall estimate of effect because of the heterogeneity between studies, but the evidence suggests that radiation-induced tissue and bone damage to the head and neck, anus, and rectum show consistent clinical improvement with HBOT. There is also moderate-quality evidence that HBOT reduces the risk of developing ORN following tooth extraction in a previously irradiated area.

Brain Injury

For TBI, moderate quality evidence consisted of seven studies that included 571 people (Bennett, 2012b). The results of two studies indicate use of HBOT results in a statistically significant decrease in the proportion of people with an unfavorable outcome one month after treatment using the Glasgow Outcome Scale (GOS) (RR for unfavorable outcome with HBOT 0.74, 95% CI 0.61 to 0.88, $P = 0.001$). This five-point scale rates the outcome from one (dead) to five (good recovery); an ‘unfavorable’ outcome was considered as a score of one, two or three. Pooled data from final follow-up showed a significant reduction in the risk of dying when HBOT was used (RR 0.69, 95% CI 0.54 to 0.88, $P = 0.003$) and suggests we would have to treat seven patients to avoid one extra death (number needed to treat [NNT] 7, 95% CI 4 to 22, moderate quality evidence). The Glasgow Coma Scale (GCS) has a total of 15 points, and two small trials reported a significant improvement in GCS for patients treated with HBOT

(mean difference [MD] 2.68 points, 95%CI 1.84 to 3.52, $P < 0.0001$), although these two trials showed considerable heterogeneity ($I^2 = 83\%$). The improvement of 2.68 points in GCS is difficult to interpret. This scale runs from three (deeply comatose and unresponsive) to 15 (fully conscious), and the clinical importance of an improvement of approximately three points will vary dramatically with the starting value (for example an improvement from 12 to 15 would represent an important clinical benefit, but an improvement from three to six would leave the patient with severe and highly dependent impairment). In general, the studies were small and carried a significant risk of bias. None described adequate randomization procedures or allocation concealment, and none of the patients or treating staff were blinded to treatment.

Evidence from six poor or very-poor-quality primary data studies are insufficient to determine if HBOT is effective in improving health outcomes among patients with brain injuries other than TBI (WA HTA, 2013).

Cerebral Palsy

There is insufficient evidence from six studies (two RCTS and four observational studies) to determine the effectiveness of HBOT for the treatment of cerebral palsy (WA HTA, 2013). Inconsistencies in the direction of the results, a paucity of studies, small sample sizes, differences in baseline characteristics, and the number of treatment sessions provided, all contributed to the low-quality grade assigned to motor function, which was considered the major outcome of interest. Fair- to poor-quality observational data suggests an improvement in motor function and other disease-specific subjective outcome measures among children receiving HBOT, but a fair-quality RCT found no additional benefit from HBOT among children receiving HBOT versus those receiving pressurized air.

Multiple Sclerosis

Moderate-quality evidence from nine trials suggests little effect of HBOT on outcomes related to MS (WA HTA, 2013). Two small, good-quality trials found modest benefits, while seven fair-quality trials found no benefit. Furthermore, the statistical benefits observed in the two positive trials are unlikely to translate into clinically significant benefits for the patient. Of note, there were no RCTs found on this topic post 1990, and there appears to be little interest in further investigation into the use of HBOT for MS.

Migraines and Cluster Headaches

Low-quality evidence from three fair-quality RCTs suggest that 40 to 45 minutes of HBOT is effective in significantly relieving an acute migraine attack (WA HTA, 2013). Just two patients need to be treated to obtain significant relief for one additional patient. There is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduce the need for rescue medication, based on

two fair quality trials. There is insufficient evidence from two studies to determine the effectiveness of HBOT for preventing, relieving, or terminating cluster headaches.

Sensorineural Hearing Loss

Low-quality evidence (due to mixed results) from eight RCTs is inconclusive as to whether there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase (WA HTA, 2013). A large systematic review suggests that HBOT is beneficial among patients who present within two weeks of onset of the disease; however, there is no evidence that the statistical benefit observed translates into a functional benefit, and the results from a recent RCT do not suggest benefit from HBOT. Moderate-quality evidence suggests that HBOT provides no added benefit to patients presenting with chronic sensorineural hearing loss.

Murad 2013 reports that for chronic idiopathic sudden sensorineural hearing loss (> 2 weeks after presentation), the quality of evidence is listed as class A using the AHA grading system. The authors report that for the outcome of any improvement in hearing, the relative effect size is 0.64 (95% CI 0.30 to 1.33), and using GRADE, has very low quality evidence; evidence from one RCT was downgraded for increased risk of bias, imprecision and indirectness.

Delayed or Non-healing Fractures

No studies met the inclusion criteria of the review that addressed this indication (Bennett, 2012a). Authors identified three ongoing RCTs. Three excluded RCTs either did not report fracture healing outcomes or had been abandoned.

Bell's Palsy

No RCTs met the inclusion criteria of the review that addressed this indication (Holland, 2012). One small RCT (n=79) that did not meet criteria because the outcome assessor was not blinded reported that patients treated with HBOT had facial function recovery more often than those treated with prednisone (RR 1.26, 95% CI 1.04 to 1.53).

Malignant Otitis Externa

No RCTs met the inclusion criteria of the review that addressed this indication (Phillips, 2013).

Carbon Monoxide Poisoning

Seven RCTs of varying quality were identified; one was excluded because it did not evaluate clinical outcomes (Buckley, 2011). Of the six remaining trials involving 1361 participants, two found a beneficial effect of HBOT for the reduction of neurologic sequelae at one month, while four others did not. One of these is an incomplete publication (an abstract of an interim analysis). Although pooled random effects meta-analysis does not suggest a significant benefit from HBOT (OR for neurological deficits 0.78, 95%CI 0.54 to 1.12), significant methodologic and statistical heterogeneity was

apparent among the trials, and this result should be interpreted cautiously. Moreover, design or analysis flaws were evident in all trials. Importantly, the conclusions of one positive trial may have been influenced by failure to adjust for multiple hypothesis testing, while interpretation of the other positive trial is hampered by a high risk of bias introduced during the analysis including an apparent change in the primary outcome. Both were also stopped early 'for benefit', which is likely to have inflated the observed effect. In contrast three negative trials had low power to detect a benefit of HBOT due to exclusion of severely poisoned patients in two and very poor follow-up in the other. One trial that was said to be finished around eight years ago has not reported the final analysis in any forum. (Strength of evidence: very low)

Murad 2013 reports that for carbon monoxide poisoning, the quality of evidence is listed as class A using the AHA grading system. The authors report that for the outcome of resolution of signs and symptoms at 4-6 weeks, the relative effect size is 0.78 (95% CI 0.54 to 1.12), and using GRADE, has very low quality evidence. Evidence from multiple RCTs was downgraded for increased risk of bias, inconsistency and imprecision.

Vascular Dementia

One study involving 64 patients was included in the review (Xiao, 2012). It compared HBOT as an adjuvant to donepezil with donepezil alone. This one study was judged to be of poor methodological quality. Patients receiving HBOT plus donepezil had significantly better cognitive function than the donepezil only group after 12 weeks of treatment, measured by the Mini-Mental State Examination (MMSE) (WMD 3.50; 95% CI 0.91 to 6.09) or by Hasegawa's Dementia Rating Scale (HDS) (WMD 3.10; 95% CI 1.16 to 5.04). There were no deaths or withdrawals, and the study did not mention safety assessment at all. Global function, behavioral disturbance and activities of daily living were not investigated in the study. (Strength of evidence: very low)

Acute Coronary Syndrome

Six trials with 665 participants contributed to this review (Bennett, 2011). There was a significant decrease in the risk of death with HBOT (RR 0.58, 95% CI 0.36 to 0.92, $P = 0.02$). The extent of heart muscle damage was lower following HBOT, as shown by a lesser rise in muscle enzyme in the blood (mean difference (MD) 493 IU, $P = 0.005$) and a better LV ejection fraction (MD 5.5%, $P = 0.001$). There was evidence from individual trials of reductions in the risk of major adverse coronary events (MACE) (RR 0.12, $P = 0.03$); re-infarction (RR 0.28, $P = 0.04$) and dysrhythmias following HBOT (RR 0.59, $P = 0.01$), and the time to relief of pain was reduced with HBOT (MD 353 minutes shorter, $P < 0.00001$). One trial suggested a significant incidence of claustrophobia in single occupancy chambers of 15% (RR of claustrophobia with HBOT 31.6, $P = 0.02$). The authors conclude:

For people with ACS, there is some evidence from small trials to suggest that HBOT is associated with a reduction in the risk of death, the volume of damaged muscle, the risk of MACE and time to relief from ischemic pain. In view of the modest number of patients, methodological shortcomings and poor reporting, this result should be interpreted cautiously. The routine application of HBOT to these patients cannot be justified from this review. (p. 4)
(Strength of evidence for risk of death: low)

Gas Gangrene

Evidence pertaining to the use of HBOT for this indication is limited to four retrospective comparison studies and 13 case series (Leof, 2012). All four of the retrospective comparison studies compared mortality rates between patients treated with HBOT and those receiving standard wound care. All four studies found that HBOT improved survival rates. One of the cohort studies included reported that amputation rates among survivors were lower for HBOT patients (18%) than for controls (75%). The significance of these findings was not reported. (Strength of evidence: low)

Optimal Dose, Frequency and Duration of HBOT

The available data from 13 studies provides insufficient evidence to determine the optimal treatment frequency, duration or dose for HBOT (WA HTA, 2013). No studies reported on the optimal duration of treatment sessions; there were mixed results from subgroup analysis involving 8 studies looking at frequency; and significant heterogeneity means that there is low confidence in the available results from five studies that looked at dose.

Harms of HBOT

There is moderate evidence suggesting that harms associated with HBOT are generally mild and self-limiting (WA HTA, 2013). The majority of reported harms include barotrauma, temporary visual disturbances, and, more rarely, oxygen toxicity. Occasional reports of seizures represent the most serious side effects. The Medical Services Advisory Committee (MSAC) of Australia reported an overall harms incidence rate of 6.3%; 17% incidence of general pain or discomfort during decompression; 4.8% incidence of ear pain; 1.5% incidence of tympanostomy tube placements; 0.9% incidence of persistent ocular changes; 0.6% incidence of ear barotrauma; 0.34% incidence of abdominal pain; and 0.1% incidence of claustrophobia.

Notable indication-specific harms found in the literature include the following:

- Among patients with late radiation tissue injury, there were reports of ear pain (16% in a trial of 150 patients), transient myopia (3% in one study 8% in another), and confinement anxiety (1.7%).

- Pooled data from two trials reported severe pulmonary complications (defined as either, rising oxygen requirements and infiltrates in chest x-ray or cyanosis and hyperpnoea so severe as to imply “impending hyperoxic pneumonia”) among 13% of TBI patients receiving HBOT compared with none in the control groups (RR, 15.57; 95% CI, 2.11-114.72).
- One study reported ear problems among 47% of children with cerebral palsy receiving HBOT versus 22% among controls (P significant but value not reported). Another study reported a 12% seizure rate and found that 35% of patients reported ear problems. Another reported that 8% of 50 children stopped treatment due to adverse events, including seizures, and one other study reported 1 seizure in an observational study of 230 patients.
- Among patients with MS, a 2011 Cochrane Collaboration review reported 77 patients (55%), across 4 trials, suffered temporary deterioration in visual acuity in the HBOT group versus 3 patients (2.3%) in the sham group (OR, 24.87; 95% CI, 1.44-428.5; NNT, 1; 95% CI, 1-2).
- Six of the case series evaluating HBOT for gas gangrene reported on harms (total N= 337). Two deaths were attributed to HBOT treatment, and seizures occurred in 7% of patients.
- Among patients with TBI, two studies reported an incidence of 13% for significant pulmonary impairment in the HBOT group versus 0% in the non-HBOT group (P = 0.007).

Differential Efficacy or Safety

The evidence is insufficient to determine the differential effectiveness and safety of HBOT according to sex, race, ethnicity, disability, wound duration, or treatment setting (WA HTA, 2013). There is evidence of very low quality suggesting that younger TBI patients may recover faster with HBOT than older patients. There is low quality evidence suggesting that radiation dose influences the effectiveness of HBOT to prevent ORN among head and neck cancer survivors. There is low quality evidence that transcutaneous oxygen measurement (TCOM) is a good predictor of response to HBOT when measured under hyperbaric conditions, and there is mixed evidence as to whether TCOM can predict response to HBOT by first measuring the response of a wound to normal air or to 100% oxygen breathed at sea level. There is insufficient evidence from poor-quality studies to determine the differential safety of HBOT across populations.

Costs of HBOT

HBOT may be cost-effective under very specific assumptions of effectiveness and costs (WA HTA, 2013). All included cost analyses found HBOT to be cost-effective or cost saving. However, the available economic evaluations were severely limited by sparse cost data and unreliable efficacy and cost estimates used to make model assumptions. Only one model was found to be robust during sensitivity analysis, making most estimates very unreliable. Overall, there is low-quality evidence to suggest that HBOT may be a cost-effective treatment under certain conditions, for certain populations and indications.

Evidence Summary

Moderate-quality evidence supports the addition of HBOT to standard wound care to promote short term wound healing and limb salvage among patients with diabetic foot ulcers with continued improvement at one year follow-up. There is insufficient evidence to determine the effect of HBOT on QOL or other health outcomes. There is also moderate-quality evidence suggesting that HBOT improves outcomes of late radiation tissue injury affecting bone and soft tissues. Moderate-quality evidence also suggests that HBOT reduces the risk of dying following TBI and may improve functional outcomes.

There is limited low-quality evidence suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, crush injuries, and surgical reconstruction (without grafts or flaps) but more study is needed to support the current evidence. Low-quality evidence (due to mixed results) is inconclusive as to whether or not there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase of the disease. HBOT may reduce the rates of relapse infection among patients with refractory osteomyelitis but further good-quality studies are necessary to confirm this finding (very low quality evidence). Low-quality evidence suggests that 40- to 45-minutes of HBOT is effective in significantly relieving an acute migraine attack, but there is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduce the need for rescue medication.

Low quality evidence suggests that HBOT may decrease the risk of death and other major adverse coronary events in patients with ACS, and may decrease the risk of death and amputation in patients with gas gangrene.

Moderate-quality evidence suggests little benefit of HBOT for the treatment of MS. Low-quality evidence suggests no benefit of HBOT for preventing, relieving, or terminating cluster headaches. There is also no evidence that HBOT is beneficial among patients presenting with chronic sensorineural hearing loss. There is insufficient evidence,

primarily due to mixed results or an overall paucity of studies, to determine if HBOT is effective for the treatment of thermal burns, cerebral palsy, brain injuries other than TBI, delayed or non-union of fractures, bell's palsy, carbon monoxide poisoning, vascular dementia or malignant otitis externa.

Overall, there is a low quality of evidence to suggest that HBOT may be a cost-effective treatment under certain conditions and for certain populations and indications, but current data are insufficient to determine the most cost-effective uses of the technology.

There is moderate-quality evidence from across studies that harms associated with HBOT are usually mild, self-limiting, and with most resolving after the termination of treatment. The most common harms include myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events are rare but do occur on occasion and can include seizures and death.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
Diabetic nonhealing wounds	Improved wound healing and limb salvage	Moderate	Moderate to high cost, offset by reduced hospitalization and other treatment costs	Moderate, favoring treatment	Recommended for coverage (<i>strong recommendation</i>), when criteria are met	Consistent evidence of effectiveness for improved wound healing for up to one year, based on 16 studies. Coverage criteria based on expert input supporting Medicare coverage criteria.
Venous ulcers	Possible improved healing	Low	Moderate	High	Not recommended for coverage (<i>weak recommendation</i>)	Two small trials find reduction in wound area, but no evidence for complete wound healing and no evidence of superior results after 30 days. Expert opinion does not recommend HBOT for this condition.
Compromised flaps and	Possible improved graft survival	Low	Moderate	Moderate	Recommended for coverage (<i>weak</i>	Four studies (3 RCTs) had mixed

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
grafts					<i>recommendation)</i>	results, with most evidence suggesting improved healing.
Surgical reconstruction without flaps and grafts	Unknown	Very Low	Moderate	High	Not recommended for coverage (weak)	The evidence is insufficient (no RCTs) to suggest that benefit exceeds harm.
Crush injuries	More complete wound healing	Low	Moderate	Moderate	Recommended for coverage (weak)	Evidence limited to one fair quality RCT showing more complete wound healing
Thermal burns	Unknown due to conflicting evidence	Very Low	Moderate	Moderate to high variability	Not recommended for coverage (weak)	Conflicting evidence from 2 RCTs prevents conclusions regarding efficacy.
Refractory osteomyelitis	Possible reduced rate of relapse	Very Low	Moderate	Moderate to high variability	Not recommended for coverage (weak)	Conflicting evidence from 2 trials prevents conclusions regarding efficacy .
Late radiation tissue injury	Improved outcomes	Moderate	Moderate	Low to moderate variability (preference towards treatment)	Recommended for coverage (<i>strong</i>)	Consistent evidence from 35 studies shows clinical improvement with HBOT
Brain injury – Acute TBI	Possible reduced risk of dying, unclear improvement in functional outcomes	Moderate	Moderate	Moderate variability	Not recommended for coverage (weak)	Evidence (7 studies) limited by high risk of bias and unclear clinical significance. Expert opinion does not recommend HBOT for this condition.
Brain injury other than TBI	Unknown	Very Low	Moderate	High variability	Not recommended for coverage (weak)	The evidence is insufficient (very poor quality) to suggest

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						that benefit exceeds harm.
Cerebral palsy	Unknown	Very Low	Moderate to high (chronic condition)	Moderate variability (some would prefer treatment in spite of insufficient evidence)	Not recommended for coverage (<i>strong</i>)	Conflicting evidence (2 RCTs) prevents conclusions regarding efficacy.
Migraine HA	Aborts HA after 40-45 minutes, but no effect on prevention or reduction in N/V or rescue meds	Low	Moderate to high (Chronic condition)	High variability	Not recommended for coverage (<i>weak</i>)	Lack of clinically important benefit based on 3 RCTs suggests that benefits do not exceed harms, particularly given logistic considerations
Cluster HA	No benefit	Very low	Moderate to high	High variability	Not recommended for coverage (<i>weak</i>)	The evidence is insufficient (2 studies) to suggest that benefit exceeds harm.
Multiple sclerosis	No benefit	Moderate	Moderate to high	Moderate variability	Not recommended for coverage (<i>strong</i>)	Nine studies had mixed results, with most (7) finding no benefit
Sensorineural hearing loss – acute	Unknown	Low	Moderate	Moderate variability	Not recommended for coverage (<i>weak</i>)	Conflicting evidence (8 RCTs) prevents conclusions regarding efficacy. Potential small benefit is likely not clinically significant.
Sensorineural hearing loss – chronic	No benefit	Low	Moderate	Low variability (preference against HBOT)	Not recommended for coverage (<i>strong</i>)	Evidence suggests no benefit from HBOT.
Delayed or non-healing fractures	Unknown	Very Low	Moderate	Low variability (preference against HBOT)	Not recommended for coverage (<i>weak</i>)	Lack of evidence (0 RCTs) prevents conclusions regarding

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						efficacy.
Bell's palsy	Unknown	Very Low	Moderate	Moderate variability	Not recommended for coverage (<i>weak</i>)	Lack of evidence (0 RCTs) prevents conclusions regarding efficacy.
Malignant otitis externa	Unknown	Very Low	Moderate	Low variability (preference against HBOT)	Not recommended for coverage (<i>weak</i>)	Lack of evidence (0 RCTs) prevents conclusions regarding efficacy.
Vascular dementia	Unknown	Very Low	Moderate to high (chronic condition)	Moderate variability	Not recommended for coverage (<i>weak</i>)	Lack of evidence (1 small poor RCT) prevents conclusions regarding efficacy.
Acute coronary syndrome	Decreased risk of death and MACE	Low	Moderate	High variability	Not recommended for coverage (<i>weak</i>)	Evidence from 6 RCTs limited by high risk of bias; concerns regarding logistic considerations. Expert opinion does not recommend HBOT for this condition.
Gas gangrene	Decreased risk of death and amputation	Low	Moderate	Low to moderate variability (preference towards treatment)	Recommended for coverage (<i>strong</i>)	Consistent evidence (4 cohort studies) suggest decreased mortality; RCT may not be reasonable.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Quality Measures

No quality measures were identified when searching the [National Quality Measures Clearinghouse](#).

Payer Coverage Policies

Coverage policies for selected payers are included here.

Medicare

A national coverage determination for hyperbaric oxygen therapy was identified in the [Medicare Coverage Database](#). Indications and limitations of coverage are detailed in Appendix D.

Washington HTA Limitations of Coverage

Hyperbaric Oxygen Therapy is a covered benefit with conditions consistent with the criteria identified in the reimbursement determination.

Limitations of Coverage

1. Crush injuries and suturing of severed limbs; as an adjunct when loss of function, limb, or life is threatened.
2. Compromised skin grafts and flaps (not for primary management of wounds).
3. Chronic refractory osteomyelitis unresponsive to conventional medical and surgical management.
4. Osteoradionecrosis; as an adjunct to conventional treatment.
5. For prevention of osteoradionecrosis associated with tooth extraction in a radiated field.
6. Soft tissue radionecrosis; as an adjunct to conventional treatment.
7. Diabetic wounds in patients who meet the following three criteria:
 - a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
 - b. Patient has a wound classified as Wagner grade III or higher; and
 - c. Patient has failed an adequate course of standard wound therapy.

Non-Covered Indicators

1. Brain injury including traumatic (TBI) and chronic brain injury
2. Cerebral Palsy
3. Multiple Sclerosis
4. Migraine or cluster headaches
5. Acute and chronic sensorineural hearing loss
6. Thermal burns
7. Non-healing venous, arterial and pressure ulcers

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

DRAFT

Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome¹

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

¹ Includes risk of bias, precision, directness, consistency and publication bias

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
870-897	Open wound, various locations
250.8	Diabetes with other specified manifestations
990	Effects of radiation, unspecified
854	Intracranial injury of other and unspecified nature
389.1	Sensorineural hearing loss
730.0-2	Osteomyelitis
346.9	Migraine headache
399.0	Cluster headache
340	Multiple sclerosis
343	Cerebral palsy
940-949	Burns
800-829	Fractures
351.0	Bell's palsy
380.14	Malignant otitis externa
986	Toxic effects of carbon monoxide
E868	Accidental poisoning by CO
E952	Suicide by gases
E962.2	Assault by gases
E982.1	Poisoning by CO, undetermined
290.40	Vascular dementia
410	Acute myocardial infarction
411.81	Acute coronary occlusion without infarction
040.0	Gas gangrene
ICD-9 Volume 3 (Procedure Codes)	
93.95	Hyperbaric oxygenation
CPT Codes	
99183	Physician attendance/supervision of hyperbaric oxygen therapy, per session
HCPCS Level II Codes	
C1300	Hyperbaric oxygen, full body chamber, per 30 minutes

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

Diabetic nonhealing wounds; Venous ulcers; Compromised flaps and grafts; Crush injuries; Late radiation tissue injury; Gas gangrene



Center for Evidence-based Policy

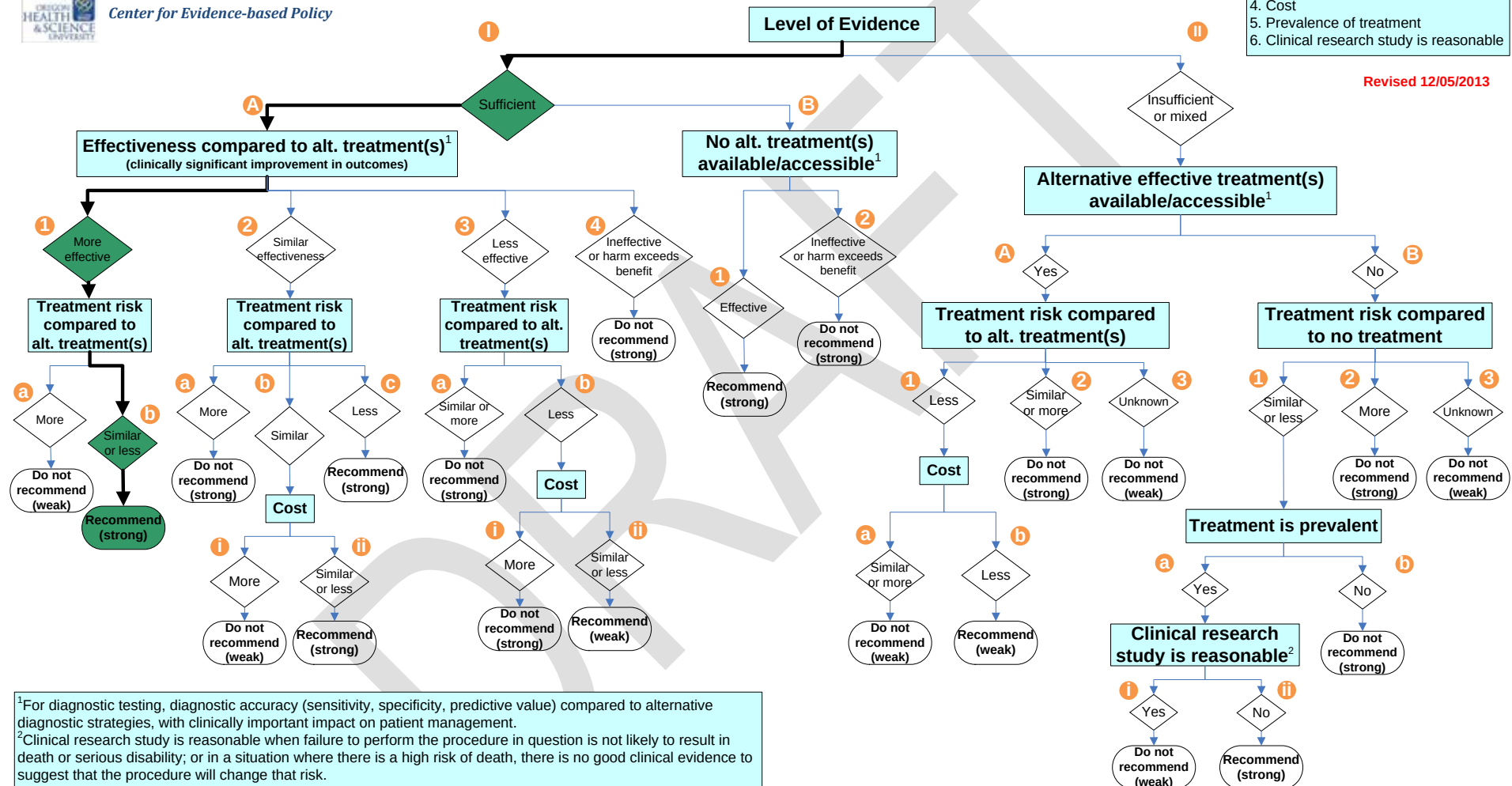
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013



Cerebral Palsy



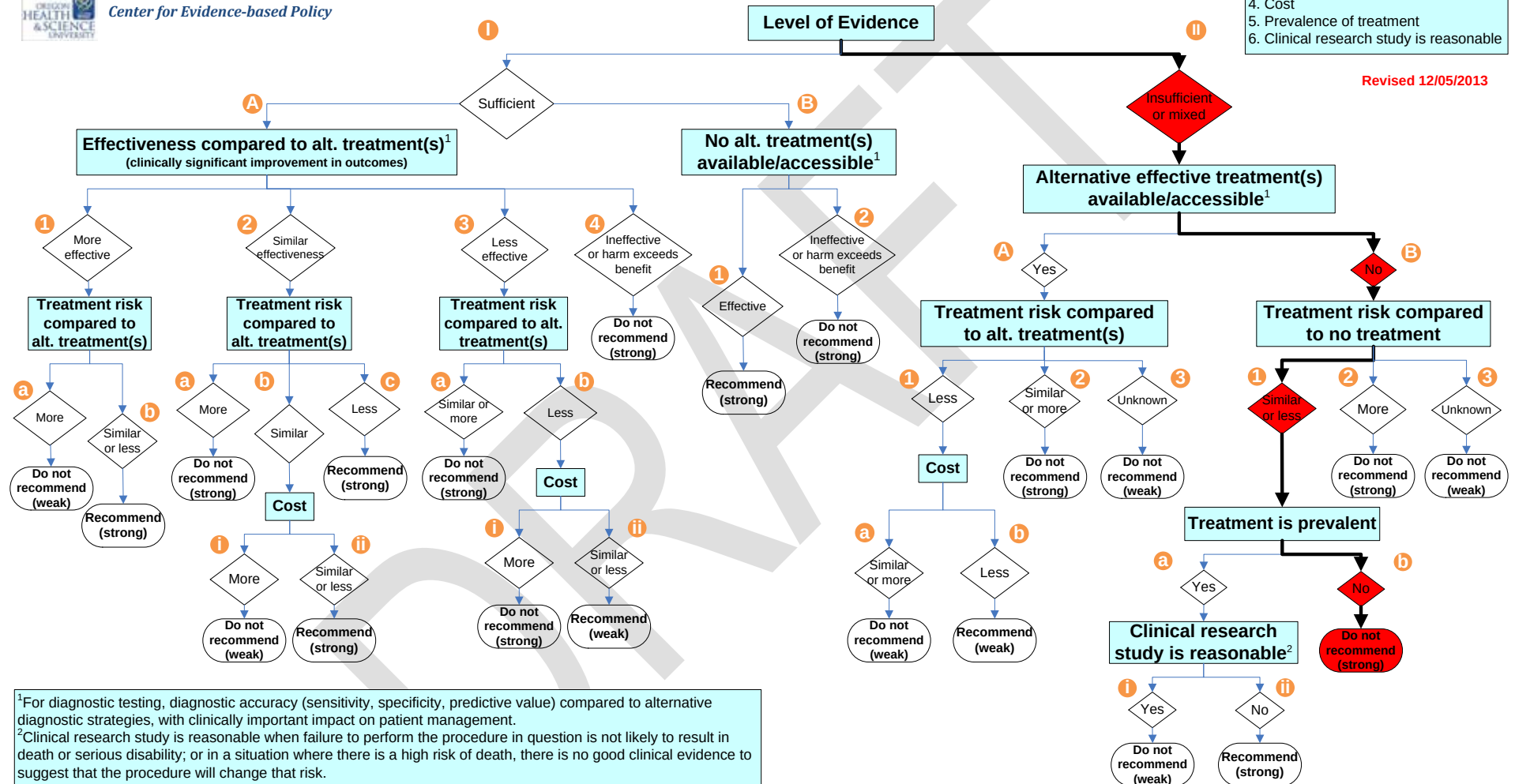
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HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

Revised 12/05/2013



Chronic sensorineural hearing loss, Acute traumatic brain injury



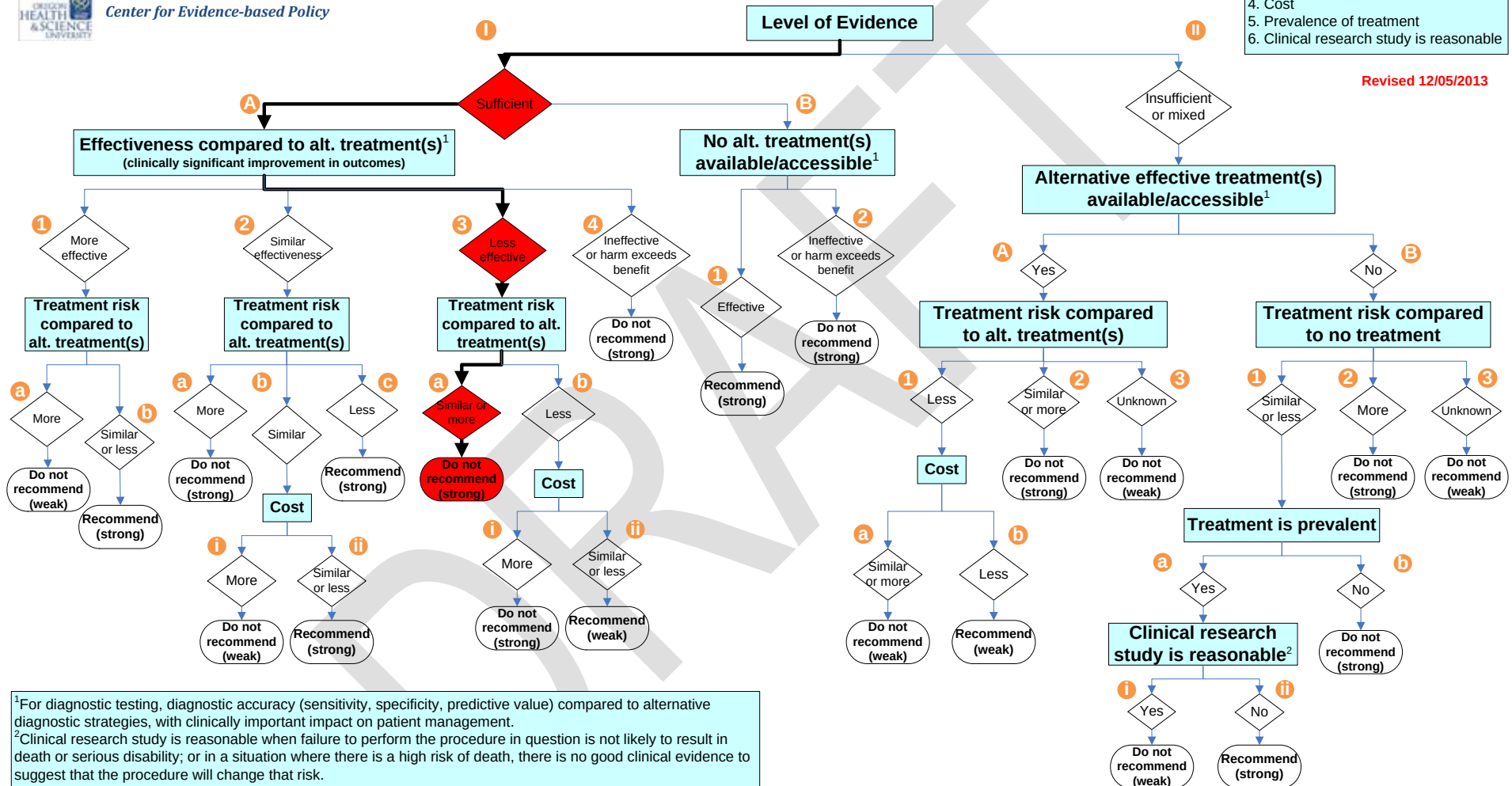
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HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

Revised 12/05/2013



Multiple sclerosis



Center for Evidence-based Policy

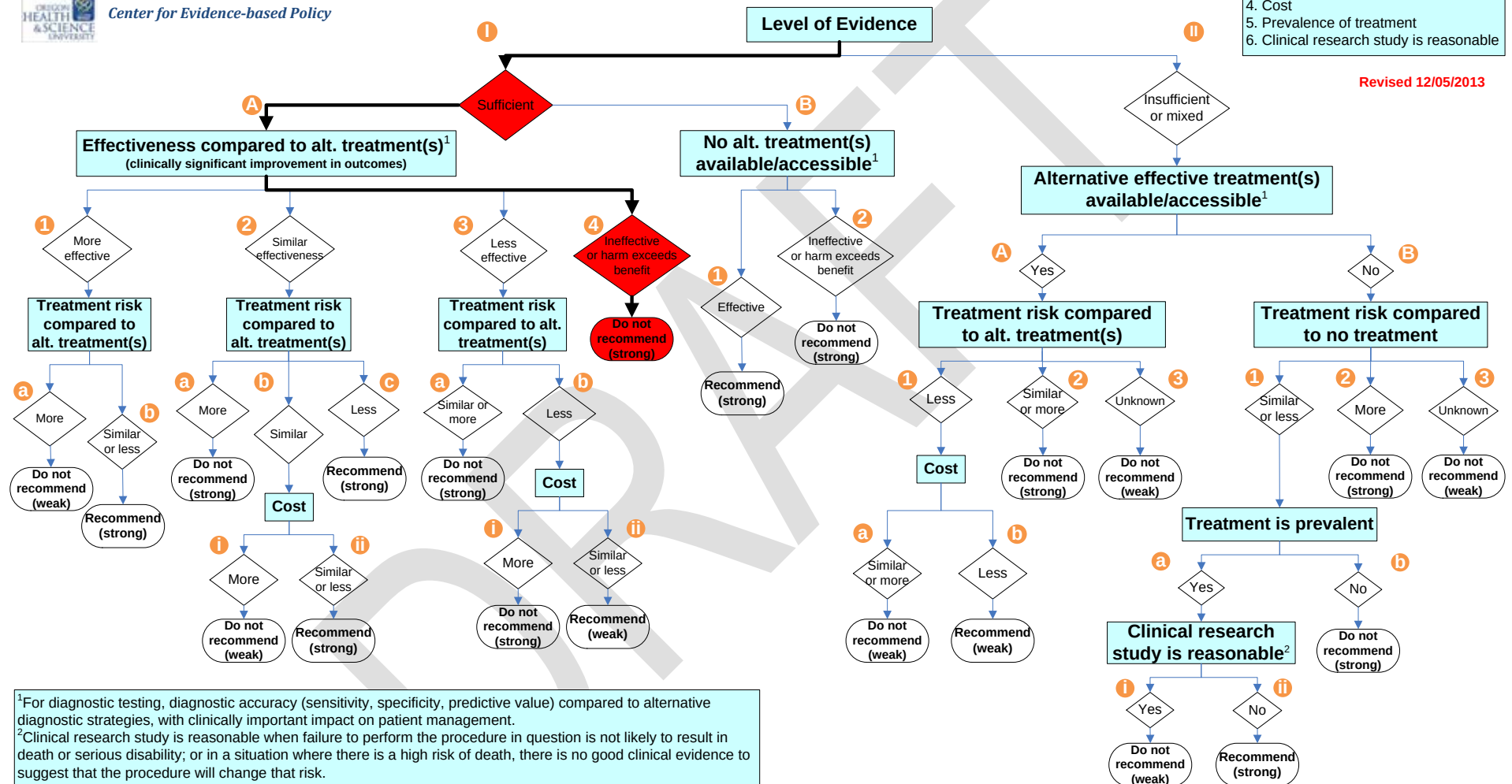
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Decision Point Priorities

1. Level of evidence
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3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

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HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Level of Evidence

I **Sufficient**

II **Insufficient or mixed**

Effectiveness compared to alt. treatment(s)¹
(clinically significant improvement in outcomes)

1 More effective

2 Similar effectiveness

3 Less effective

4 Ineffective or harm exceeds benefit

Treatment risk compared to alt. treatment(s)

a More

b Similar or less

Cost

i More

ii Similar or less

Recommend (strong)

Do not recommend (strong)

Recommend (weak)

Do not recommend (weak)

No alt. treatment(s) available/accessible¹

1 Effective

2 Ineffective or harm exceeds benefit

Recommend (strong)

Do not recommend (strong)

Alternative effective treatment(s) available/accessible¹

A Yes

B No

Treatment risk compared to alt. treatment(s)

1 Less

2 Similar or more

3 Unknown

Cost

a Similar or more

b Less

Recommend (weak)

Do not recommend (weak)

Treatment risk compared to no treatment

1 Similar or less

2 More

3 Unknown

Do not recommend (strong)

Do not recommend (weak)

Treatment is prevalent

a Yes

b No

Clinical research study is reasonable²

i Yes

ii No

Recommend (strong)

Do not recommend (strong)

Do not recommend (weak)

1For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.

2Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Revised 12/05/2013

Brain injury other than TBI; Migraines; Cluster headache; Acute sensorineural hearing loss; Delayed or non-healing fractures; Bell's palsy; Malignant otitis externa; Vascular dementia; Thermal burns



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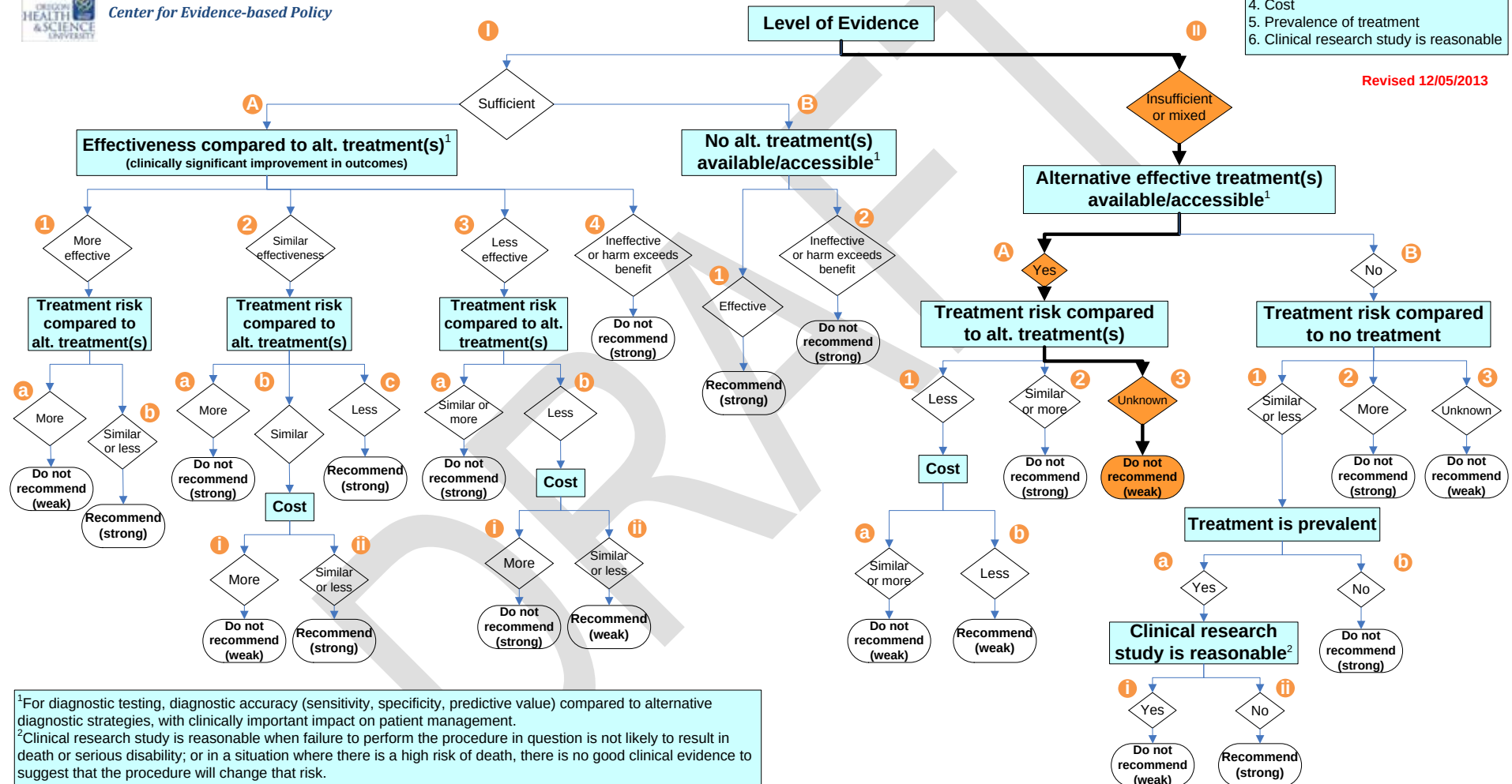
HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

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Surgical reconstruction without flaps and grafts; Refractory osteomyelitis



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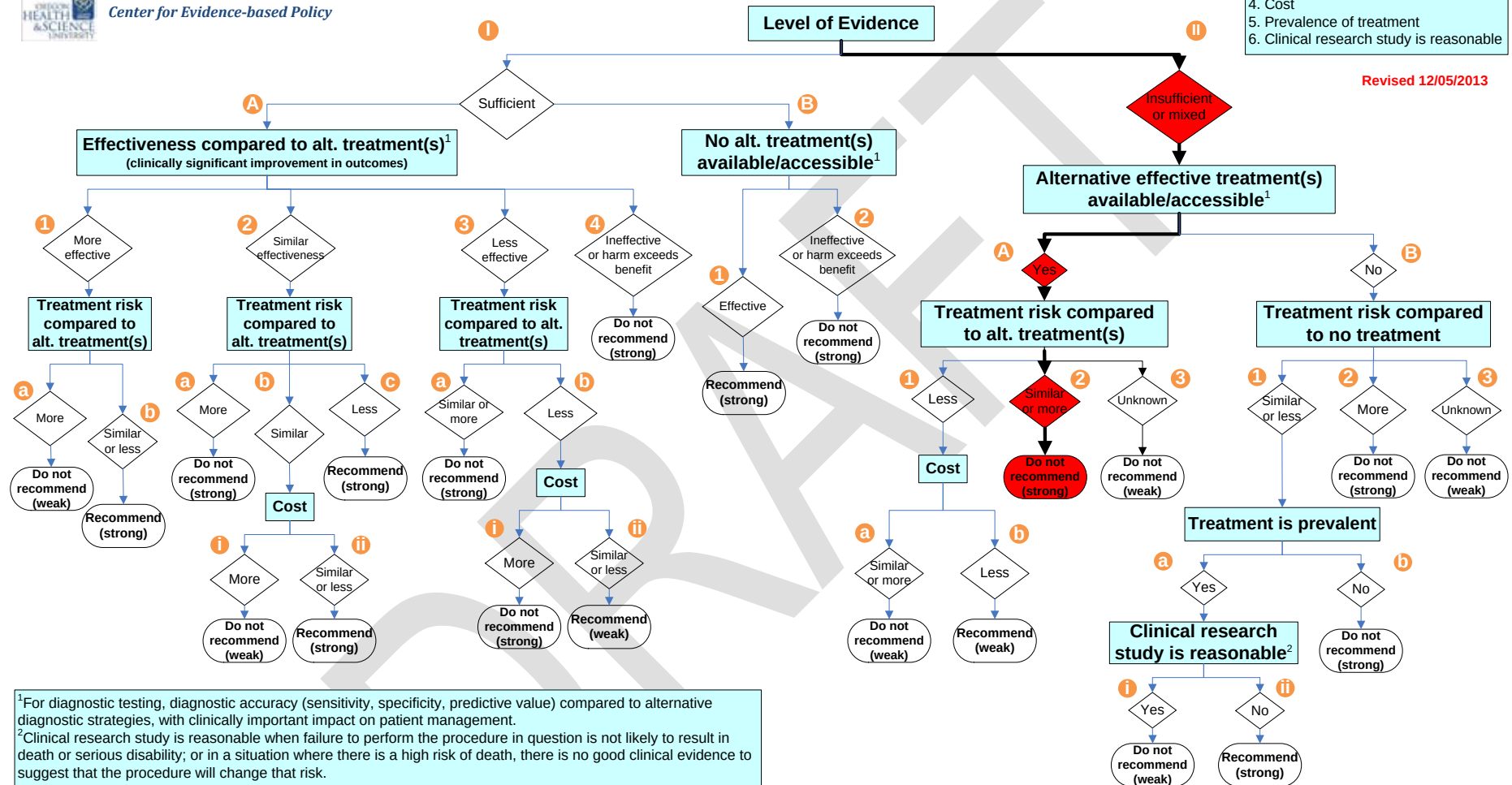
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Refer to HERC Guidance Development Framework Principles for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013



Appendix D. CMS National Coverage Determination

National Coverage Determination: Hyperbaric Oxygen Therapy

Publication Number: 100-3

Manual Section Number: 20.29

Effective Date: 6/19/2006

Indications and Limitations of Coverage

A. Covered Conditions

Program reimbursement for HBO therapy will be limited to that which is administered in a chamber (including the one man unit) and is limited to the following conditions:

1. Acute carbon monoxide intoxication,
2. Decompression illness,
3. Gas embolism,
4. Gas gangrene,
5. Acute traumatic peripheral ischemia. HBO therapy is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
6. Crush injuries and suturing of severed limbs. As in the previous conditions, HBO therapy would be an adjunctive treatment when loss of function, limb, or life is threatened.
7. Progressive necrotizing infections (necrotizing fasciitis),
8. Acute peripheral arterial insufficiency,
9. Preparation and preservation of compromised skin grafts (not for primary management of wounds),
10. Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management,
11. Osteoradionecrosis as an adjunct to conventional treatment,
12. Soft tissue radionecrosis as an adjunct to conventional treatment,
13. Cyanide poisoning,
14. Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment,
15. Diabetic wounds of the lower extremities in patients who meet the following three criteria:
 - a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
 - b. Patient has a wound classified as Wagner grade III or higher; and
 - c. Patient has failed an adequate course of standard wound therapy.

The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30-days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBO therapy. Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

B. Noncovered Conditions

All other indications not specified under §270.4(A) are not covered under the Medicare program. No program payment may be made for any conditions other than those listed in §270.4(A).

No program payment may be made for HBO in the treatment of the following conditions:

1. Cutaneous, decubitus, and stasis ulcers.
2. Chronic peripheral vascular insufficiency.
3. Anaerobic septicemia and infection other than clostridial.
4. Skin burns (thermal).
5. Senility.
6. Myocardial infarction.
7. Cardiogenic shock.
8. Sickle cell anemia.
9. Acute thermal and chemical pulmonary damage, i.e., smoke inhalation with pulmonary insufficiency.
10. Acute or chronic cerebral vascular insufficiency.
11. Hepatic necrosis.
12. Aerobic septicemia.
13. Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease).
14. Tetanus.
15. Systemic aerobic infection.
16. Organ transplantation.
17. Organ storage.
18. Pulmonary emphysema.
19. Exceptional blood loss anemia.

- 20. Multiple Sclerosis.
- 21. Arthritic Diseases.
- 22. Acute cerebral edema.

DRAFT

National Coverage Determination (NCD) for Hyperbaric Oxygen Therapy (20.29)

Tracking Information

Publication Number

100-3 Manual Section Number

20.29 Manual Section Title

Hyperbaric Oxygen Therapy

Version Number

3 Effective Date of this Version

6/19/2006 Implementation Date

6/19/2006

Description Information

Benefit Category

Incident to a physician's professional Service

Outpatient Hospital Services Incident to a Physician's Service

Physicians' Services

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Item/Service Description

CIM 35-10

For purposes of coverage under Medicare, hyperbaric oxygen (HBO) therapy is a modality in which the entire body is exposed to oxygen under increased atmospheric pressure.

Indications and Limitations of Coverage

A. Covered Conditions

Program reimbursement for HBO therapy will be limited to that which is administered in a chamber (including the one man unit) and is limited to the following conditions:

Acute carbon monoxide intoxication,

Decompression illness,

Gas embolism,

Gas gangrene,

Acute traumatic peripheral ischemia. HBO therapy is a valuable adjunctive

National Coverage Determination (NCD) for Hyperbaric Oxygen Therapy (20.29)

treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.

Crush injuries and suturing of severed limbs. As in the previous conditions, HBO therapy would be an adjunctive treatment when loss of function, limb, or life is threatened.

Progressive necrotizing infections (necrotizing fasciitis),

Acute peripheral arterial insufficiency,

Preparation and preservation of compromised skin grafts (not for primary management of wounds),

Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management,

Osteoradionecrosis as an adjunct to conventional treatment,

Soft tissue radionecrosis as an adjunct to conventional treatment,

Cyanide poisoning,

Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment,

Diabetic wounds of the lower extremities in patients who meet the following three criteria:

Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;

Patient has a wound classified as Wagner grade III or higher; and

Patient has failed an adequate course of standard wound therapy.

The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 –days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBO therapy. Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

B. Noncovered Conditions

All other indications not specified under §270.4(A) are not covered under the Medicare program. No program payment may be made for any conditions other than those listed in §270.4(A).

No program payment may be made for HBO in the treatment of the following conditions:

Cutaneous, decubitus, and stasis ulcers.

Chronic peripheral vascular insufficiency.

Anaerobic septicemia and infection other than clostridial.

Skin burns (thermal).

Senility.

National Coverage Determination (NCD) for Hyperbaric Oxygen Therapy (20.29)

Myocardial infarction.
Cardiogenic shock.
Sickle cell anemia.
Acute thermal and chemical pulmonary damage, i.e., smoke inhalation with pulmonary insufficiency.
Acute or chronic cerebral vascular insufficiency.
Hepatic necrosis.
Aerobic septicemia.
Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease).
Tetanus.
Systemic aerobic infection.
Organ transplantation.
Organ storage.
Pulmonary emphysema.
Exceptional blood loss anemia.
Multiple Sclerosis.
Arthritic Diseases.
Acute cerebral edema.

C. Topical Application of Oxygen

This method of administering oxygen does not meet the definition of HBO therapy as stated above. Also, its clinical efficacy has not been established.

Therefore, no Medicare reimbursement may be made for the topical application of oxygen.

Cross Reference

§270.5 of this manual.

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Transmittal Information

Transmittal Number

48

Coverage Transmittal Link

<http://www.cms.gov/transmittals/downloads/R48NCD.pdf>

Revision History

07/01/1997 - Clarified coverage limited to conditions listed under §35-10.A.

Effective date 08/11/1997. (TN 102)

04/01/1999 - Clarified covered conditions and physician supervision requirement.

Effective date 05/01/1999. (TN 112)

10/19/2000 - Manualized program memorandum AB-00-15 (dated 4/1/2000) and clarified that "preparation and preservation of compromised skin graft" in section 35-10A.9 is not for primary management of wounds. Effective date NA. (TN 129) (CR 1138)

12/27/2002 - Expanded coverage for treatment of diabetic wounds of the lower

National Coverage Determination (NCD) for Hyperbaric Oxygen Therapy (20.29)

extremities in patients that meet three criteria. Effective date 04/01/2003. (TN 164) (CR 2388)

03/2006 - Technical corrections to the NCD Manual. Effective date 06/19/2006. (TN48) (CR4278)

01/2013 - CMS translated the information for this policy from ICD-9-CM/PCS to ICD-10-CM/PCS according to HIPAA standard medical data code set requirements and updated any necessary and related coding infrastructure. These updates do not expand, restrict, or alter existing coverage policy. Implementation date:

04/01/2013 Effective date: 10/1/2015. (TN 1165) (CR 8109)

05/2014 - CMS translated the information for this policy from ICD-9-CM/PCS to ICD-10-CM/PCS according to HIPAA standard medical data code set requirements and updated any necessary and related coding infrastructure. These updates do not expand, restrict, or alter existing coverage policy. Implementation date:

10/06/2014 Effective date: 10/1/2015. (TN 1388) (TN 1388) (CR 8691)

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National Coverage Analyses (NCAs)

National Coverage Analyses (NCAs)

This NCD has been or is currently being reviewed under the National Coverage Determination process. The following are existing associations with NCAs, from the National Coverage Analyses database.

Original consideration for Hyperbaric Oxygen Therapy for Hypoxic Wounds and Diabetic Wounds of the Lower Extremities (CAG-00060N) opens in new window
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Additional Information

Other Versions

Hyperbaric Oxygen Therapy - Version 2, Effective between 4/1/2003 - 6/19/2006

Hyperbaric Oxygen Therapy - Version 1, Effective between 10/19/2000 - 4/1/2003

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USA

National Coverage Determination (NCD) for Hyperbaric Oxygen Therapy (20.29)

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HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Emeritus Physician and Clinical Professor of Medicine, Seattle, WA <i>[Submitted April 21, 2014]</i>
B	Medical Director, Springfield, OR <i>[Submitted June 1, 2014]</i>
C	Medical Director, Wound Healing and Hyperbaric Medicine, Adventist Medical Center, Portland, OR (appointed expert) <i>[Submitted June 30, 2014]</i>

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

Public Comment Grouped by Commenter

Ident.	#	Comment	Disposition
A	1	According to one website (biomedexperts.com), I am the #1 expert in the world on carbon monoxide (CO) poisoning, based upon the fact that I have more published more papers in the medical literature on the topic (46) than anyone ever has. I understand that you are considering elimination of reimbursement for hyperbaric oxygen treatment of CO poisoning. I am writing to tell you that I believe that would be a mistake.	Thank you for taking the time to comment.
	2	Last year, I served as the Clinical Expert for the State of Washington Health Technology Assessment of hyperbaric oxygen therapy. You may find it interesting that we did not even consider three commonly treated diagnoses where hyperbaric oxygen is considered proven, primary treatment -- decompression sickness, arterial gas embolism, and CO poisoning.	Thank you for providing this information, along with the transcript of the WA HTA meeting.
	3	I understand that your group is going back and re-evaluating yet another time clinical studies that are now over a decade old. You will not find the answer in meta-analyses such as that done by the Cochrane Group or the American Society of Emergency Medicine. All clinical trials in the area have had some flaws, some more than others. They have all used different endpoints (some clinically irrelevant) and have had varying degrees of follow-up (some even using questionnaires self-administered by the patient at home when they would not return for re-evaluation). All have also used different protocols for treatment of hyperbaric and control patients (one hospitalizing control patients not receiving hyperbaric treatment for three to six days of oxygen by mask, something that is not even done at their own institution or any other hospital in the world). There is no surprise that averaging six totally different studies yields no firm conclusions and the usual recommendation that “more good quality studies are needed.” Well, it has been over a decade since Weaver published his clinical trial as lead article in the <i>New England Journal of Medicine</i>. No trials randomizing hyperbaric oxygen with normobaric oxygen are underway at this time, to my knowledge. I would probably be aware of it if there were any.	HTAS is aware of this controversy, and has elected not to make a recommendation regarding coverage or non-coverage of HBOT for CO poisoning.
	4	In the meantime, what is a managing physician to do? When you get severe CO poisoning tonight because of malfunction of your furnace and are taken to the emergency department, the physician there may call a regional or national expert in hyperbaric medicine for advice. Do you want the expert to say, “I don’t know what to do because I am waiting for more high quality clinical trials to be performed and published”? Of course not. You would want the expert’s opinion based upon his or her synthesis of the data available. And that opinion might be to give hyperbaric oxygen in selected cases.	See comment #3

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

Ident.	#	Comment	Disposition
	5	The most common hyperbaric treatment performed for CO poisoning in the US is one treatment, followed by up to two additional treatments if the patient remains symptomatic. The treatment is typically done as an outpatient and the goal is prevention of chronic brain injury. The alternative is oxygen by mask in the emergency department until the patient's blood carbon monoxide level is normal and the patient is asymptomatic (usually 6-12 hours).	Thank you for this information.
	6	The most similar experimental approach to this common practice was the study by Weaver and that is why most experts in the field use it for guidance instead of meta-analyses that give no management recommendations and simply call for additional research. Weaver demonstrated that a practical hyperbaric protocol reduced the incidence of chronic brain sequelae by 50% at one year, as compared to oxygen at sea level pressure.	There were methodologic problems with the Weaver study, as noted in the coverage guidance. Because of this controversy, HTAS has removed any reference to this condition in the coverage recommendations.
	7	I am sure that the cost of treating patients with CO poisoning with hyperbaric oxygen does not even show up on your state budget radar screen. Of an estimated 50,000 emergency department visits for CO poisoning in the US annually, only about 1,500 (3%) are treated with hyperbaric oxygen. The rest are treated in emergency departments (which may actually be more expensive in some situations, depending on the hospital's emergency department hourly charge for occupancy of a room). My speculation is that you are talking about less than \$20,000 annually for hyperbaric oxygen treatment of selected carbon monoxide-poisoned patients in Oregon. Is your group willing to deny that and accept the responsibility that you are instead allowing you citizens to develop chronic brain injury because "more well designed clinically studies are needed"? I hope not.	Thank you for this information See comment #3; HTAS is not recommending against coverage for CO poisoning.
B	1	Thank you for the opportunity to provide public comment regarding hyperbaric oxygen therapy (HBOT). This is a subject of considerable concern to the citizens of Oregon.	Thank you for taking the time to comment.
	2	Attached is a review published in the prestigious <i>British Medical Journal</i> regarding evidence based medicine and the effectiveness of the parachute. Although it was written as satire, it points out a crucial concept relevant to your current endeavor defining indications for HBOT.	HTAS is aware of the parachute example, and in fact, it has been referenced by public commenters for a variety of previous topics that HTAS has considered.
	3	Higher levels of evidence are based on large scale human Randomized Controlled Trials (RCT), which we believe reflects medical reality. But, as the <i>BMJ</i> article symbolizes, not everything in reality can be reduced to such large scale RCT's for many reasons, not the least of which is the ability to collect large control populations, with very similar characteristics, willing or ethically appropriate to forgo a recognized treatment in the name of science. That is to say, there are simply not sufficient numbers of people willing, nor should be selected, to jump out of an airplane without a parachute in order to prove the value of the parachute for those who do. That does not negate the effectiveness of the parachute.	HTAS is aware of this and agrees that RCTs are not always feasible. When they are not can be considered feasible is a matter of common sense to some, but a matter of opinion to others. Indeed, whether or not a clinical trial is reasonable is explicitly considered in the guidance development framework attached to every coverage guidance (see pages 30-36). In the parachutes example, clearly no one would disagree with the feasibility of performing a RCT.

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

Ident.	#	Comment	Disposition
	4	We have the same difficulty with HBOT. There is a paucity of level 1A evidence for HBOT, not for lack of interest or motivation, but due to the practical and ethical impediments to producing a good RCT. In the case of the diabetic foot ulcer, for example, how can we possibly find a large cohort stratified for consistency in diabetes control, medications required for that control, medical comorbidities, obesity, smoking history, arterial disease, degree of neuropathy, quality of footwear, access to medical care and socioeconomic factors, all of which directly impact the outcome of the wound as confounding variables. Rather than negate the value of lower levels of evidence, especially experimental studies which are at the bottom of the “evidence pyramid”, this is an inherent, hidden detraction of higher levels of evidence, including an RCT. It is erroneous to equate a well-designed RCT in an animal model with “poor” evidence.	HTAS is not entirely clear on the point that the commenter is making. We agree that stratifying a cohort based on a number of factors known to influence the outcome of procedure is challenging, but can usually be accomplished statistically in the analysis. A well designed RCT in the animal model is not “poor evidence”, but has limited applicability in humans.
		The second point I will try to make is the problem of consolidating the entire spectrum of skin grafts and flaps into a single diagnostic category. There is a vast difference between a split thickness skin graft, a large, complex myocutaneous surgical flap, and a traumatic compromised tissue flap. It is erroneous to compare these as the same condition in assessing the effectiveness of HBOT for “grafts and flaps”. It is here where the parachute problem becomes especially pertinent. In my experience treating patients with HBOT, one of the most urgent needs for this therapy is in a woman with breast reconstruction in which the nipple/areolar complex becomes compromised postoperatively. Hyperbaric oxygen is the treatment of choice as the nipple/areola becomes dusky, purple, dying and, I might add, physically and psychologically irreplaceable tissue. This is an emergency situation, but does not threaten life or limb. You will never see any RCT supporting the effectiveness of HBOT in this situation. The evidence will always be, at best, deductive and based on experimental models, low level “poor” evidence. But I can assure you that if this situation arises with you or a loved one, you ARE going to want HBOT and you are going to want it NOW. It would be erroneous for the State of Oregon to disallow, or even delay in any way, insurance coverage of this crucial treatment of a potentially devastating disfigurement on the basis of lack of evidence that will never exist. Although considerably more rare, the same may be said of sudden blindness in acute central retinal artery occlusion, or deafness in acute sensorineural hearing loss. Carbon Monoxide poisoning is yet another example where human RCT studies will never exist.	The coverage guidance document currently recommends coverage of HBOT for compromised flaps and grafts. Is the commenter suggesting that coverage NOT be recommended for some subset of flaps and grafts? If so, which subset is not defined. Central retinal artery occlusion is not addressed in this coverage guidance. See comments A3-7 regarding CO poisoning. Regarding acute sensorineural hearing loss, the appointed expert provided additional information, referencing a 2012 Cochrane review and the AAO practice guideline. This information was reviewed by HTAS at their April meeting, and is repeated in comment #C4.
	5	I appreciate the due diligence being done by the Oregon Health Evidence Review Commission. I know you will read this with due consideration. I hope you will all enjoy the parachute	Thank you for your comment.

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

Ident.	#	Comment	Disposition
		"study", but understand the seriousness of its underlying message.	
C	1	Thank you for the opportunity to provide additional comments regarding the OHA technology assessment on hyperbaric oxygen therapy. In large part, I have no disagreement with the recommendations of the technology assessment. I appreciate all of the work that has gone into the review by the OHA, and I will make this as brief as possible.	Thank you for your comment.
	2	There are three indications for which the HERC assessment does not recommend hyperbaric medicine that are all indications that have been reviewed and approved by the UHMS (thermal burns, refractory osteomyelitis, acute idiopathic sudden sensorineural hearing loss). The current UHMS indications book uses AHA criteria and not GRADE methodology, so it is difficult to use GRADE to argue for the use of HBOT. Dr. Murad's paper comparing the AHA criteria with GRADE is very informative, but has limitations in that it asks one single question and one single outcome for each hyperbaric indication. This limits the ability of a heterogenous body of literature to provide high quality, consistent answers for a single patient population.	HTAS does not disagree regarding the use of GRADE in this instance. HTAS has incorporated the Murad review into this coverage guidance.
	3	I am currently chair of the UHMS Clinical Practice Guideline Oversight Committee, and Dr. Murad is a member of the oversight committee as well. We are currently undertaking a more detailed review of all of the indications for HBOT using GRADE methodology, so we will shortly have a better ability to provide a more direct answer for these indications. My request would be for the HERC take these new publications under consideration (after they are published) in order to update their guidance documents.	HTAS will be sure to review this additional information when this coverage guidance is updated.
	4	Until then, please consider the comments regarding ISSHL that I have already been submitted to the committee. In brief, the Cochrane review on ISSHL did find that there was a significant improvement in the decibel level of hearing gain, but questioned the clinical significance of that improvement. I have provided the WHO definitions for hearing loss, showing that there was a significant improvement from moderate and severe hearing loss to minimal hearing loss, which does not require the use of hearing aids. Additionally, the American Academy of Otolaryngology and Head and Neck Surgery recommends HBOT for ISSHL (CPG attached), as there are no other treatment options that have had a similar improvement in hearing, which can be life-altering.	The reference provided is a process document outlining the methods used by the AAO to develop their practice guidelines. The AAO practice guideline on ISSHL was previously submitted by the commenter, and response was provided in another document (HBOT Supplemental Review: Additional Review of Evidence Provided by Public Commenter) and already reviewed by the committee. Commenter's previous statements regarding amount of hearing improvement demonstrated in the Cochrane review, and WHO hearing loss definitions, are correct, and are repeated below for ease of consideration: "for patients with severe hearing loss (61-80 dB loss) as defined by the World Health Organization (WHO), the improvement was 37.7 dB. For patients with moderate hearing loss (41-60 dB), the

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

Ident.	#	Comment	Disposition
			improvement in hearing was 19.3 dB. Using the WHO grades for hearing impairment, this represents a significant improvement from both of these categories to the slight hearing loss (26-40 dB) category (see attached slides courtesy of Heather Murphy-Lavoie, MD), which does not usually require a hearing aid. Considering that the costs of hearing aids are between \$1500-3000 per pair, need to be replaced every few years, and do not provide fully functional hearing, a limited course of HBOT (\$2000-5000 for a series of 10 sessions) may be a more cost effective and superior clinical result.” The previous response to this comment is repeated below: The American Academy of Otolaryngology Clinical Practice Guideline (Stachler 2012) states the following with regard to use of HBOT for sudden hearing loss: “Value judgments: Although hyperbaric oxygen therapy (HBOT) is not widely available in the United States and is not recognized by many US clinicians as an intervention for ISSNHL, the panel felt that the level of evidence for hearing improvement, albeit modest and imprecise, was sufficient to promote greater awareness of HBOT as an intervention for ISSNHL.” The authors of the guideline reference the SR included in the WA HTA report (Bennett 2007), and in summarizing this review, state the following: “Although the chance of a 50% improvement was not significantly increased following HBOT, the chance of a 25% increase was. Data indicated that a physician would need to treat 5 patients with HBOT therapy to improve 1 person’s hearing by 25%. Whether this is truly clinically significant is debatable.” A literature search performed by the guideline authors identified one additional RCT published after the date of the SR which found no significant difference between HBOT and the control arm in the percentage of patients who regained hearing either

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy

Disposition of Public Comments

Ident.	#	Comment	Disposition
			moderately or completely. The authors conclude with the following: “Given the small number of patients in the trials reviewed, methodological shortcomings, and poor reporting, the reported findings of benefit should be interpreted cautiously. The substantial cost, the potential adverse effects (including barotrauma), a question of the clinical significance of reported benefits, and the confounding effect of cointerventions (steroids, antivirals, rheologic agents) make it difficult to weigh benefits and harms.”

HERC Coverage Guidance – Indications For Hyperbaric Oxygen Therapy Disposition of Public Comments

References Provided by Commenters

Commenter	References
A	(1) Weaver, L. K., Hopkins, R. O., Chan, K. J., Churchill, S., Elliott, C. G., Clemmer, T. P., et al. (2002). Hyperbaric oxygen for acute carbon monoxide poisoning. <i>New England Journal of Medicine</i> , 347(14), 1057-1067.
B	(1) Smith, G., & Pell, J. P. (2003). Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. <i>Bmj</i> , 327(7429), 1459-1461.
C	(1) Rosenfeld, R. M., Shiffman, R. N., Robertson, P. (2013). Clinical Practice Guideline Development Manual, Third Edition: A Quality-Driven Approach for Translating Evidence into Action. <i>Otolaryngology -- Head and Neck Surgery</i> 148: S1-S55.

Percutaneous Interventions for Cervical Spine Pain

Question: How should the HTAS Coverage Guidance regarding percutaneous interventions for cervical spine pain be applied to the Prioritized List?

Question source: Health Technology Assessment Subcommittee

Issue: HTAS approved a new Coverage Guidance at their July, 2014 meeting. This CG needs final approval by HERC at the August, 2014 meeting. The summary of the coverage guidance is shown below:

HERC COVERAGE GUIDANCE

Therapeutic cervical spinal epidural injections are recommended for coverage for cervical spine pain with radiculopathy of six weeks duration (*weak recommendation*) only when all of the following criteria are met:

- documented neuroforaminal stenosis (without infection or neoplasia)
- radicular pain in a corresponding dermatomal distribution,
- pain is intractable and conservative therapy has failed,
- fluoroscopic guidance or CT guidance is utilized,
- interlaminar approach is utilized,
- no more than two injections without clinically meaningful improvement in pain and function, and
- maximum of three injections in six months.

Epidural steroid injections of the cervical spine are not recommended for coverage (*strong recommendation*) for other types of neck pain or for headache.

Therapeutic cervical intraarticular facet joint injections and therapeutic cervical medial branch blocks are not recommended for coverage for facet joint pain (*strong recommendation*).

Facet joint radiofrequency neurotomy is recommended for coverage (*weak recommendation*) only when all the following criteria are met:

- at least 3 months of moderate to severe pain with functional impairment,
- pain is predominantly axial and not associated with radiculopathy,
- conservative therapy has failed, and
- complete or nearly complete pain relief (80% or greater) following fluoroscopically guided, low-volume local anesthetic blocks of the medial branch nerves, performed on two separate occasions using two commonly-used agents with different anticipated durations of action.

Percutaneous Interventions for Cervical Spine Pain

Current Prioritized List status (note: line numbers refer to January 1, 2015 Prioritized List)

CODES	DESCRIPTION	LOCATION	STAFF RECOMMENDATIO N
ICD-9 Diagnosis Codes			
720.9	Unspecified inflammatory spondylopathy	50 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHRPATHIES	No change
721	Spondylosis , various	412 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT OR 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT	No change
722	Degeneration/displacement intervertebral disc, various	374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT 545	No change
723	Spinal stenosis, brachial neuritis or radiculitis, various	412 515 PERIPHERAL NERVE DISORDERS Therapy: MEDICAL THERAPY 541 PERIPHERAL NERVE DISORDERS Therapy: SURGICAL TREATMENT 545 588 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT	No change
724	Spinal stenosis, various	374,412,545,588	No change
738.4	Acquired spondylolisthesis	588	No change
ICD-10 Diagnosis Codes			
M43.00-3	Spondylolysis	588	No change
M43.10-3	Spondylolisthesis	588	No change
M47.10-3	Other spondylosis with myelopathy	412	No change
M47.20-3	Other spondylosis with radiculopathy	374	No change
M47.811-3, M47.819	Spondylosis without myelopathy or radiculopathy	545	No change
M47.891-3	Other spondylosis	545	No change
M48.00-3	Spinal stenosis	412,588	No change
M50	Cervical disc disorders	374	No change
M54.10-3	Radiculopathy	374	No change

Percutaneous Interventions for Cervical Spine Pain

M54.2	Cervicalgia	374,545	No change
CPT Codes			
62310	Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic	Ancillary	Add to lines 374,412, 545,588 with a new guideline note Advise DMAP to remove from the Ancillary List
64479-80	Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance; cervical or thoracic, single level and each additional	Excluded	Keep Excluded Add entry to new excluded list
64490-64492	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoro or CT), cervical, thoracic, lumbar or sacral; single, second or third level	Excluded	Add 64490-64492 to lines 412,545,588 with a new guideline note Advise DMAP to remove 64490-64492 from the Excluded List
64633-64634	Destruction by neurolytic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoro or CT), cervical, thoracic, lumbar or sacral; single, second or third level	Excluded	Add 64633 and 64634 to lines 412, 545,588 with a new guideline note Advise DMAP to remove 64633 and 64634 from the Excluded List
0213T–0215T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, cervical, thoracic, lumbar or sacral; single, second or third level	Excluded	No change
77003	Fluoroguide for spine injection	Ancillary	No change

Percutaneous Interventions for Cervical Spine Pain

Relevant Guidelines

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Lines 374,545

Diagnoses are included on Line 374 when neurologic impairment or radiculopathy is present, as defined as:

- A) Markedly abnormal reflexes
- B) Segmental muscle weakness
- C) Segmental sensory loss
- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 545.

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no “red flag” conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table.

Electromyography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4

Low Back Pain - Potentially Serious Conditions (“Red Flags”) and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	· History of cancer with new onset of LBP	MRI	ESR
	· Unexplained weight loss · Failure to improve after 1 month · Age >50 years · Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	· Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	· Fever · Intravenous drug use · Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	· Urinary retention · Motor deficits at multiple levels · Fecal incontinence · Saddle anesthesia	MRI	None
Vertebral compression fracture	· History of osteoporosis · Use of corticosteroids · Older age	Lumbosacral plain radiography	None

Percutaneous Interventions for Cervical Spine Pain

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Ankylosing spondylitis	· Morning stiffness · Improvement with exercise · Alternating buttock pain · Awakening due to back pain during the second part of the night · Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	· Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month · Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	· Radiculopathic signs** present >1 month · Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI***	Consider EMG/NCV
Spinal stenosis	· Radiating leg pain · Older age · Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	· Spinal stenosis symptoms present >1 month	MRI**	Consider EMG/NCV

* Level of evidence for diagnostic evaluation is variable

** Radiculopathic signs are defined for the purposes of this guideline as in Guideline Note 37 with any of the following:

- A. Markedly abnormal reflexes
- B. Segmental muscle weakness
- C. Segmental sensory loss
- D. EMG or NCV evidence of nerve root impingement
- E. Cauda equina syndrome,
- F. Neurogenic bowel or bladder
- G. Long tract abnormalities

*** Only if patient is a potential candidate for surgery or epidural steroid injection

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: *Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society*. Ann Intern Med. 2007; 147:478-491.

Utilization data:

Based on claims data analysis for the past 6 months, 63210 paired with diagnoses from the following lines (January 1, 2015 PL):

154 CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY

374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

412 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT

484 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY

515 PERIPHERAL NERVE DISORDERS

545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

588 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT

612 DISORDERS OF SOFT TISSUE

Percutaneous Interventions for Cervical Spine Pain

HERC staff recommendations (October 1, 2014/January 1, 2015 Prioritized List):

- 1) Add 63210 (Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic) to lines 400/374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT, 434/412 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT, 562/545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT, 607/588 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT
 - a. Add a new guideline note regarding cervical epidural steroid injections as shown below
 - b. Advise DMAP to remove 63210 from the Ancillary List
- 2) Add an entry to the new "excluded list" for CPT 64479-64480, 64490-64495, 0213T–0218T
- 3) Add 64490-64492 (Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (flouro or CT), cervical) to lines 434/412, 562/545, 607/588
 - a. Advise DMAP to remove 64490-64492 from the Excluded List
 - b. Utilization to be specified in the facet joint radiofrequency neurotomy guideline as shown below
- 4) Add 64633 and 64634 (Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); cervical or thoracic, single or additional facet joints) to lines 434/412, 562/545, 607/588
 - a. Advise DMAP to remove 64633 and 64634 from the Excluded List
 - b. Adopt a new guideline note regarding facet joint radiofrequency neurotomy as shown below

Percutaneous Interventions for Cervical Spine Pain

GUIDELINE NOTE XXX CERVICAL SPINAL EPIDURAL INJECTIONS

Lines 400,434,507,562 (October 1, 2014 PL)

Lines 374,412,545,588 (January 1, 2015 PL)

Cervical spinal epidural injections (CPT 62310) are **not** included on these lines for use in diagnostic testing.

Cervical spinal epidural injections (CPT 62310) for therapeutic purposes are included on these for cervical spine pain with radiculopathy of 6 weeks duration when all of the following criteria are met:

- 1) documented neuroforaminal stenosis (without infection or neoplasia)
- 2) radicular pain in a corresponding dermatomal distribution,
- 3) pain is intractable and conservative therapy has failed,
- 4) fluoroscopic guidance or CT guidance is utilized,
- 5) interlaminar approach is utilized,
- 6) no more than two injections without clinically meaningful improvement in pain and function, AND
- 7) maximum of three injections in six months.

Epidural steroid injections of the cervical spine are not included on these lines for treatment of other types of neck pain or for headache.

GUIDELINE NOTE XXX FACET JOINT RADIOFREQUENCY NEUROTOMY AND DIAGNOSTIC INJECTIONS

Lines 434,562,607 (October 1, 2014 PL)

Lines 412,545,588 (January 1, 2015 PL)

Paravertebral facet joint diagnostic injections (CPT 64490-64492) are included on these lines only when done as a diagnostic precursor to facet joint radiofrequency neurotomy as specified in #4 below.

Facet joint radiofrequency neurotomy (CPT 64633, 64634) is included on these lines only when all the following criteria are met:

- 1) at least 3 months of moderate to severe pain with functional impairment,
- 2) pain is predominantly axial and not associated with radiculopathy,
- 3) conservative therapy has failed, and
- 4) complete or nearly complete pain relief (80% or greater) following fluoroscopically guided, low-volume local anesthetic blocks of the medial branch nerves, performed on two separate occasions using two commonly-used agents with different anticipated durations of action.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PERCUTANEOUS INTERVENTIONS FOR CERVICAL SPINE PAIN

DRAFT for 8/14/2014 VbBS Meeting Materials

HERC COVERAGE GUIDANCE

Therapeutic cervical spinal epidural injections are recommended for coverage for cervical spine pain with radiculopathy of six weeks duration (*weak recommendation*) only when all of the following criteria are met:

- documented neuroforaminal stenosis (without infection or neoplasia)
- radicular pain in a corresponding dermatomal distribution,
- pain is intractable and conservative therapy has failed,
- fluoroscopic guidance or CT guidance is utilized,
- interlaminar approach is utilized,
- no more than two injections without clinically meaningful improvement in pain and function, and
- maximum of three injections in six months.

Epidural steroid injections of the cervical spine are not recommended for coverage (*strong recommendation*) for other types of neck pain or for headache.

Therapeutic cervical intraarticular facet joint injections and therapeutic cervical medial branch blocks are not recommended for coverage for facet joint pain (*strong recommendation*).

Facet joint radiofrequency neurotomy is recommended for coverage (*weak recommendation*) only when all the following criteria are met:

- at least 3 months of moderate to severe pain with functional impairment,
- pain is predominantly axial and not associated with radiculopathy,
- conservative therapy has failed, and
- complete or nearly complete pain relief (80% or greater) following fluoroscopically guided, low-volume local anesthetic blocks of the medial branch nerves, performed on two separate occasions using two commonly-used agents with different anticipated durations of action.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted Sources

Hashimoto, R., Raich, A., Ecker, E., Henrikson, N., Wallace, L., Dettori, J., & Chou, R. (2011). *Spinal injections*. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/spinal_injections.html

Little, A., Pettinari, C., Vandegriff, S., Leof, A., Rahman, B., Zoller, E., Kriz, H., Gerrity, M., & King, V. (2013). *Spinal injections: Update to the March 2011 WA HTA report*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Hashimoto, R., Holmer, H., Sherry, N., & Skelly, A. (2014). *Facet neurotomy*. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from <http://www.hca.wa.gov/hta/Pages/neurotomy.aspx>

Additional Sources

Cohen, S.P., Bicket, M.C., Jamison, D., Wilkinson, I., & Rathmell, J.P. (2013). Epidural steroids: A comprehensive, evidence-based review. *Regional Anesthesia and Pain Medicine*, 38(3), 175-200. doi: 10.1097/AAP.0b013e31828ea086.

Lee, S.H., Kim, K.T., Kim, D.H., Lee, B.J., Son, E.S., & Kwack, Y.H. (2012). Clinical outcomes of cervical radiculopathy following epidural steroid injection: a prospective study with follow-up for more than 2 years. *Spine (Phila Pa 1976)*, 37(12), 1041-1047. doi: 10.1097/BRS.0b013e31823b4d1f.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Chronic neck pain (defined as neck pain that persists more than three months) is common. Risk factors for spinal pain, including neck pain, include increasing age, spinal or disc degeneration, poor posture, anxiety, depression, and injuries. It can be attributed to a number of pathologic changes in the spine, including the following:

- Degenerative disc disease
- Herniated nucleus pulposus
- Spinal stenosis
- Facet joint syndrome
- Whiplash

Medical treatments available for chronic neck pain include non-invasive interventions such as physical therapy, pharmacologic therapy, psychological therapy, exercise, and spinal manipulation. For those patients with inadequate response to those treatments, spinal injections may be considered. Spinal injections involve the injection of an anti-inflammatory agent such as a steroid and/or an anesthetic agent into the spaces in and around the spinal nerves and joints. Types of spinal injection include epidural and facet joint injections and medial branch blocks. The latter two are generally used for pain believed to originate in the facet joint. It has been estimated that the point prevalences of facet joint pain are 10-15% in the low back and 45-55% in the neck. The primary symptom suggestive of facet joint pain is paraspinal tenderness at the affected facet joints, although other symptoms may be present as well. Diagnosis of facet joint pain cannot be accurately made by physical exam or imaging studies alone and diagnostic nerve blocks (medial branch blocks) may be the most accurate assessment method. Epidural injections deliver medication into the epidural space of the spine to decrease inflammation of the nerve root. Two approaches are possible in the neck. The interlaminar approach involves placement of the needle between the lamina of the vertebrae, delivering medication to both the right and left sides of the inflamed area. The transforaminal approach involves placement of the needle in the neural foramen, treating one side at a time.

Facet joint injections deliver the medications (anesthetic with or without a corticosteroid) into the facet joints and include several approaches. Medial branch blocks involve injection of the medication into the area of the medial branch of the posterior primary

ramus. Prior to steroid injections, controlled diagnostic blocks (medial branch blocks) of the joint or the nerves that supply the joint are often performed using local anesthetic. A positive block indicates that pain is eliminated and the affected nerve has been identified as the source of pain.

Once the facet joint is determined to be the source of pain as indicated by a positive diagnostic block, then prolonged pain relief may be achieved with destruction of the nerves to the affected joint in a procedure called facet neurotomy. Neurotomy does not cure the source of pain, but instead cuts off the pain signal from the brain by damaging the nerve. Different types of facet neurotomy are available, but the most common type employs radiofrequency needles to destroy the nerve tissue with heat generated by an electric current. During this procedure, the skin is anesthetized with a local anesthetic and the radiofrequency needles are advanced using guidance to confirm that the needles are properly positioned at the affected nerves. Then a radiofrequency current is applied to disrupt the ability of the nerves to transmit pain signals to the brain.

There are three types of radiofrequency (RF) neurotomy: standard, pulsed and cooled. Pulsed RF neurotomy delivers short bursts of radiofrequency current rather than the continuous flow utilized in non-pulsed RF neurotomy. Pulsed neurotomy allows the nerve tissue to cool between bursts, and is reported to reduce the destruction of neighboring tissue. Some other names used for this procedure include percutaneous radiofrequency denervation, nerve ablation, neurolysis, medial branch neurotomy, medial branch rhizotomy, and articular rhizolysis. Other types of facet neurotomy involve chemical ablation (application of ethyl alcohol, phenol, or sodium morrhuate; cryoablation (application of extreme cold); or laser ablation (application of laser beams) of the medial branch nerves to destroy the nerves and reduce or eliminate pain.

Evidence Review

Trusted Sources

These reports include studies of adults with sub-acute or chronic neck pain due to conditions including (but not limited to) degenerative disc disease, radiculopathy, disc herniation, spinal stenosis and facet joint pain. Evaluated treatments included epidural injections, intraarticular facet injections, medial branch blocks and facet neurotomy. Studies reporting on diagnostic injections (selective nerve root blocks), extraspinal injections (except as a comparator), chemonucleolysis, intradiscal electrothermal therapy and coblation nucleoplasty were excluded. Comparators included any placebo injection (water, saline, local anaesthetic) or non-placebo controls. For efficacy, only randomized controlled trials (RCTs) were included.

A total of seven RCTs were identified that reported on efficacy. Studies were limited to the following populations:

- Chronic neck pain without disc herniation or radiculitis (one study)
- Chronic neck pain with disc herniation or radiculitis (one study)
- Chronic neck pain with resistant cervicobrachialgia (one study)
- Chronic neck pain of facet origin (two studies)
- Cervical post-surgery syndrome (one study)
- Cervical spinal stenosis (one study)

Most of the included studies evaluated one injection technique (interlaminar epidural, facet joint or medial branch block) and compared steroid plus local anaesthetic injection to local anaesthetic alone. However, the trial of patients with resistant cervicobrachialgia compared epidural steroid plus local anaesthetic injection to posterior neck muscle injection with the same substances. The one trial that evaluated facet joint injections compared steroid injection (without local anaesthetic) to local anaesthetic injection.

Efficacy/Effectiveness

For trials comparing cervical epidural steroid injections with:

- Placebo injections for neck pain with disc herniation and radiculitis, there is no benefit based on data from one lower-quality RCT (strength of evidence = very low).
- Placebo injections for neck pain without disc herniation and radiculitis, there is no benefit based on data from one lower-quality RCT (strength of evidence = very low).
- Intramuscular injections for neck pain with disc compression and radiculitis, there is evidence that epidural injections were superior based on data from one lower-quality RCT (strength of evidence = very low).
- Placebo injections for post-surgery syndrome, there is no benefit based on data from one fair quality RCT (strength of evidence = very low).
- Placebo injections for cervical spinal stenosis, there is no benefit based on data from one fair quality RCT (strength of evidence = very low).

For trials comparing cervical intraarticular facet joint steroid injections with:

- Placebo injections for confirmed facet joint pain, there is no benefit based on data from one lower-quality RCT (strength of evidence = very low).

For trials comparing cervical medial branch blocks with:

- Placebo injections for confirmed facet joint pain, there is no benefit based on data from one lower-quality RCT (strength of evidence = very low).

For trials comparing different approaches for administering cervical epidural steroids:

- There were no significant differences between anterolateral and posterolateral approaches in estimated change from baseline in pain score or disability index at two weeks or two months. There is no apparent difference in efficacy based on differing approaches for administering cervical epidural steroids (strength of evidence = very low).

For trials comparing RF neurotomy with:

- Sham neurotomy in patients with confirmed facet joint pain (based on 100% response to three medial branch blocks), significantly more patients in the RF neurotomy group had freedom from “accustomed pain” (risk difference, 50% (95% CI, 18% to 82%) (P = 0.0110) based on evidence from one small (N=24) RCT (strength of evidence = very low).

Table 1. Efficacy/Effectiveness

Indication	Population characteristics	Comparator	Strength of Evidence	Conclusions
Cervical Epidural Steroid Injections				
Neck pain with disc herniation and radiculitis	Cervical disc herniation or radiculitis, chronic neck pain > 6 months duration, no spinal stenosis unless accompanied by disc herniation, no prior cervical spine surgery, opioid use stable/ controlled	Placebo epidural injection (local anaesthetic)	Very low	No benefit in terms of pain, function, or opioid use at both three and twelve months or on employment at twelve months based on data from one RCT.
Neck pain without disc herniation and radiculitis	Negative diagnosis of facet joint pain (by use of local anaesthetic blocks), absence of disc herniation/ radiculitis or spinal stenosis, chronic neck/arm pain > 6 months duration, opioid use stable/ controlled	Placebo epidural injection (local anaesthetic)	Very low	No benefit in terms of pain, function, or opioid use at both three and twelve months or on employment at twelve months based on data from one RCT.

Indication	Population characteristics	Comparator	Strength of Evidence	Conclusions
Neck pain with disc compression and radiculitis	Chronic resistant cervicobrachialgia, continued pre-study treatments (medications, PT). Full text only available for purchase	Intramuscular injection (saline and local anaesthetic)	Very low	Epidural injections were superior to intramuscular injections in the posterior neck in terms of pain, analgesic use, and employment at one week and twelve months based on data from one RCT.
Post-surgery syndrome	Cervical post-surgery syndrome, surgery > 1 year previously with continued pain for at least 6 months after surgery, opioid use stable/ controlled	Placebo epidural injection (local anaesthetic)	Very low	No benefit in terms of pain or disability at 3, 6 and 12 months based on data from one RCT.
Cervical spinal stenosis	Cervical central spinal stenosis with or w/o foraminal stenosis, age > 30, chronic neck pain of at least 6 on a scale of 1-10, at least 6 months duration, failed to improve with conservative management (PT, chiro, exercise, drugs, bed rest), opioid use stable/ controlled	Placebo epidural injection (local anaesthetic)	Very low	No benefit in terms of pain or disability at 3, 6 and 12 months based on data from one RCT.
Cervical Intraarticular Facet Joint Steroid Injections				
Confirmed facet joint pain	Neck pain lasting > 3 months due to MVA with documented positive response to medial branch block	Placebo facet injection (local anaesthetic)	Very low	No benefit in terms of the length of pain relief based on one RCT. No long-term data was reported.
Cervical Medial Branch Blocks (local anaesthetic + steroid, ± Sarapin*)				
Confirmed facet joint	Non-specific neck pain > 6 months	Placebo injection	Very low	No benefit in terms of pain or function at both three

Indication	Population characteristics	Comparator	Strength of Evidence	Conclusions
pain	duration, confirmed facet joint pain (response to local anaesthetic blocks), no radicular symptoms, failed conservative management (PT, chiro, exercise, drugs, bed rest), opioid use not heavy, continued previous interventions	(local anaesthetic ± Sarapin)		and twelve months or on opioid use or employment at twelve months based on one RCT.
Facet Neurotomy				
Confirmed facet joint pain	Failed conservative management (mean duration of pain 34 to 44 months), responded to 3 MBBs (100% pain relief)	Sham RF neurotomy	Very low	Significantly more patients in the RF neurotomy group had freedom from “accustomed pain” (risk difference, 50% (95% CI, 18% to 82%) (P = 0.01)
Cervicogenic headache	Cervicogenic HA of at least 2 years duration, rated at least 50 out of 100 on VAS, considerable pain at least 2 days/wk, no prior neck surgery	Injection of major occipital nerve	Low	No difference between groups in headache relief or a composite measure of success at 2 months
Facet joint pain	Patients with previously successful RF neurotomy	None – 3 case series	Very low	Patients are likely to experience a similar response to subsequent RF neurotomy procedures as they experienced during their first RF neurotomy procedure

*Sarapin is a suspension of powdered sarracenia purpurea (pitcher plant). This study had a total of four patient groups, but outcomes were not reported by use of this product.

Harms

- Major complications are rare following injections into the cervical spine and included a life-threatening generalized anaphylactic reaction, grand-mal seizure, dural puncture, subarachnoid puncture, and local hematoma. There were no cases of death or paralysis in the included studies, although there have been case reports of each in the published literature.
- Multiple publications have addressed the outbreak in fungal infections and deaths that resulted from the use of contaminated steroid preparations when delivering epidural steroid injections. As of December 27, 2012, there had been 620 cases of fungal meningitis, stroke presumed due to fungal meningitis, other central nervous system-related infection or septic arthritis attributed to the contamination, and 39 deaths.
- Other major complications were reported in case series of a mixture of lumbar and cervical spinal injection patients and included chest pain, tachycardia/hypertension, significant transient hypertensive episode, hematoma, dural puncture, and a severe vasovagal reaction.
- Minor complications are more common following lumbar or cervical spinal injections but are generally transient in nature, and include pain at the injection site, increased radicular pain/numbness/weakness, nerve root irritation, superficial infections, sympathetic blockade, facial flushing or rash, vasovagal reactions/fainting, headache, gastric complaints, dizziness, pruritus, irregular periods, and insomnia.
- With proper protective measures, total radiation exposure to the physician was within normal limits following a mean of 923 procedures (range, 100 to 1819) with an average length of radiation exposure of 9.8 seconds/procedure (range, 4.9 to 15.2) in all five case series identified.

Table 2. Harms

Spinal Injections	Strength of Evidence	Conclusions
Major complications	High	Major complications are rare following injections into the cervical spine. There were no cases of death or paralysis in the included studies, although there have been case reports of each in the published literature. In five RCTs, there were reports of subarachnoid puncture in 3/710 injections or patients and no reports of dural puncture or death. In four case series there were reports of life-threatening generalized anaphylactic reaction (1 case), grand-mal seizure (1 case), dural puncture (2 cases), and local hematoma (1 case) in

Spinal Injections	Strength of Evidence	Conclusions
		7240 injections or patients. In three case reports of a mix of lumbar and cervical spinal injection patients, there was one case of each of the following major complications in 6935 injections: chest pain, tachycardia/hypertension, significant transient hypertensive episode, hematoma, dural puncture, and a severe vasovagal reaction.
Minor complications	High	Minor complications are more common but are generally transient in nature. They were rare as reported in 5 RCTs. One non-randomized study reported an overall minor complication rate of 1.64%. Complications included: pain at the injection site, increased usual pain, transient pain/weakness, nerve root irritation, transient global amnesia, superficial infections, sympathetic blockade, vasovagal reactions, facial flushing, headache, nausea.
Vascular puncture	Low	The mean incidence of intravascular puncture following fluoroscopically guided cervical spinal injections was 15.6% (range, 4.0–19.4%) as reported in two studies. These studies evaluated the incidence but not the consequences of intravascular injection. The TruCath Spinal Injection System™ may decrease the incidence of vascular puncture.
Radiation exposure to the physician	Low	With proper protective measures, total radiation exposure was within normal limits following a mean of 923 procedures (range, 100 – 1819) with an average length of radiation exposure of 9.8 seconds/procedure (range, 4.9 – 15.2) in all five case series identified.

For RF neurotomy, the only adverse event reported more frequently for RF neurotomy compared to sham was numbness in the area of the treated nerves. Other adverse events reported were psoriatic rash and pain associated with the procedure, neither of which differed significantly from the sham group. Overall strength of the evidence is low.

Additional Sources

Because of the weak evidence base for ESI, the subcommittee chose to consider additional evidence that was provided by the HERC-appointed expert for this topic. The expert provided a systematic review and a retrospective cohort study, both described below.

Cohen 2013

This review included an extensive search of the literature, and all study types were included. However, details of the search, including number and type of studies, were not provided. Authors state that “recommendations were based on a conglomeration of factors including weighted evidence ..., consensus guidelines when relevant, and perceived bias” (p. 175). No quality assessment of included studies was completed, and there was no explicit link between the evidence and recommendations. The review provides a summary of the literature and recommendations for use of epidural steroids in the spine.

Pertaining to injection approach:

There are two different approaches for delivering epidural steroids in the cervical region, interlaminar (IL) and transforaminal (TF). An interlaminar injection involves passage of the needle through the ligamentum flavum in the posterior midline of the spine. Advantages of this approach are purported to be a higher likelihood that the injected medication will reach adjacent spinal levels and the ability to treat bilateral pain. Disadvantages include the potential for dural puncture and the dorsal deposition of the medication, which is more distant from the site of pathology. The transforaminal approach involves placement of the needle within the neuroforamen. Theoretical advantages are that it is the most target specific, carries a lower risk of dural puncture and is associated with a greater incidence of ventral spread. However, they are associated with a higher risk of catastrophic neurological complications.

Pertaining to the efficacy of ESI in the cervical region:

For interlaminar injections, the authors cite three systematic reviews, one of which was supportive of the efficacy of ESI for a variety of conditions, while the other two reported that ESIs are probably effective in the short-term. One of these stated that definitive evidence was lacking, and that the evidence was stronger for herniated disc and non-osseous central stenosis. The other reported that evidence was lacking for long-term efficacy.

For transforaminal injections, the authors report a single RCT, but multiple nonrandomized studies reporting both short and long term efficacy. They also note multiple reports of potentially catastrophic complications. The authors recommend the following:

“Overall, the literature suggests that although the TF approach may be more efficacious than the IL or caudal approaches, the difference in effect size is small. In the cervical, thoracic, and midlumbar to high lumbar regions, the increased risk

for catastrophic neurological complications should preclude the use of TF ESI as a first-line treatment.” (p. 181)

Lee 2012

Lee (2012) is a retrospective cohort study in which 98 patients who received cervical ESI for cervical radiculopathy without major neurologic deficit were followed for two years, then were analyzed based on whether they received spine surgery or not. Patients must have failed 4 weeks of conservative therapy and not have myelopathy or definite motor weakness. The injection was repeated up to 3 times at 1 to 2 week intervals, if pain relief was insufficient (less than 80% improved). Authors report that patients received an average of 1.8 ESI, and that at the 2-year follow up point, 80.6% of patients had not had surgery.

Analysis of clinical factors associated with proceeding to surgery found that having had a previous episode of cervical radiculopathy, pre-ESI pain score and post-ESI pain score were the only correlated factors. Fifteen percent of patients in the non-surgery group had a previous episode of cervical radiculopathy, compared to 42% in the surgery group ($p=0.02$). Prior to ESI, patients in the non-surgery group had a mean visual analogue scale (VAS) score for arm pain of 6.1, compared to 8.2 in the surgical group. Post ESI, the non-surgical group had a mean VAS pain score of 2.8 compared to 6.9 for the surgical group ($p<0.001$ for both). Factors for which there was no statistically significant difference between groups included gender, age, duration of symptoms, type of symptoms, compensation or number of ESI.

Evidence Summary

There is no evidence of benefit of epidural steroid injections compared with placebo injections for neck pain in patients either with or without disc herniation and radiculitis, post-surgery syndrome or cervical spinal stenosis. On the other hand, epidural injections appear to be superior to intramuscular injections in patients with disc compression and radiculitis. Conclusions regarding the efficacy of ESI from other sources are mixed, but suggest if they are effective, it is likely only short-term. One study suggests that ESI may result in a decreased risk of cervical surgery. There is no evidence of benefit of cervical intraarticular facet joint steroid injections or medial branch blocks compared with placebo injections for confirmed facet joint pain. There is no apparent difference in efficacy based on differing approaches for administering cervical epidural steroids. There is limited evidence of benefit of RF neurotomy in patients with confirmed facet joint pain.

Major complications are rare following injections into the cervical spine but can include a life-threatening generalized anaphylactic reaction, grand-mal seizure, dural and subarachnoid puncture, paralysis and death. Expert opinion in one review notes multiple

reports of potentially catastrophic complications using a transforaminal injection approach and recommends against their use, despite similar or better efficacy compared to intralaminar approaches. An outbreak in fungal infections and deaths that resulted from the use of contaminated steroid preparations when delivering epidural steroid injections occurred in 2012. Minor complications are more common but are generally transient in nature. No major complications of RF neurotomy have been reported.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage Recommendation	Rationale
Epidural steroid injections	Balance may result in some net benefit	Effectiveness evidence: Very low Harms evidence: High	Moderate	Moderate to high, given some may prefer interventional vs. pharmacologic vs. lifestyle or more conservative interventions	Recommended for coverage, only when all the following criteria are met: documented neuroforaminal stenosis (without infection or neoplasia); radicular pain in a corresponding dermatomal distribution; pain is intractable and conservative therapy has failed, fluoroscopic guidance or CT guidance is utilized; interlaminar approach is utilized; no more than two injections without clinically meaningful improvement in pain and function; and maximum of three injections in six months. (<i>weak recommendation</i>)	Though quality of evidence from trusted sources is very low, there is evidence from additional sources, namely a retrospective single cohort study, of some benefit when the recommended criteria are met. Additionally, other payer policies include a similar recommendation, namely Medicare and Washington State's payer policies.
Facet joint injections	No benefit	Effectiveness evidence: Very low Harms evidence:	Moderate	Moderate to high, given some may prefer interventional	Not recommended for coverage (<i>strong recommendation</i>)	No net benefit; some harms

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage Recommendation	Rationale
		High		vs. pharmacologic vs. lifestyle or more conservative interventions		
Therapeutic medial branch blocks	No benefit	Effectiveness evidence: Very low Harms evidence: High	Moderate	Moderate to high, given some may prefer interventional vs. pharmacologic vs. lifestyle or more conservative interventions	Not recommended for coverage (<i>strong recommendation</i>)	No net benefit; not common practice; some harms
RF neurotomy	Some evidence of benefit, minimal harms	Effectiveness evidence: Very low Harms evidence: High	Moderate	Moderate to high, given some may prefer interventional vs. pharmacologic vs. lifestyle or more conservative interventions	Recommended for coverage, only when all of the following criteria are met: at least 3 months of moderate to severe pain with functional impairment; pain is predominantly axial and not associated with radiculopathy; conservative therapy has failed; and at least 80% improvement from initial pain level following fluoroscopically-guided, low- volume local anesthetic blocks of the medial branch nerves, performed on two separate occasions. (<i>weak recommendation</i>)	Though quality of evidence from trusted sources is very low, the evidence shows there is some benefit when the recommended criteria are met. Coverage with these criteria was recommended by appointed expert.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Quality Measures

No pertinent quality measures were identified when searching the [National Quality Measures Clearinghouse](#).

Professional Society Guidelines

Guidelines reviewed in the WA HTA Spinal Injections report (Hashimoto, 2011) are included in Appendix D.

Payer Coverage Policies

Coverage policies for selected payers are included here.

Medicare

Two local coverage determinations were identified in the [Medicare Coverage Database](#).

- [L30481 Epidural and Transforaminal Epidural Injections](#)
- [L33842 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy](#)

Medicare coverage guidance is detailed in Appendix E.

Washington HTA Limitations of Coverage

Therapeutic Epidural Injections in the lumbar or cervical-thoracic spine for chronic pain are a covered benefit when all of the following conditions are met:

- For treatment of radicular pain
- With fluoroscopic guidance or CT guidance
- After failure of conservative therapy
- No more than two without clinically meaningful improvement in pain and function, and
- Maximum of 3 in 6 months

COMMITTEE DELIBERATIONS – VALUE-BASED BENEFITS SUBCOMMITTEE

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

DRAFT

Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome¹

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

¹ Includes risk of bias, precision, directness, consistency and publication bias

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
720.9	Unspecified inflammatory spondylopathy
721	Spondylosis , various
722	Degeneration/displacement intervertebral disc, various
723	Spinal stenosis, brachial neuritis or radiculitis, various
724	Spinal stenosis, various
738.4	Acquired spondylolisthesis
ICD-10 Diagnosis Codes	
M43.00-3	Spondylolysis
M43.10-3	Spondylolisthesis
M47.10-3	Other spondylosis with myelopathy
M47.20-3	Other spondylosis with radiculopathy
M47.811-3, M47.819	Spondylosis without myelopathy or radiculopathy
M47.891-3	Other spondylosis
M48.00-3	Spinal stenosis
M50	Cervical disc disorders
M54.10-3	Radiculopathy
M54.2	Cervicalgia
ICD-9 Volume 3 (Procedure Codes)	
03.91	Injection of anesthetic into spinal canal for analgesia
03.92	Injection of another agent into spinal canal
CPT Codes	
62310	Inject spine cervical/thoracic
64479	Inj foramen epidural c/t
64480	Inj foramen epidural add-on
64490- 64495	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (flouro or CT), cervical, thoracic, lumbar or sacral; single, second or third level
64633- 64636	Destruction by neurolytic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (flouro or CT), cervical, thoracic, lumbar or sacral; single, second or third level
64479-80	Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance; cervical or thoracic, single level and each additonal
64490-2	Injection(s), diagnostic or therapeutic agent, paravertebral facet joint (or nerves innervating that joint), with imaging guidance; cervical or thoracic, single level and each additional
0213T– 0218T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, cervical, thoracic, lumbar or sacral; single, second or third level
77003	Fluoroguide for spine injection
HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

Facet Joint Injections, Therapeutic Medial Branch Blocks



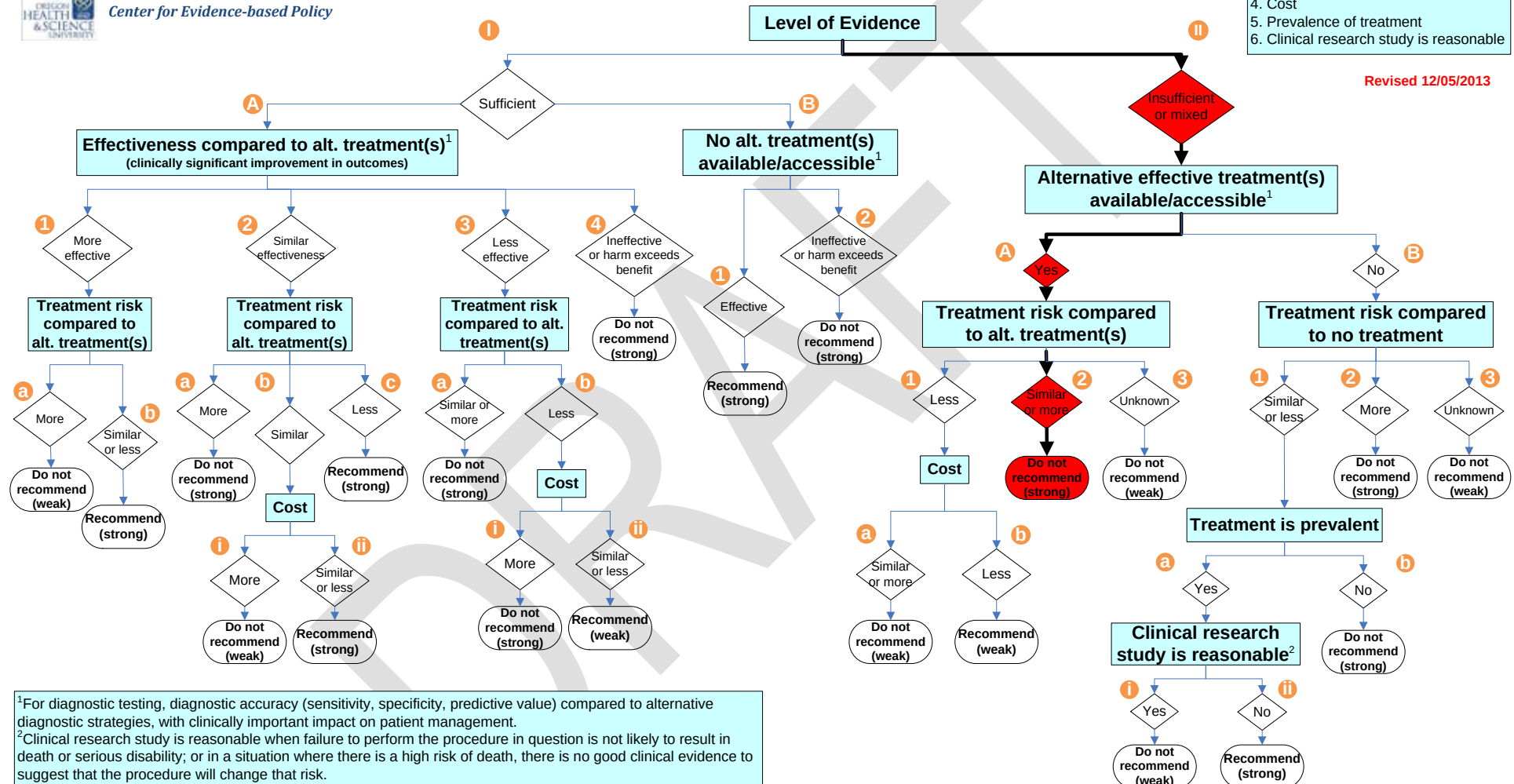
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

Revised 12/05/2013



Epidural Steroid Injections, RF Neurotomy



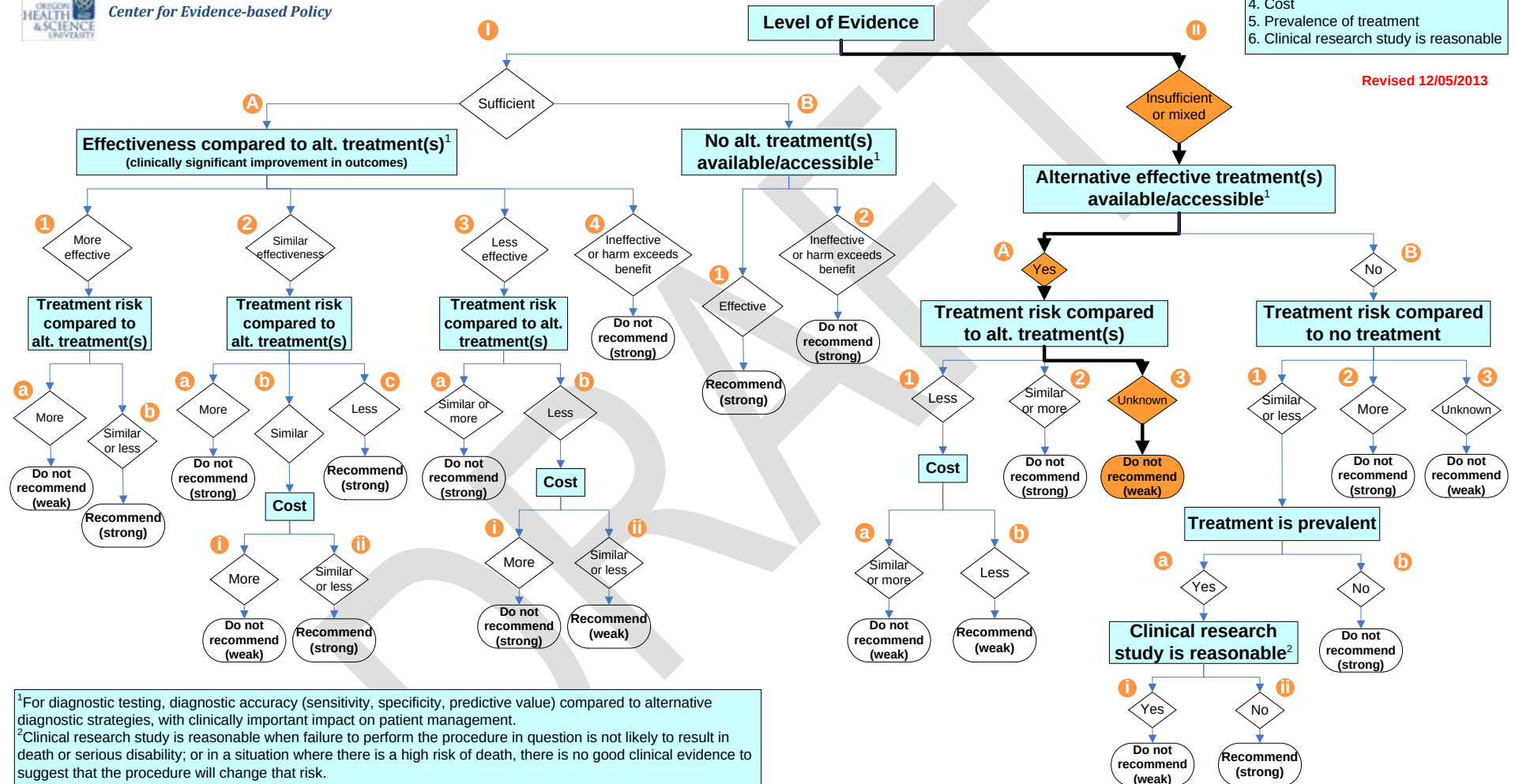
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

Revised 12/05/2013



Appendix D. Guidelines Included in the WA HTA Spinal Injections Report

Hashimoto, R., Raich, A., Ecker, E., Henrikson, N., Wallace, L., Dettori, J., & Chou, R. (2011). *Spinal Injections*. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/spinal_injection_draft_report.pdf

Fourteen guidelines were reported in this report. Of those, five pertain to cervical pain. One of those addressed chronic pain in general, was from 2008 and could not be retrieved, therefore was not assessed further. At the request of HERC staff, the quality of the other four guidelines was rated using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration. A summary of the pertinent recommendations and the quality rating of each guideline is presented in the table below:

Guideline	Recommendations	Quality
American Society of Interventional Pain Physicians. (2009) Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain (NGC:007428). [Updated in 2013]. http://asipp.org/Guidelines.htm	Cervical discography is indicated only when a treatment is available to test the diagnostic hypothesis of discogenic pain of the cervical spine in individuals who have been properly selected and screened to eliminate other sources of cervical pain. There is good evidence for disc herniation and fair evidence for axial or discogenic pain, central spinal stenosis, and post cervical surgery syndrome. Cervical interlaminar epidural injections are indicated for these conditions with appropriate indications. Diagnostic cervical facet joint nerve blocks are recommended in patients with somatic or non-radicular neck pain or headache and upper extremity pain, with duration of pain of at least 3 months, without preponderance of evidence of discogenic pain, disc herniation, or evidence of radiculitis. There is fair evidence for conventional radiofrequency neurotomy and therapeutic facet joint nerve blocks with limited evidence for intraarticular injections. Consequently, the recommendation is that therapeutic facet joint nerve blocks or conventional radiofrequency neurotomy may be provided based on the response from controlled diagnostic blocks.	Poor
Institute for Clinical Systems Improvement. (2009). <i>Assessment and management of chronic pain</i> (NGC:007602). [Updated in 2013]. https://www.icsi.org/guidelines_more/ca	Examples of commonly used therapeutic procedures are as follows. Facet joint injection Facet joints are an important source of spinal pain in the cervical and lumbar regions. These joints can be reliably anesthetized by way of fluoroscopically guided joint injections. Generally, a depot corticosteroid is administered concomitantly, which may provide short-term benefit for a subset of patients. However, clinical trials have failed to demonstrate any sustained therapeutic benefits following facet joint corticosteroid injections (<i>Nelemans, 2005 [Systematic Review]</i>).	Poor

Guideline	Recommendations	Quality
talog_guidelines_and_more/catalog_guidelines/catalog_neurological_guidelines/pain/	Percutaneous radiofrequency neurotomy Percutaneous radiofrequency (RF) neurotomy (sometimes erroneously referred to as facet rhizotomy) is a treatment for neck or back pain generated by facet joints. Properly selected candidates for this procedure should experience complete or nearly complete relief of their pain following fluoroscopically guided, low-volume local anesthetic blocks of the medial branch nerves that innervate the pain-generating joint(s). To minimize false-positive results, an equivalent degree of relief of appropriate pharmacologic duration should be carefully documented on two separate occasions, using two different types of local anesthetic. The radiofrequency procedure is performed by placing an insulated needle electrode with an exposed tip adjacent to and in parallel with the medial branch nerves that supply the target joint(s). Radiofrequency current applied to the electrode then heats the adjacent tissues and coagulates the nerve supply to the joint. For the procedure to be effective, multiple lesions must be performed at each nerve location, using electrodes of sufficient diameter. The nerves do regenerate over time, so pain relief is not permanent, but the procedure can be repeated. Radiofrequency neurotomy can provide pain relief for carefully selected patients, but this procedure should be performed only by an experienced pain medicine physician in the context of a longitudinal and comprehensive care plan. Proper patient selection and appropriate technique in positioning the radiofrequency electrodes are absolutely essential to the success of the procedure (<i>Bogduk, 2008 [Low Quality Evidence]; Nath, 2008 [Moderate Quality Evidence]; Hooten, 2005 [Guideline]</i>). Controversy in the literature regarding the efficacy of lumbar radiofrequency neurotomy has arisen from fundamentally flawed clinical trials that have used inappropriate patient selection criteria, and improper procedural technique. Epidural corticosteroid injections Epidural corticosteroid injections are one of the most commonly performed interventions for treatment of spinal pain with a radicular component. All epidural injections should be performed by an experienced physician, under fluoroscopic guidance, using contrast injection to detect vascular uptake and to demonstrate the injectate spread pattern. There are three approaches to the epidural space, including a transforaminal, intralaminar and a caudal technique. Limited evidence was found to support the efficacy of this procedure (<i>Riew, 2000 [High Quality Evidence]; Carette, 1997 [High Quality Evidence]; Dilke, 1973 [High Quality Evidence]</i>). Transforaminal epidural injection Transforaminal epidural injections can be used to determine the spinal level that is the source of radicular pain. The risks of cervical transforaminal epidural steroid injections have been well documented in case reports (<i>Beckman, 2006 [Low Quality Evidence]; Tiso, 2004</i>	

Guideline	Recommendations	Quality
	<i>[Low Quality Evidence]; Furman, 2003 [Low Quality Evidence]</i>). Specifically, cervical transforaminal epidural steroid injections have been associated with spinal cord and brain injuries resulting in permanent neurological deficits and/or death. These adverse events have been caused by uptake of particulate corticosteroids into radicular or vertebral arteries, producing embolization, severe vasospasm, and either brain or spinal cord infarction. For cervical procedures, it is recommended that only non-particulate corticosteroids be utilized. These procedures should be performed only by an experienced pain medicine physician with access to and knowledge of the use of appropriate imaging equipment and patient monitoring facilities, and should be performed only in the context of a longitudinal care plan, as directed and coordinated by a pain medicine physician (<i>Bogduk, 2008 [Low Quality Evidence]; Tiso, 2004 [Low Quality Evidence]</i>).	
Work Loss Data Institute. (2008). <i>Neck and upper back (acute & chronic)</i> (NGC:006563). [Updated 2011]. Unable to retrieve full guideline (subscription only). http://www.guideline.gov/content.aspx?id=33185	This guideline was not available without full subscription to the WLDI. Review of the summary on the NGC recommends consideration of ESI on the 4th visit, 3-4 weeks after onset of pain, only in those with neurologic findings, only for those “severe cases hoping to avoid surgery”.	Unable to assess quality without access to full guideline
Work Loss Data Institute. (2008). <i>Pain (chronic)</i> (NGC:006564). [Updated 2011]. Unable to retrieve full guideline (subscription only). http://www.guideline.gov/content.aspx?id=33188	This guideline was not available without full subscription to the WLDI. Review of the summary on the NGC did not specifically address neck pain, but states that epidural steroid injections and facet blocks are recommended. Additional information about indications is not provided in the NGC summary.	Unable to assess quality without access to full guideline

Appendix E. CMS Local Coverage Decisions

L30481 Epidural and Transforaminal Epidural Injections

Original Effective Date: For services performed on or after 04/15/2010

Revision Effective Date: For services performed on or after 02/01/2014

Jurisdiction: Includes Oregon

Coverage Indications, Limitations, and/or Medical Necessity

Epidural injections are used for acute and chronic pain, in addition to cancer pain management. Epidural injections are utilized both for diagnostic and therapeutic purposes.

A multi-disciplinary or collaborative comprehensive evaluation (e.g. orthopedics, neurologist, neurosurgeon, physiatrist, anesthesiologist, pain medicine specialist, and/or attending physician), is recommended prior to initiating a trial of these injections for relief of chronic recurrent pain.

Epidural steroid injections, both interlaminar/translaminar and transforaminal should be used only in the presence of radiculopathy.

Indications for Diagnostic and Therapeutic Epidural Injections

Diagnostic interlaminar/translaminar or caudal epidural steroid injections are seldom used. Although the medication injected can sometimes be confined to a limited area, bilateral effects and spread to adjacent levels often occur.

Therapeutic interlaminar/translaminar or caudal epidural injections and infusions of opioid, local anesthetic, or other medications may be used for the treatment of acute and chronic pain or cancer pain.

Epidural injections (interlaminar/translaminar or caudal) may be used for the following.

- Acute obstetric, post traumatic and postoperative pain
- Advanced cancer pain, primary or metastatic
- Acute/sub acute and chronic pain syndrome including cervical, thoracic and lumbar pain with radiculopathy and intervertebral disc disease (with neuritis or radiculitis) with or without myelopathy that has failed to respond to adequate conservative management.
- Nerve root injuries and neuropathic pain and post traumatic including post laminectomy syndrome (failed back syndrome).
- Spinal cord myelopathy
- Complex regional pain syndrome
- Epidural scarring from prior infection, hemorrhage and/or surgery

- Multiple rib fractures
- Vertebral compression fractures
- Post herpetic neuralgia and herpes zoster
- Phantom limb pain

Indications for Diagnostic and Therapeutic Transforaminal Epidural Injections

Transforaminal epidural injection is a selective injection of the cervical, thoracic, lumbar or sacral nerve roots with proximal spread of contrast or local anesthetic through the neural foramen to the epidural space. With the aid of fluoroscopic or computed tomography (CT) imaging, the needle tip is placed within or adjacent to the lateral margin of the neural foramen and contrast material is injected to obtain a neurogram and visualize spread of the injected solution.

A small volume of local anesthetic is injected (less than or equal to 1.0 ml) in order to perform a diagnostic reproducible blockade of a specific nerve root. The diagnostic usefulness is lost if more than 1.0 ml of local anesthetic is injected (the block becomes unreliable since the spread of anesthetic to adjacent levels and structures likely occurs).

Diagnostic transforaminal epidural injections are appropriate for the following purposes.

- To differentiate the level of radicular nerve root pain.
- To differentiate radicular from non radicular pain
- To evaluate a discrepancy between imaging studies and clinical findings
- To identify the source of pain in the presence of multi-level nerve root compression
- To identify the level of pathology at a previous operative site

It might be necessary to perform injections at two different nerve root levels on the same date of service. When multiple levels of nerve root compression or stenosis is suspected to be responsible for the patient's symptoms, presence of the compression or stenosis on imaging studies should be documented in the medical record.

Therapeutic transforaminal epidural injections are appropriate for the following purposes:

Corticosteroid can be added as a therapeutic measure. Injections for therapeutic reasons can be of greater volume. The transforaminal injection can be performed for diagnostic, therapeutic or both purposes.

- Radicular pain resistant to more conservative measures or when surgery is contraindicated.
- Post-decompressive radiculitis or post surgical scarring

- Monoradicular pain, confirmed by diagnostic block in which a surgically correctible lesion cannot be identified
- Treatment of acute herpes zoster or post herpetic neuralgia

General Indications and Limitations

Epidural (interlaminar/translaminar or caudal) and transforaminal epidural corticosteroid injections should not exceed a series of three, per spinal region, within a six-month period when used as treatment for a pain disorder other than treatment for cancer pain. These may be performed at intervals of one week or greater. With each subsequent injection the medical record should clearly document the interval effects from the prior injection(s). Appropriate reasons for a repeat injection are: (a) significant improvement in the patient's symptoms from the prior injection, even if relapsed, or (b) carefully documented technical reasons that it is appropriate to repeat the procedure even if no prior improvement and (c) patients with persistent pain in whom the imaging findings suggest that the pathology should respond to corticosteroid injection. In the absence of a compelling technical reason, it is not appropriate to repeat a procedure a third time if there has been no improvement from the two preceding.

If corticosteroids are used, consideration should be given to the potential complications of repetitive corticosteroid administration.

Many of these procedures, such as those in the peri-operative period, may not require fluoroscopy.

For treatment of chronic pain, the standard of care is that these procedures be performed under fluoroscopic or CT guided imaging. Therefore injections for chronic pain performed without imaging guidance will be considered not medically necessary.

Fluoroscopic guidance **must** be utilized in the performance of single nerve root/transforaminal injections to ensure the precise placement of the needle and medications injected.

Anti-spasmodic drugs administered intrathecally (e.g., baclofen) to treat chronic intractable spasticity are addressed in the Infusion Pump NCD Pub. 100-3 Sec. 280.14. The CPT description of procedure codes 62310, 62311, 62318 and 62319 include anesthetic, antispasmodic, opioid, steroid, other solution; therefore the spasticity conditions are included in this LCD.

L33842 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy

Original Effective Date: For services performed on or after 03/05/2014

Revision Effective Date: For services performed on or after 03/05/2014

Jurisdiction: Oregon

Coverage Indications, Limitations, and/or Medical Necessity

Introduction:

This policy does not address sacral conditions or injections or neurotomies. Sacral injections, identified on the claim by the ICD-9 code 724.6, are not subject to the requirements of this LCD.

Facet joints are paired diarthrodial articulations of the superior and inferior articular processes of adjacent vertebrae. The medial branches (MB) of the dorsal rami of the segmental nerves innervate facet joints and the MB nerves from the two adjacent dorsal rami innervate each joint. [Exceptions to this rule are the C2-3 facet joint, which is innervated by the third occipital nerve; and the L5-S1 facet joint, which is innervated by the L4 MB and the L5 dorsal ramus.]

Facet joint injection techniques are used in the diagnosis and/or treatment of chronic neck and back pain. However, the evidence of clinical efficacy and utility has not been well-established in the medical literature, which is replete with non-comparable and inadequately designed studies. Further, there is a singular dearth of long-term outcomes reports. This is particularly problematic given the steroid dosages administered. These drugs alone may develop the relief experienced by patients but are associated with serious adverse health events and could as well be administered orally. Hence, ongoing coverage requires outcomes reporting as described in this LCD to allow future analysis of clinical efficacy.

Definitions

- A zygapophyseal (aka facet) joint “level” refers to the zygapophyseal joint or the two medial branch (MB) nerves that innervate that zygapophyseal joint.
- A “session” is defined as all injections/blocks/RF procedures performed on one day and includes medial branch blocks (MBB), intraarticular injections (IA), facet cyst ruptures, and RF ablations.
- A “region” is all injections performed in cervical/thoracic or all injections performed in lumbar (not sacral) spinal areas.
- “Diagnosis” of facet-mediated pain requires the establishment of pain relief following dual medial branch blocks (MBBs) performed at different sessions.

Neither physical exam nor imaging has adequate diagnostic power to confidently distinguish the facet joint as the pain source.

Indications

- Patient must have history of at least 3 months of moderate to severe pain with functional impairment and pain is inadequately responsive to conservative care such as NSAIDs, acetaminophen, physical therapy (as tolerated).
- Pain is predominantly axial and not associated with radiculopathy or neurogenic claudication.
- There is no non-facet pathology that could explain the source of the patient's pain, such as fracture, tumor, infection, or significant deformity.
- Clinical assessment implicates the facet joint as the putative source of pain.

General Procedure Requirements:

- Pre-procedural documentation must include a complete initial evaluation including history and an appropriately focused musculoskeletal and neurological physical examination. There should be a summary of pertinent diagnostic tests or procedures justifying the possible presence of facet joint pain.
- A procedure note must be legible and include sufficient detail to allow reconstruction of the procedure. Required elements of the note include a description of the techniques employed, nerves injected and sites(s) of injections, drugs and doses with volumes and concentrations as well as pre and post-procedural pain assessments. With RF neurotomy, electrode position, cannula size, lesion parameters, and electrical stimulation parameters and findings must be specified and documented.
- Facet joint interventions (diagnostic and/or therapeutic) must be performed under fluoroscopic or computed tomographic (CT) guidance. Facet joint interventions performed under ultrasound guidance will not be reimbursed.
- A hard (plain radiograph with conventional film or specialized paper) or digital copy image or images which adequately document the needle position and contrast medium flow (excluding RF ablations and those cases in which using contrast is contra-indicated, such as patients with documented contrast allergies), must be retained and submitted if requested.
- In order to maintain target specificity, total IA injection volume must not exceed 1.0 mL per cervical joint or 2 mL per lumbar joint, including contrast. Larger volumes may be used only when performing a purposeful facet cyst rupture in the lumbar spine.
- Total MBB anesthetic volume shall be limited to a maximum of 0.5 mL per MB nerve for diagnostic purposes and 2ml for therapeutic. For a third occipital nerve block, up to 1.0 mL is allowed for diagnostic and 2ml for therapeutic purposes.

- In total, no more than 100 mg of triamcinolone or methylprednisolone or 15 mg of betamethasone or dexamethasone or equivalents shall be injected during any single injection session.
- Both diagnostic and therapeutic facet joint injections may be acceptably performed without steroids.

Provider Qualifications

Provider Qualifications' requirements must be met. Patient safety and quality of care mandate that healthcare professionals who perform Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy are appropriately experienced and/or trained to provide and manage the services. The CMS Manual System, Pub. 100-8, Program Integrity Manual, Chapter 13, Section 5.1 (<http://www.cms.hhs.gov/manuals/downloads/pim83c13.pdf>) underscores this point and states that "reasonable and necessary" services must be "ordered and/or furnished by qualified personnel." Services will be considered medically reasonable and necessary only if performed by appropriately experienced and/or formally trained providers.

The following training requirement applies only to those providers who have not provided these specific interventional pain management services on a regular basis (at least two times per month) during the ten years prior to the effective date of this LCD as may be established by claims billings. A basic requirement of payment is training and/or credentialing by a formal residency/fellowship program and/or other training program that accredited by a nationally-recognized body and whose core curriculum includes the performance and management of the procedures addressed in this policy. Recognized accrediting bodies include only those whose program accreditation gains the trainee eligibility to sit for a healthcare-related licensing exam or licensing itself, which in turn allows the licensee to perform these procedures. At a minimum, training must cover and develop an understanding of anatomy and drug pharmacodynamics and kinetics, the technical performance of the procedure(s) and utilization of the required associated imaging modalities, and the diagnosis and management of potential complications from the intervention.

The following credentialing requirement applies to all providers of the services addressed in this policy. If the practitioner works in a hospital facility at any time and/or is credentialed by a hospital for any procedure, the practitioner must be credentialed to perform the same procedure in the outpatient setting.

Diagnostic Facet Joint Injections

- Dual MBBs are necessary to diagnose facet pain due to the unacceptably high false positive rate of single MBB injections.

- A second confirmatory MBB is allowed if documentation indicates the first MBB produced $\geq 80\%$ relief of primary (index) pain and duration of relief is consistent with the agent employed.
- Intraarticular facet block will not be reimbursed as a diagnostic test unless medial branch blocks cannot be performed due to specific documented anatomic restrictions.

Therapeutic Injections

- Medial Branch Blocks may provide temporary or long-lasting or permanent relief of facet-mediated pain. Injections may be repeated if the first MBB results in significant pain relief ($> 50\%$) for at least 3 months. (See Limitations section for total number of injections that may be performed in one year.)
- Intraarticular injections may be covered for treatment of defined facet pain a) above or below a posterior spinal fusion when technical performance of MBBs is precluded, and/or b) when thermal RF neurotomy is precluded due to an implantable spinal cord stimulator or cardiac pacemaker or c) for rupture of symptomatic synovial cyst. Injections for these conditions and for axial pain with an arthritic joint may be repeated if the first intraarticular injection results in significant pain relief ($> 50\%$) for at least 3 months. (See Limitations section for total number of injections that may be performed in one year.)
- Recurrent pain at the site of previously diagnosed facet pain (dual MBBs) may be treated without additional diagnostic blocks if $> 50\%$ pain relief from the previous blocks lasted at least 3 months.

Thermal Medial Branch Radiofrequency Neurotomy (includes RF and microwave technologies):

- Only when dual MBBs provide $\geq 80\%$ relief of the primary or index pain and duration of relief is consistent with the agent employed may facet joint denervation with RF medial branch neurotomy be considered.
- Repeat denervation procedures involving the same joint will only be considered medically necessary if the patient experienced $\geq 50\%$ improvement of pain and improvement in patient specific ADLs documented for at least 6 months.

Limitations of Coverage:

- A maximum of five (5) facet joint injection sessions inclusive of medial branch blocks, intraarticular injections, facet cyst rupture and RF ablations may be performed per year in the cervical/thoracic spine and five (5) in the lumbar spine.
- For each covered spinal region (cervical/thoracic or lumbar), no more than two (2) thermal RF sessions will be reimbursed in any calendar year, involving no more than four (4) joints per session, e.g., two (2) bilateral levels or four (4) unilateral levels.

- Neither conscious sedation nor Monitored Anesthesia Care (MAC) is routinely necessary for intraarticular facet joint injections or medial branch blocks and are not routinely reimbursable. Individual consideration may be given for payment in rare unique circumstances if the medical necessity of sedation is unequivocal and clearly documented.
- Non-thermal RF modalities for facet joint denervation including chemical, low grade thermal energy (<80 degrees Celsius), as well as pulsed RF are not covered.
- Intraarticular and/or extraarticular facet joint prolotherapy is not covered.

HERC Coverage Guidance – Percutaneous Interventions for Cervical Spine Pain

Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	North American Spine Society (NASS), Burr Ridge, IL <i>[Submitted June 6, 2014]</i>

HERC Coverage Guidance – Percutaneous Interventions for Cervical Spine Pain

Disposition of Public Comments

Public Comments

Ident.	#	Comment	Disposition
A	1	NASS agrees with a majority of the HERC guidance regarding coverage for therapeutic cervical spinal epidural injections for chronic cervical pain with radiculopathy. Regarding indications, in addition to the documentation of herniated intervertebral disc, other anatomic causes of radiculopathy should also be included such as: • Neuroforaminal stenosis; • Central stenosis, disc protrusions; and/or • Segmental spondylosis with radicular pain. NASS strongly agrees that all cervical epidural injections or selective nerve root blocks should be performed with fluoroscopic or CT-guidance.	Thank you for taking the time to comment. HTAS acknowledges that there are other anatomic causes of radiculopathy and has changed the criteria in the coverage recommendation to the following: “documented neuroforaminal stenosis (without infection or neoplasia)”
	2	NASS would like to clarify also that an epidural injection can be appropriately performed by either an interlaminar approach or a transforaminal approach. The HERC reference to a translaminar approach is incorrect as there is no translaminar approach with these injections and the terminology to reference either an interlaminar or a transforaminal approach should be corrected in your policy guidance. NASS also wishes to clarify, as referenced in your policy, the utility of diagnostic spinal nerve (root) blocks in the treatment and/or diagnosis of cervical radicular pain. These blocks use a foraminal approach and share the same CPT codes (64479-64480) as the technically similar transforaminal epidural injection.	These terms translaminar and interlaminar are used interchangeably in the WA HTA report and in CMS coverage decisions. Terminology changed to reflect your suggestions in the body of the guidance; however, when this term is used in coverage policies, no change has been made. The diagnostic blocks referred to in the coverage guidance are medial branch blocks, and the CPT codes utilized (64490-2) are different than those referred to by the commenter. Diagnostic spinal nerve root blocks (64479-80) were not reviewed in this document. Text in the guidance document has been clarified and

HERC Coverage Guidance – Percutaneous Interventions for Cervical Spine Pain

Disposition of Public Comments

Ident.	#	Comment	Disposition
			CPT codes added.
	3	Although many patients may respond to conservative treatment (rest, NSAIDs, PT), in patients with moderate to severe radicular pain with resulting functional limitations (i.e., inability to work, etc.) and appropriate correlated imaging findings, cervical epidural injections are indicated in the acute and sub-acute phases of treatment and is an appropriate conservative treatment option in this patient population.	All studies in the evidence review included only patients with chronic neck pain. When this was defined, it was pain of > 6 months duration or more. The background section of this document reports the definition of chronic to be greater than 3 months. HTAS has revised the box language to specify that coverage is recommended for pain of at least 6 weeks duration.
	4	NASS would like to recommend the Health Evidence Review Commission to include a transparent evidentiary table that will allow users to access and review available supporting literature as well as provide a definition of chronic for further clarification.	Links to the supporting literature, when publically available, are provided on page 2 of the guidance document. See comment 3 regarding definition of chronic.
	5	Please click on the link below for the NASS coverage recommendations on cervical epidural injections and diagnostic spinal nerve blocks for your reference: https://www.spine.org/Pages/PolicyPractice/Coverage/CoverageRecommendations.aspx	Thank you for providing this information.

HERC Coverage Guidance – Percutaneous Interventions for Cervical Spine Pain Disposition of Public Comments

References Provided by Commenters

Commenter	References
A	NASS. (2014). Cervical Epidural Injections And Diagnostic Spinal Nerve Block. https://www.spine.org/Documents/PolicyPractice/CoverageRecommendations/CervicalEpiduralInjections.pdf

Section 6.0

Guidelines

Guideline Note 37

Question: should GN 37 be amended to clarify intent?

Question source: Tracy Muday, OHP Medical Director

Issue: GN37 was extensively reviewed with the low back pain treatment coverage guidances. Before these revisions, the guideline specified that that patient was required to have **objective evidence of** neurologic impairment. The word objective was removed from the guideline for unclear reasons.

HERC staff recommendation:

- 1) Modify GN37 to read as shown below

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Lines 374,545

Diagnoses are included on Line 374 when [objective evidence of](#) neurologic impairment or radiculopathy is present, as defined as:

- A) Markedly abnormal reflexes
- B) Segmental muscle weakness
- C) Segmental sensory loss
- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 545.

Rehabilitation Guideline

Question: What type of restrictions should be placed on physical and occupational therapies and other rehabilitative therapies?

Question source: HERC staff

Issues:

- 1) The current guideline with different visit numbers based on age without medical justification is not allowed under the ACA
- 2) At the May, 2014 meeting, the VBBS adopted a modified guideline without any visit limits
- 3) Medical Director feedback indicates that some type of numerical limits are strongly desired. The modified guideline shown in the recommendations section has been reviewed by the Medical Directors and they have no objections or comments.
- 4) HERC staff are concerned about lack of coverage for neurologic injuries, which may take longer to rehab and may vary on when rehab can begin

Current guideline:

GUIDELINE NOTE 6, REHABILITATIVE THERAPIES

Lines 37,50-52,64,74-76,78,80,85,89,90,94,95,98-101, 108, 109, 115, 116, 122, 129, 139, 141-143,145,146,158,161,167,179,184,185,189, 190, 192, 194, 195, 201, 202, 208, 209,216,226,237,239,270,271,273,274,279,288,289,293,297,302,304,307-309, 318, 336,342,349, 350, 363, 367, 369, 375,376,378, 382,384,385,387, 400,406, 407, 434, 441,443,448,455,467,478,489,493,507,516,535,549,562, 580, 597,619,638

Physical, occupational and speech therapy, and cardiac and vascular rehabilitation, are covered for diagnoses paired with the respective CPT codes, depending on medical appropriateness, for up to 3 months immediately following stabilization from an acute event.

Following the 3 month stabilization after an acute event, or, in the absence of an acute event, the following number of combined physical and occupational therapy visits are allowed per year, depending on medical appropriateness:

- Age < 8: 24
- Age 8-12: 12
- Age > 12: 2

And the following number of speech therapy visits are allowed per year, depending on medical appropriateness (with the exception of swallowing disorders, for which limits do not apply):

- Age < 8: 24

Rehabilitation Guideline

- Age 8-12: 12
- Age > 12: 2

Whenever there is a change in status, regardless of age, such as surgery, botox injection, rapid growth, an acute exacerbation or for evaluation/training for an assistive communication device, the following additional visits are allowed:

- 6 visits of speech therapy and/or
- 6 visits of physical or occupational therapy

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Guideline adopted in May, 2014

GUIDELINE NOTE 6, REHABILITATIVE THERAPIES

Lines 37,50-52,64,74-76,78,80,85,89,90,94,95,98-101,108,109,115, 116,122, 129, 139,141-143,145,146,158,161,167,179,184,185,189,190,192,194, 195,201, 202, 208,209,216,226,237,239,270,271,273,274,279,288,289,293,297,302,304,307-309,318,336,342,349,350,363,367,369,375,376,378, 382,384,385,387,400, 406, 407,434,441,443,448,455,467,478,489,493,507,516,535,549,562,580,597,619,638

Physical, occupational and speech therapy, and cardiac and vascular rehabilitation are only included on these lines when the following criteria are met:

- 1) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide physical, occupational, or speech therapy,
- 2) there is objective, measurable documentation of progress toward the therapy plan of care goals and objectives,
- 3) the therapy plan of care requires the skills of a therapist, and
- 4) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

Rehabilitation Guideline

HERC staff recommendation:

- 1) Adopt the modified rehabilitation guideline as shown below
 - a. Consider adding a clause excepting neurologic injuries from visit limits

GUIDELINE NOTE 6, REHABILITATIVE THERAPIES

Lines 37,50-52,64,74-76,78,80,85,89,90,94,95,98-101, 108, 109, 115, 116, 122, 129, 139, 141-143,145,146,158,161,167,179,184,185,189, 190, 192, 194, 195, 201, 202, 208, 209,216,226,237,239,270,271,273,274,279,288,289,293,297,302,304,307-309, 318, 336,342,349, 350, 363, 367, 369, 375,376,378, 382,384,385,387, 400,406, 407, 434, 441,443,448,455,467,478,489,493,507,516,535,549,562,580, 597,619,638

A total of 30 visits per year of rehabilitative therapy (physical, occupational and speech therapy, and cardiac and vascular rehabilitation) are included on these lines when medically appropriate. Additional visits, not to exceed 30 visits per year, may be authorized in exceptional circumstances, such as in cases of rapid growth/development. Physical, occupational and speech therapy, and cardiac and vascular rehabilitation are only included on these lines when the following criteria are met:

- 1) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the therapy,
- 2) there is objective, measurable documentation of clinically significant progress toward the therapy plan of care goals and objectives,
- 3) the therapy plan of care requires the skills of a medical provider, and
- 4) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Possible additional wording:

Spinal cord injuries, traumatic brain injuries, or cerebral vascular accidents are not subject to the visit limitations during the first year after an acute injury.

Lymphedema Guideline

Issues: The current lymphedema guideline needs three modifications due to recent VBBS decisions:

- 1) A new lymphedema line was created at the May, 2014 VBBS meeting which combined all lymphedema diagnoses, which currently are on 3 separate lines. The current lymphedema guideline needs to be modified to reflect this line change for the next biennial review List.
- 2) At the May, 2014 meeting, sub-committee members expressed interest in making very clear their intent to cover treatments for lymphedema, including compression stockings, even when no ulcer or other complication was present. Experts suggested putting this coverage intent into the lymphedema guideline.

HERC staff recommendations:

- 1) Modify the lymphedema guideline as shown below (#1) for the October 1 List until the next biennial review List
- 2) Modify the lymphedema guideline as shown below (#2) beginning with the next biennial review List

#1 (October 1, 2014 Prioritized List)

GUIDELINE NOTE 43, LYMPHEDEMA

Lines 427,577,579

Lymphedema treatments are included on these lines when medically appropriate. These services are to be provided by a licensed practitioner who is certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; <http://www.clt-lana.org>). Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE THERAPIES. It is the intent of the HERC that compression dressings and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

#2 (Biennial review List)

GUIDELINE NOTE 43, LYMPHEDEMA

Lines ~~427,577,579~~ XXX (new lymphedema line)

Lymphedema treatments are included on this line ~~these lines~~ when medically appropriate. These services are to be provided by a licensed practitioner who is certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; <http://www.clt-lana.org>). Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE THERAPIES. It is the intent of the HERC that compression dressings and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

Dentures Guideline and Rule Conflict

Question: What should be done about a conflict between the removable prosthodontics guideline and rule?

Question source: Katie Noah, Willamette Dental; DMAP

Issue:

Katie Noah noticed a discrepancy between DMAP rules and Guideline Note 62. Under the Dental Services Program Rulebook, 410-123-1260, the rule shows that under 21 is 4 missing posterior teeth but over 21 is 6 missing posterior teeth for the benefit.

<http://www.dhs.state.or.us/policy/healthplan/guides/dental/123rb010112.pdf>

However, Guideline note 62 states that **4** or more posterior missing teeth per arch are required, not **6**.

On 1/1/2012, DMAP changed the coverage rules so adults age 21+ could only receive coverage of a partial dentures if they are missing 6 or more posterior or one or more anterior teeth. This was a benefit reduction and made coverage different for adults versus children. The guideline did not change at the same time. The rationale for this was:

“Limits on some dental services for adult clients (age 21 and older) due to reduced payments to managed Dental Care Organizations (DCOs) to comply with budget limitations required by the 2011 Legislative Assembly in SB 5529. This will help assure access to services through sufficient provider networks will be maintained following this approximate 11% reduction in capitation rates.”

Prioritized List Status:

Line: 477
Condition: DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) (See Guideline Note 62)
Treatment: REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES)
HCPCS: D5110-D5212, D5520-D5761, D5820, D5821

GUIDELINE NOTE 62, REMOVEABLE PROSTHODONTICS

Line 477

Must have one or more anterior teeth missing or four or more posterior teeth missing per arch with resulting space equivalent to that loss demonstrating inability to masticate; third molars are not a consideration when counting missing teeth (D5211, D5212).

HERC staff assessment and recommendations: The Prioritized List and DMAP rules are in conflict due to further changes made in response to legislative budget needs.

- 1) Delete Guideline Note 62

Adenoidectomy

Question: When is adenoidectomy alone indicated and/or effective?

Question source: Tracy Muday, MD, OHP Medical Director

Issue:

From Dr. Muday:

We have lots of requests for adenoidectomy alone for young kids, usually under 4, sometimes under 2. My understanding of why they are doing the adenoidectomy alone is related to the risk of adenotonsillectomy in the younger group, and they feel that the adenoidectomy alone is likely to improve the kid's symptoms.

Truthfully, my 3 ENTs have a gestalt of kids that they feel need tubes or adenoidectomy. The diagnosis that they use for this adjusts itself depending on what is covered. When OME was above the line, all the tubes were done with a dx of OME. When OME went below the line, they started paying attention to who had recurrent AOM, and that became the diagnosis. When we put limits on adenoidectomy with tubes for OME, they started coding for OSA and sinusitis

Adenoidectomy for chronic otitis media

Adenoidectomy for treatment of chronic otitis media was extensively reviewed in 2012 and guideline revisions made to clarify when this procedure is appropriate. Adenoidectomy was reaffirmed as a treatment for possible children with chronic otitis media receiving their second set of tubes in the Chronic Otitis Media guideline.

Adenoidectomy for chronic sinusitis

Adenoidectomy for chronic sinusitis was reviewed in 2008. Some evidence was found that younger children (younger than age 12) may benefit for adenoidectomy for chronic sinusitis, but overall the body of evidence was scanty. Adenoidectomy was added to the chronic sinusitis line based mainly on expert opinion. It was noted that "If surgery is indicated, evidence shows that adenoidectomy should be performed before endoscopic sinus surgery (which is currently covered)." Adenoidectomy was added to the chronic sinusitis line for children younger than age 12 (42830, 42835).

Adenoidectomy for OSA

The obstructive sleep apnea guideline (GN 118) was extensively reviewed in 2013, but adenoidectomy as a single procedure was not reviewed. Evidence presented during this review focused on adenotonsillectomy.

Adenoidectomy

Current List placement:

CPT	Code Description	Current Lines
42820	Tonsillectomy and adenoidectomy; younger than age 12	47 CONGENITAL AIRWAY OBSTRUCTION WITH OR WITHOUT CLEFT PALATE 51 DEEP ABSCESES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 68 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE 206 SLEEP APNEA AND NARCOLEPSY 370 STREPTOCOCCAL SORE THROAT AND SCARLET FEVER; VINCENT'S DISEASE; ULCER OF TONSIL; UNILATERAL HYPERTROPHY OF TONSIL 556 CHRONIC DISEASE OF TONSILS AND ADENOIDS
42821	Tonsillectomy and adenoidectomy; age 12 or over	47,68,51,206,370,556
42830	Adenoidectomy, primary; younger than age 12	47,51,206, 470 CHRONIC SINUSITIS 481 CHRONIC OTITIS MEDIA 556
42831	Adenoidectomy, primary; age 12 or over	47,51,206,481,556
42835	Adenoidectomy, secondary; younger than age 12	47,51,206,470,481,556
42836	Adenoidectomy, secondary; age 12 or over	47,51,206,481,556

GUIDELINE NOTE 35, SINUS SURGERY

Lines 366,470

Sinus surgery indicated in the following circumstances:

A) 4 or more episodes of acute rhinosinusitis in one year

OR

B) Failure of medical therapy of chronic sinusitis including all of the following:

- Several courses of antibiotics AND
- Trial of inhaled and/or oral steroids AND
- Allergy assessment and treatment when indicated AND
- One or more of the following:
 - Findings of obstruction of active infection on CT scan
 - Symptomatic mucocele
 - Negative CT scan but significant disease found on nasal endoscopy

OR

C) Nasal polyposis causing or contributing to sinusitis

OR

D) Complications of sinusitis including subperiosteal or orbital abscess, Pott's puffy tumor, brain abscess or meningitis

OR

E) Invasive or allergic fungal sinusitis

OR

F) Tumor of nasal cavity or sinuses

OR

G) CSF rhinorrhea

Adenoidectomy

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 47,51,370,556

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with:

- A) Five documented attacks of strep tonsillitis in a year or 3 documented attacks of strep tonsillitis in each of two consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed;
- B) Peritonsillar abscess requiring surgical drainage; or,
- C) Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

See Guideline Note 118 for diagnosis and treatment of obstructive sleep apnea in children.

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 317,481

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 317. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 481.

For coverage to be considered on either Line 317 or Line 481, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay (should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected).

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children over 3 years who are having their second set of tubes.

GUIDELINE NOTE 118, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN

Line 206

Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by

Adenoidectomy

1. nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR
2. nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
3. use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
4. consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

1. high risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
2. children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),
3. children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese.

Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

1. undergone surgery or are not candidates for surgery, AND
2. have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use
- Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

Adenoidectomy

Evidence—Adenoidectomy for chronic sinusitis

No NICE or SIGN guidances found

AAP and IDSA guidelines on chronic sinusitis in children addressed only diagnostic criteria and antibiotic treatment. Neither addressed surgery

- 1) **van den Aardweg 2010**, Cochrane review of adenoidectomy for chronic nasal symptoms in children
 - a) N=1 study with 76 subjects who underwent adenoidectomy for improvement in episodes of common colds
 - b) The risk differences were non-significant, being 2% (95% CI -18% to 22%) and -11% (95% CI -28% to 7%) after 12 and 24 months, respectively.
 - c) **Authors' conclusions:** Current evidence regarding the effect of adenoidectomy on recurrent or chronic nasal symptoms or nasal obstruction alone is sparse, inconclusive and has a significant risk of bias.
- 2) **Brietzke 2008**, meta-analysis of adenoidectomy for treatment of pediatric rhinosinusitis
 - a) N=9 studies (10-121 subjects)
 - i) 6 cohort, 4 case-control
 - b) All studies showed that sinusitis symptoms or outcomes improved in half or more patients after adenoidectomy.
 - c) The summary estimate of the proportion of patients who significantly improved after adenoidectomy was 69.3% (95% CI = 56.8—81.7%, $p < 0.001$).
 - d) Conclusion: Adenoidectomy reduces caregiver reported symptoms of chronic rhinosinusitis in a majority of pediatric patients. Given its simplicity, low risk profile, and apparent effectiveness, adenoidectomy should be considered first line therapy for medically refractory, uncomplicated pediatric rhinosinusitis.

Evidence: adenoidectomy for OSA

1) **Shintani 1998**, cohort study

- a. N=13 children who underwent adenoidectomy alone (part of a larger cohort study of 134 children with OSA who underwent various surgical interventions)
 - i. Adenoidectomy was only indicated for children without tonsillar hypertrophy.
- b. Significant improvements of AHI and the lowest SaO₂ were noted 2 months after the treatments in 84.5% (11:13) of children undergoing adenotonsillectomy only and in 75.4% (86:114) of children undergoing adenotonsillectomy
- c. 2 out of the 13 adenoidectomy alone children required repeat surgery within 4-9 months for recurrent OSA compared to 0 of the adenotonsillectomy group

2) **Hensley 2011**, review of adenoidectomy for OSA

- a. N=6 studies included with adenoidectomy for OSA, including Shintani 1998
 - i. 1 cohort study of 206 children who underwent adenoidectomy for OSA. Follow up 3-5 years. Questionnaire results showed 74–87% improvement in symptoms. No PSG data.
 - ii. 1 prospective cohort with 21 children with adenoidectomy, part of larger study with various surgical interventions. Analysis performed for whole group – reduction in mean AHI 11.04→2.14.
 - iii. 3 retrospective cohort studies, looked at rate of re-operation after adenoidectomy. 0.55-29% had subsequent tonsillectomy/ revision adenoidectomy. (N=100-13,005)

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Other guidelines

- 1) **AAP practice guideline 2012** for treatment of OSA in children
 - a. Adenotonsillectomy is very effective in treating OSAS. Adenoidectomy or tonsillectomy alone may not be sufficient, because residual lymphoid tissue may contribute to persistent obstruction.

Expert Input—Adenoidectomy for OSA

Derek Lam, MD, OHSU ENT

I'll have to take some time to do a more thorough literature review so I can provide some evidence, but off the top of my head I can tell you that there are definitely patients, especially younger ones, say 12-24 months for whom adenoidectomy alone may absolutely be an appropriate procedure for OSA. Often this may be the primary source of obstruction when the tonsils are small, and there is far less morbidity related to an adenoidectomy than a T&A (less pain, less potential for bleeding, faster recovery). As such, I think it would be a mistake to removal OSA as an indication for adenoidectomy alone. Because that would effectively put ENTs like myself in the uncomfortable position of recommending a T&A in order to get surgery authorized when an adenoidectomy alone would potentially suffice in situations where patients are clearly obstructing and need to have surgery. Admittedly this is a relatively uncommon clinical scenario, but certainly not so uncommon as to warrant removing this as an indicated procedure for OSA.

Dr. Ericka King, MD, OHSU ENT

I agree with Derek that there is certainly a cohort for whom adenoidectomy alone is a reasonable surgical intervention. There is fairly limited data, but I was able to find one study that directly assessed the question: Shintani et al. Int J Pediatr Otorhinolaryngol 1998; 44:51. In this study, they selected children with an AHI of >10. Those with minimal tonsillar hypertrophy underwent adenoidectomy alone, with n=13. In this group, 84.5% demonstrated improvement on postop sleep study (defined as reduction of AHI by at least 1/2, with SpO2 nadir >85%). In the same study, kids that underwent T&A interestingly only had a 75.4% rate of improvement. This is obviously a small study and limited, but one of the few out there. The risks and recovery associated with adenoidectomy alone are much lower than a tonsillectomy, and I feel it is a very reasonable and valuable intervention in selected young children (<3 yrs) with isolated adenoid hypertrophy and history/PSG suggestive of OSA.

Expert Input—adenoidectomy for chronic sinusitis

Dr. Ericka King, MD, OHSU ENT

I disagree that the evidence supporting adenoidectomy is poor; actually it's fairly robust. The role in CRS is likely to be due to biofilm formation/ functioning of the adenoid pad as a bacterial reservoir; there is excellent evidence for this that I don't have time to summarize right now. Clinically, adenoidectomy alone has been shown to result in significant improvement in many studies, which are variably powered. Here are a few:

- Takahashi et al. Acta Otorhinolaryngol Belg 1997; 51:85. This study looked at 78 kids aged 5-7 with sinusitis and COMET; 45 underwent adenoidectomy alone, the other 33 were controls. They found an improvement in symptoms with 56% after adenoidectomy vs 24% of the control group.
- Vanderberg et al. Arch Otolaryngol Head Neck Surg 1997; 123:675. This group looked at 48 kids with CRS, and found complete or near complete symptom resolution in 58%,

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some improvement in 21%, and minimal/no improvement in 21% after adenoidectomy alone.

- Ramadan et al. Laryngoscope 2004; 114:2103. The authors studied 202 children with chronic or recurrent acute sinusitis by clinical and CT criteria that failed extensive medical management. They were randomized to endoscopic sinus surgery (ESS) + adenoidectomy, ESS alone, or adenoidectomy alone. These groups showed 87.%, 75%, and 52% improvement rates respectively, with children 6 years and under less likely to improve than older children (60% vs 84% overall).

Maximal medical management generally consists of prolonged antibiotics (3-6 weeks depending on the paper), nasal steroids and saline irrigations. This is a very difficult regimen for many young children, particularly the topical therapies. Additionally, for very good reasons we are trying to avoid CT scanning, particularly in young children. Thus, especially for young kids, I feel it is very reasonable to start with an adenoidectomy instead of a trial of medical therapy.

Summary: Evidence supports use of adenoidectomy for medically refractory chronic sinusitis in children. Based on limited evidence, adenoidectomy alone appears to be effective for treatment of OSA in children without tonsillar hypertrophy.

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Staff recommendations:

- 1) Continue coverage of adenoidectomy for chronic sinusitis in children
 - a. Clarify GN 35 to indicate when adenoidectomy is indicated as shown below
 - i. Consider whether inhaled or oral steroids are appropriate in young children
- 2) Clarify coverage for adenoidectomy for OSA in children in GN 118 as shown below

GUIDELINE NOTE 35, SINUS SURGERY

Lines 366,470

Sinus surgery ([other than adenoidectomy](#)) is indicated in the following circumstances:

- A) 4 or more episodes of acute rhinosinusitis in one year

OR

- B) Failure of medical therapy of chronic sinusitis including all of the following:
- Several courses of antibiotics AND
 - Trial of inhaled and/or oral steroids AND
 - Allergy assessment and treatment when indicated

AND

- One or more of the following:
- Findings of obstruction of active infection on CT scan
- Symptomatic mucocele
- Negative CT scan but significant disease found on nasal endoscopy

OR

- C) Nasal polyposis causing or contributing to sinusitis

OR

- D) Complications of sinusitis including subperiosteal or orbital abscess, Pott's puffy tumor, brain abscess or meningitis

OR

- E) Invasive or allergic fungal sinusitis

OR

- F) Tumor of nasal cavity or sinuses

OR

- G) CSF rhinorrhea

[Adenoidectomy \(CPT 42830, 428305\) is included on line 470 only for treatment of children with chronic sinusitis who fail appropriate medical therapy.](#)

GUIDELINE NOTE 118, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN

Line 206

Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by

5. nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR
6. nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
7. use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR

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8. consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

4. high risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
5. children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),
6. children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese.

Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present.

Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

3. undergone surgery or are not candidates for surgery, AND
4. have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use
- Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

Adenoidectomy for recurrent or chronic nasal symptoms in children (Review)

van den Aardweg MTA, Schilder AGM, Herkert E, Boonacker CWB, Rovers MM



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[Intervention Review]

Adenoidectomy for recurrent or chronic nasal symptoms in children

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ABSTRACT

Background

Adenoidectomy, surgical removal of the adenoids, is a common ENT operation worldwide in children with recurrent or chronic nasal symptoms. A systematic review on the effectiveness of adenoidectomy in this specific group has not previously been performed.

Objectives

To assess the effectiveness of adenoidectomy versus non-surgical management in children with recurrent or chronic nasal symptoms.

Search strategy

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 30 March 2009.

Selection criteria

Randomised controlled trials comparing adenoidectomy, with or without tympanostomy tubes, versus non-surgical management or tympanostomy tubes alone in children with recurrent or chronic nasal symptoms. The primary outcome studied was the number of episodes, days per episode and per year with nasal symptoms and the proportion of children with recurrent episodes of nasal symptoms. Secondary outcomes were mean number of episodes, mean number of days per episode and per year, and proportion of children with nasal obstruction alone.

Data collection and analysis

Two authors assessed trial quality and extracted data independently.

Main results

Only one study included children scheduled for adenoidectomy because of recurrent or chronic nasal symptoms or middle ear disease. In this study no beneficial effect of adenoidectomy was found. The numbers in this study were, however, small ($n = 76$) and the quality of the study was moderate. The outcome was improvement in episodes of common colds. The risk differences were non-significant, being 2% (95% CI -18% to 22%) and -11% (95% CI -28% to 7%) after 12 and 24 months, respectively.

A second study included children with recurrent acute otitis media ($n = 180$). As otitis media is known to be associated with nasal symptoms, the number of days with rhinitis was studied as a secondary outcome measure. The risk difference was non-significant, being -4 days (95% CI -13 to 7 days).

Authors' conclusions

Current evidence regarding the effect of adenoidectomy on recurrent or chronic nasal symptoms or nasal obstruction alone is sparse, inconclusive and has a significant risk of bias.

High quality trials assessing the effectiveness of adenoidectomy in children with recurrent or chronic nasal symptoms should be initiated.

PLAIN LANGUAGE SUMMARY

Adenoidectomy for recurrent of chronic nasal symptoms in children

Infections of the upper respiratory tract, presenting as recurrent nasal symptoms (nasal discharge with or without nasal obstruction) are very common in children. Removal of the adenoids (adenoidectomy) is a surgical procedure that is frequently performed in these children. It is thought that adenoidectomy prevents recurrence of nasal symptoms.

Our review, which includes two studies (256 children), shows that it is uncertain whether adenoidectomy is effective in children with recurrent or chronic nasal symptoms. Further high quality trials are needed.

BACKGROUND

Incidence

Adenoidectomy is one of the most frequently performed surgical procedures in children in Western countries. Annual adenoidectomy rates, however, differ between countries, from 127/10,000 children per year in Belgium, 101/10,000 children per year in the Netherlands and 39/10,000 children per year in England to 24/10,000 and 17/10,000 children per year in the United States and Canada, respectively ([Schilder 2004](#)).

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Indications for adenoidectomy include recurrent or chronic nasal discharge, recurrent episodes of acute otitis media (AOM), persistent otitis media with effusion (OME) and symptoms of upper airway obstruction. In most cases children are operated on for a combination of nasal and middle ear symptoms. The operation

involves removing the adenoids - a nasopharyngeal reservoir of potential respiratory pathogens and a potential cause of obstruction of the nasal airway. As such, nasal breathing is thought to improve and recurrence of nasal discharge is thought to decrease.

Evidence for adenoidectomy

At present the effectiveness of adenoidectomy in children with recurrent or chronic nasal symptoms remains uncertain and practice is experience-based rather than evidence-based. Some surgeons prefer to perform adenoidectomy in these children, whereas others do not. In previous systematic reviews for *The Cochrane Library* the effectiveness of 1) grommets (ventilation tubes) for recurrent acute otitis media in children ([McDonald 2008](#)), 2) grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children ([Lous 2005](#)) and 3) tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis ([Burton 2009](#)) have all been assessed. For adenoidectomy in children with nasal symptoms no such review



Adenoidectomy outcomes in pediatric rhinosinusitis: A meta-analysis^{☆,☆☆}

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KEYWORDS

Adenoidectomy;
Pediatric rhinosinusitis;
Otolaryngology;
Evidence-based
medicine

Summary

Objective: To evaluate the currently available literature regarding the reported effectiveness of adenoidectomy alone in the management of medically refractory pediatric chronic rhinosinusitis.

Methods: The MEDLINE and EMBASE databases were systematically searched for English language manuscripts reporting on effectiveness of adenoidectomy alone in management of medically refractory pediatric rhinosinusitis. Additional manuscripts were identified by manual searching. Random effects modeling was performed to produce summary estimates of adenoidectomy effectiveness.

Results: Nine studies met the inclusion criteria. Six were cohort studies (level 2b) and four were case series (level 4). Mean sample size was 46 subjects (range = 10–121) with grand mean age of 5.8 years (range 4.4–6.9 years). All studies showed that sinusitis symptoms or outcomes improved in half or more patients after adenoidectomy. Eight studies were sufficiently similar to undergo meta-analysis. The summary estimate of the proportion of patients who significantly improved after adenoidectomy was 69.3% (95% CI = 56.8–81.7%, $p < 0.001$). The possibility of author bias was explored as one author group contributed a large proportion of patients to the study group.

Conclusion: Adenoidectomy reduces caregiver reported symptoms of chronic rhinosinusitis in a majority of pediatric patients. Given its simplicity, low risk profile, and apparent effectiveness, adenoidectomy should be considered first line therapy for medically refractory, uncomplicated pediatric rhinosinusitis.

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The effect of adenotonsillectomy in children with OSA

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Abstract

Adenotonsillar hypertrophy and abnormal facial morphology are thought to be important for the occurrence of obstructive sleep apnea syndrome (OSA). We evaluated the effects of adenoidectomy and/or tonsillectomy and the relationship between the treatment results and facial morphology in 134 children with OSA. Significant improvements in apnea-hypopnea index (AHI) and lowest blood oxygen saturation (SaO_2) were noted and 78.5% of the patients improved after adenoidectomy and/or tonsillectomy. Additional operations were needed in two out of 13 cases of the adenoidectomy group and two out of four cases of the adeno-monotonsillectomy group. In the adenotonsillectomy group, the unimproved children tended to have smaller tonsils, narrower epipharyngeal airspace, and more poorly-developed maxillary and mandibular protrusion than the improved children. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Obstructive sleep apnea; Adenoidectomy; Tonsillectomy; Cephalometric analysis

1. Introduction

Obstructive sleep apnea (OSA) has been recognized as an important entity in children [3]. The symptoms of OSA are snoring, apnea, and open mouth [5]. Continuity of upper airway obstruction may lead to abnormal facial morphology [13], chest deformation [7] and growth retardation [5,11,15]. In severe cases, arrhythmia, right-sided heart failure, and cor pulmonale (pulmonary hy-

pertension) may also be noted [1,8,9,11,16], and in some cases, they can cause death. Adenotonsillar hypertrophy is the most common cause of obstructive sleep apnea in children [9,16]. In children with OSA, adenoidectomy and/or tonsillectomy are often the initial treatment [2]. The symptoms of OSA such as snoring, apnea, mouth breathing and poor school performance have been shown by several studies to be improved following adenotonsillectomy [9,17]. However, not every child with large tonsils and adenoids has symptoms of OSA. In our previous study [14], it was suspected that the abnormal facial morphology in OSA

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JOURNAL CLUB

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How effective is adenoidectomy alone for treatment of obstructive sleep apnoea in a child who presents with adenoid hypertrophy?

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Clinical Scenario

A girl aged 20 months presents with parental concern about loud snoring and increased work of breathing when sleeping. On examination, she has adenoid facies (a long, narrow face with mouth open¹ and small Grade 1/4 tonsils (using the Brodsky Grading System)).² A lateral neck X-ray shows enlarged adenoids obstructing the nasal airway. The child has a history of two ear infections, both of which occurred in the 12 months prior to presentation, and both are resolved after a single course of oral antibiotics. There is no family or personal history of atopy, and skin prick testing was negative for common allergens. Nasal steroid spray had been previously prescribed, but after her parents found this, which led to little improvement, they stopped the treatment. An overnight sleep study showed mild obstructive sleep apnoea (OSA) with an index of obstructive/mixed respiratory events of 9.2 events/h, a minimum oxygen saturation of 87% and no carbon dioxide retention.

Our ear, nose and throat (ENT) surgeon reviewed the 20-month girl and suggested that the most appropriate surgery would be adenoidectomy without tonsillectomy.

Structured clinical question

'In children with OSA and adenoid hypertrophy without tonsil hypertrophy (P) does adenoidectomy alone (I) comparing sleep studies (polysomnography (PSG)) before and after surgery (C) provide acute relief of OSA (O)'.

Search Strategy

The OVID database was searched from the years 1950 to the present. The Medical Subject Headings' terms 'adenoidectomy' and 'pediatric' and 'airway obstruction/or sleep disorders/or sleep apnea, obstructive/or sleep apnea syndromes/or sleep/or polysomnography' were combined. Key journals (such as *SLEEP*) and conference proceedings (Australasian Sleep Association 2006–2008) were hand searched, and pertinent grey data were included in the search. The search was conducted in this manner recommended by evidence-based practice guidelines.

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The search resulted in 226 articles, which were reviewed by title and/or abstract, to ascertain if the study investigated adenoidectomy alone, as a separate procedure to adenotonsillectomy, as the primary intervention. Only publications in English were reviewed. A final 38 papers addressed adenoidectomy as a separate procedure; 25 were relevant to the clinical question, and of these, the seven studies that included evaluation of adenoidectomy alone were most appropriate and are tabulated later. This technique facilitated a rigorous, unbiased review of the literature (Table 1). The last three studies in the table examined longer-term requirements for additional surgery after adenoidectomy.^{10–12}

What is the best paper to answer my question?

The study by Shintani et al. in 1998⁸ was chosen because it included the most comprehensive analysis of obstructive apnoea in a group of patients with studies undertaken before and after adenoidectomy. The study included 134 ENT surgery candidates, aged 1–9 years of age, and provided specific data about 13 children who had adenoidectomy alone. Although the primary outcome variables were cephalometrics to measure facial dimensions, the study evaluated the short-term outcome of adenoidectomy on OSA with 2 months follow-up after the procedure. The severity of the sleep apnoea was quantified for children undergoing adenoidectomy alone using a modified PSG that included respiratory inductive plethysmography (trace of chest wall movement with respiratory efforts) and SaO₂, performed pre-operatively and then 2 months post-operatively. Children who underwent adenoidectomy alone showed significant reduction in apnoea hypopnoea index (AHI) and in SaO₂ nadir. The study found significant ($P < 0.005$) improvement in AHI and SaO₂ after adenoidectomy alone. The rate of improvement in AHI and lowest SaO₂ was higher for children who underwent adenoidectomy (84.5%) than for those who underwent adenotonsillectomy (75.4%). Facial morphology was not analysed in the children who underwent adenoidectomy alone. ENT surgery was required for two adenoidectomy patients, who were both 2 years of age.

Using the Critical Appraisal Toolkit for Cohort Studies,¹³ we found that the study asked a clearly focused question that was applicable to the children undergoing adenoidectomy alone, as a subgroup. A cohort study is a good way of answering the question. Only children with a pre-operative PSG result demonstrating an AHI > 10/h were recruited into the OSA arm of the study. Exclusion criteria included developmental delay,

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Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome

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CLINICAL PRACTICE GUIDELINE

Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome

abstract

FREE

OBJECTIVES: This revised clinical practice guideline, intended for use by primary care clinicians, provides recommendations for the diagnosis and management of the obstructive sleep apnea syndrome (OSAS) in children and adolescents. This practice guideline focuses on uncomplicated childhood OSAS, that is, OSAS associated with adenotonsillar hypertrophy and/or obesity in an otherwise healthy child who is being treated in the primary care setting.

METHODS: Of 3166 articles from 1999–2010, 350 provided relevant data. Most articles were level II–IV. The resulting evidence report was used to formulate recommendations.

RESULTS AND CONCLUSIONS: The following recommendations are made. (1) All children/adolescents should be screened for snoring. (2) Polysomnography should be performed in children/adolescents with snoring and symptoms/signs of OSAS; if polysomnography is not available, then alternative diagnostic tests or referral to a specialist for more extensive evaluation may be considered. (3) Adenotonsillectomy is recommended as the first-line treatment of patients with adenotonsillar hypertrophy. (4) High-risk patients should be monitored as inpatients postoperatively. (5) Patients should be reevaluated postoperatively to determine whether further treatment is required. Objective testing should be performed in patients who are high risk or have persistent symptoms/signs of OSAS after therapy. (6) Continuous positive airway pressure is recommended as treatment if adenotonsillectomy is not performed or if OSAS persists postoperatively. (7) Weight loss is recommended in addition to other therapy in patients who are overweight or obese. (8) Intranasal corticosteroids are an option for children with mild OSAS in whom adenotonsillectomy is contraindicated or for mild postoperative OSAS. *Pediatrics* 2012;130:576–584

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common condition in childhood and can result in severe complications if left untreated. In 2002, the American Academy of Pediatrics (AAP) published a practice guideline for the diagnosis and management of childhood OSAS.¹ Since that time, there has been a considerable increase in publications and research on the topic; thus, the guidelines have been revised.

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KEY WORDS

snoring, sleep-disordered breathing, adenotonsillectomy, continuous positive airway pressure

ABBREVIATIONS

AAP—American Academy of Pediatrics

AHI—apnea hypopnea index

CPAP—continuous positive airway pressure

OSAS—obstructive sleep apnea syndrome

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The recommendations in this report do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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The purposes of this revised clinical practice guideline are to (1) increase the recognition of OSAS by primary care clinicians to minimize delay in diagnosis and avoid serious sequelae of OSAS; (2) evaluate diagnostic techniques; (3) describe treatment options; (4) provide guidelines for follow-up; and (5) discuss areas requiring further research. The recommendations in this statement do not indicate an exclusive course of treatment. Variations, taking into account individual circumstances, may be appropriate.

This practice guideline focuses on uncomplicated childhood OSAS—that is, the OSAS associated with adenotonsillar hypertrophy and/or obesity in an otherwise healthy child who is being treated in the primary care setting. This guideline specifically excludes infants younger than 1 year of age, patients with central apnea or hypoventilation syndromes, and patients with OSAS associated with other medical disorders, including but not limited to Down syndrome, craniofacial anomalies, neuromuscular disease (including cerebral palsy), chronic lung disease, sickle cell disease, metabolic disease, or laryngomalacia. These important patient populations are too complex to discuss within the scope of this article and require consultation with a pediatric subspecialist.

Additional information providing justification for the key action statements and a detailed review of the literature are provided in the accompanying technical report available online.²

METHODS OF GUIDELINE DEVELOPMENT

Details of the methods of guideline development are included in the accompanying technical report.² The AAP selected a subcommittee composed of pediatricians and other experts in the fields of sleep medicine, pulmonology, and otolaryngology, as well as experts

from epidemiology and pediatric practice to develop an evidence base of literature on this topic. The committee included liaison members from the AAP Section on Otolaryngology-Head and Neck Surgery, American Thoracic Society, American Academy of Sleep Medicine, American College of Chest Physicians, and the National Sleep Foundation. Committee members signed forms disclosing conflicts of interest.

An automated search of the literature on childhood OSAS from 1999 to 2008 was performed by using 5 scientific literature search engines.² The medical subject heading terms that were used in all fields were snoring, apnea, sleep-disordered breathing, sleep-related breathing disorders, upper airway resistance, polysomnography, sleep study, adenoidectomy, tonsillectomy, continuous positive airway pressure, obesity, adiposity, hypopnea, hypoventilation, cognition, behavior, and neuropsychology. Reviews, case reports, letters to the editor, and abstracts were not included. Non-English-language articles, animal studies, and studies relating to infants younger than 1 year and to special populations (eg, children with craniofacial anomalies or sickle cell disease) were excluded. In several steps, a total of 3166 hits was reduced to 350 articles, which underwent detailed review.² Committee members selectively updated this literature search for articles published from 2008 to 2011 specific to guideline categories. Details of the literature grading system are available in the accompanying technical report.

Since publication of the previous guidelines, there has been an improvement in the quality of OSAS studies in the literature; however, there remain few randomized, blinded, controlled studies. Most studies were questionnaire or polysomnography based. Many studies used standard definitions for pediatric polysomnography scoring, but

the interpretation of polysomnography (eg, the apnea hypopnea index [AHI] criterion used for diagnosis or to determine treatment) varied widely. The guideline notes the quality of evidence for each key action statement. Additional details are available in the technical report.

The evidence-based approach to guideline development requires that the evidence in support of each key action statement be identified, appraised, and summarized and that an explicit link between evidence and recommendations be defined. Evidence-based recommendations reflect the quality of evidence and the balance of benefit and harm that is anticipated when the recommendation is followed. The AAP policy statement, “Classifying Recommendations for Clinical Practice Guidelines,”³ was followed in designating levels of recommendation (see Fig 1 and Table 1).

DEFINITION

This guideline defines OSAS in children as a “disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns,”⁴ accompanied by symptoms or signs, as listed in Table 2. Prevalence rates based on level I and II studies range from 1.2% to 5.7%.^{5–7} Symptoms include habitual snoring (often with intermittent pauses, snorts, or gasps), disturbed sleep, and daytime neurobehavioral problems. Daytime sleepiness may occur, but is uncommon in young children. OSAS is associated with neurocognitive impairment, behavioral problems, failure to thrive, hypertension, cardiac dysfunction, and systemic inflammation. Risk factors include adenotonsillar hypertrophy, obesity, craniofacial anomalies, and neuromuscular disorders. Only the first 2 risk factors are

Evidence Quality	Preponderance of Benefit or Harm	Balance of Benefit and Harm
A. Well designed RCTs or diagnostic studies on relevant population	Strong Recommendation	Option
B. RCTs or diagnostic studies with minor limitations;overwhelmingly consistent evidence from observational studies	Recommendation	
C. Observational studies (case-control and cohort design)	Option	
D. Expert opinion, case reports, reasoning from first principles	Option	No Rec
X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm	Strong Recommendation	
	Recommendation	

FIGURE 1

Evidence quality. Integrating evidence quality appraisal with an assessment of the anticipated balance between benefits and harms if a policy is carried out leads to designation of a policy as a strong recommendation, recommendation, option, or no recommendation. RCT, randomized controlled trial; Rec, recommendation.

discussed in this guideline. In this guideline, obesity is defined as a BMI >95th percentile for age and gender.⁸

KEY ACTION STATEMENTS

Key Action Statement 1: Screening for OSAS

As part of routine health maintenance visits, clinicians should inquire whether the child or adolescent snores. If the answer is affirmative or if a child or adolescent presents with signs or symptoms of OSAS (Table 2), clinicians should perform

a more focused evaluation. (Evidence Quality: Grade B, Recommendation Strength: Recommendation.)

Evidence Profile KAS 1

- Aggregate evidence quality: B
- Benefit: Early identification of OSAS is desirable, because it is a high-prevalence condition, and identification and treatment can result in alleviation of current symptoms, improved quality of life, prevention of sequelae, education of parents, and decreased health care utilization.

- Harm: Provider time, patient and parent time.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: Panelists believe that identification of a serious medical condition outweighs the time expenditure necessary for screening.
- Role of patient preferences: None.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Recommendation.

Almost all children with OSAS snore,^{9–11} although caregivers frequently do not volunteer this information at medical visits.¹² Thus, asking about snoring at each health maintenance visit (as well as at other appropriate times, such as when evaluating for tonsillitis) is a sensitive, albeit nonspecific, screening measure that is quick and easy to perform. Snoring is common in children and adolescents; however, OSAS is less common. Therefore, an affirmative answer should be followed by a detailed history and examination to determine whether further evaluation for OSAS is needed (Table 2); this clinical evaluation alone

TABLE 1 Definitions and Recommendation Implications

Statement	Definition	Implication
Strong recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.	It would be prudent for clinicians to follow a recommendation, but they should remain alert to new information and sensitive to patient preferences.
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to one approach over another.	Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.
No recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.	Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

TABLE 2 Symptoms and Signs of OSAS

History
Frequent snoring (≥ 3 nights/wk)
Labored breathing during sleep
Gasps/snorting noises/observed episodes of apnea
Sleep enuresis (especially secondary enuresis) ^a
Sleeping in a seated position or with the neck hyperextended
Cyanosis
Headaches on awakening
Daytime sleepiness
Attention-deficit/hyperactivity disorder
Learning problems
Physical examination
Underweight or overweight
Tonsillar hypertrophy
Adenoidal facies
Micrognathia/retrognathia
High-arched palate
Failure to thrive
Hypertension

^a Enuresis after at least 6 mo of continence.

does not establish the diagnosis (see technical report). Occasional snoring, for example, with an upper respiratory tract infection, is less of a concern than snoring that occurs at least 3 times a week and is associated with any of the symptoms or signs listed in Table 2.

Key Action Statement 2A: Polysomnography

If a child or adolescent snores on a regular basis and has any of the complaints or findings shown in Table 2, clinicians should either (1) obtain a polysomnogram (Evidence Quality A, Key Action strength: Recommendation) OR (2) refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation (Evidence quality D, Key Action strength: Option). (Evidence Quality: Grade A for polysomnography; Grade D for specialist referral, Recommendation Strength: Recommendation.)

Evidence Profile KAS 2A: Polysomnography

- Aggregate evidence quality: A
- Benefits: Establish diagnosis and determine severity of OSAS.

- Harm: Expense, time, anxiety/discomfort.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: Panelists weighed the value of establishing a diagnosis as more important than the minor potential harms listed.
- Role of patient preferences: Small because of preponderance of evidence that polysomnography is the most accurate way to make a diagnosis.
- Exclusions: See Key Action Statement 2B regarding lack of availability.
- Intentional vagueness: None.
- Strength: Recommendation.

Evidence Profile KAS 2A: Referral

- Aggregate evidence quality: D
- Benefits: Subspecialist may be better able to establish diagnosis and determine severity of OSAS.
- Harm: Expense, time, anxiety/discomfort.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: Panelists weighed the value of establishing a diagnosis as more important than the minor potential harms listed.
- Role of patient preferences: Large.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Option.

Although history and physical examination are useful to screen patients and determine which patients need further investigation for OSAS, the sensitivity and specificity of the history and physical examination are poor (see accompanying technical report). Physical examination when the child is awake may be normal, and the size of the tonsils cannot be used to predict the presence of OSAS in an individual child. Thus, objective testing is required. The gold standard test

is overnight, attended, in-laboratory polysomnography (sleep study). This is a noninvasive test involving the measurement of a number of physiologic functions overnight, typically including EEG; pulse oximetry; oronasal airflow, abdominal and chest wall movements, partial pressure of carbon dioxide (P_{CO_2}); and video recording.¹³ Specific pediatric measuring and scoring criteria should be used.¹³ Polysomnography will demonstrate the presence or absence of OSAS. Polysomnography also demonstrates the severity of OSAS, which is helpful in planning treatment and in postoperative short- and long-term management.

Key Action Statement 2B: Alternative Testing

If polysomnography is not available, then clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography. (Evidence Quality: Grade C, Recommendation Strength: Option.)

Evidence Profile KAS 2B

- Aggregate evidence quality: C
- Benefit: Varying positive and negative predictive values for establishing diagnosis.
- Harm: False-negative and false-positive results may underestimate or overestimate severity, expense, time, anxiety/discomfort.
- Benefits-harms assessment: Equilibrium of benefits and harms.
- Value judgments: Opinion of the panel that some objective testing is better than none. Pragmatic decision based on current shortage of pediatric polysomnography facilities (this may change over time).
- Role of patient preferences: Small, if choices are limited by availability;

families may choose to travel to centers where more extensive facilities are available.

- Exclusions: None.
- Intentional vagueness: None.
- Strength: Option.

Although polysomnography is the gold standard for diagnosis of OSAS, there is a shortage of sleep laboratories with pediatric expertise. Hence, polysomnography may not be readily available in certain regions of the country. Alternative diagnostic tests have been shown to have weaker positive and negative predictive values than polysomnography, but nevertheless, objective testing is preferable to clinical evaluation alone. If an alternative test fails to demonstrate OSAS in a patient with a high pretest probability, full polysomnography should be sought.

Key Action Statement 3: Adenotonsillectomy

If a child is determined to have OSAS, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery (see Table 3), the clinician should recommend adenotonsillectomy as the first line of treatment. If the child has OSAS but does not have adenotonsillar hypertrophy, other treatment should be considered (see Key Action Statement 6). Clinical judgment is required to determine the benefits of adenotonsillectomy compared with other treatments in obese children with varying degrees of adenotonsillar hypertrophy. (Evidence Quality: Grade B, Recommendation Strength: Recommendation.)

Evidence Profile KAS 3

- Aggregate evidence quality: B
- Benefit: Improve OSAS and accompanying symptoms and sequelae.

- Harm: Pain, anxiety, dehydration, anesthetic complications, hemorrhage, infection, postoperative respiratory difficulties, velopharyngeal incompetence, nasopharyngeal stenosis, death.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: The panel sees the benefits of treating OSAS as more beneficial than the low risk of serious consequences.
- Role of patient preferences: Low; continuous positive airway pressure (CPAP) is an option but involves prolonged, long-term treatment as compared with a single, relatively low-risk surgical procedure.
- Exclusions: See Table 3.
- Intentional vagueness: None.
- Strength: Recommendation.

Adenotonsillectomy is very effective in treating OSAS. Adenoidectomy or tonsillectomy alone may not be sufficient, because residual lymphoid tissue may contribute to persistent obstruction. In otherwise healthy children with adenotonsillar hypertrophy, adenotonsillectomy is associated with improvements in symptoms and sequelae of OSAS. Postoperative polysomnography typically shows a major decrease in the number of obstructive events, although some obstructions may still be present. Although obese children may have less satisfactory results, many will be adequately treated with

TABLE 3 Contraindications for Adenotonsillectomy

Absolute contraindications
No adenotonsillar tissue (tissue has been surgically removed)
Relative contraindications
Very small tonsils/adenoid
Morbid obesity and small tonsils/adenoid
Bleeding disorder refractory to treatment
Submucous cleft palate
Other medical conditions making patient medically unstable for surgery

adenotonsillectomy; however, further research is needed to determine which obese children are most likely to benefit from surgery. In this population, the benefits of a 1-time surgical procedure, with a small but real risk of complications, need to be weighed against long-term treatment with CPAP, which is associated with discomfort, disruption of family lifestyle, and risks of poor adherence. Potential complications of adenotonsillectomy are shown in Table 4. Although serious complications (including death) may occur, the rate of these complications is low, and the risks of complications need to be weighed against the consequences of untreated OSAS. In general, a 1-time only procedure with a relatively low morbidity is preferable to lifelong treatment with CPAP; furthermore, the efficacy of CPAP is limited by generally suboptimal adherence. Other treatment options, such as anti-inflammatory medications, weight loss, or tracheostomy, are less effective, are difficult to achieve, or have higher morbidity, respectively.

Key Action Statement 4: High-Risk Patients Undergoing Adenotonsillectomy

Clinicians should monitor high-risk patients (Table 5) undergoing adenotonsillectomy as inpatients postoperatively. (Evidence Quality: Grade B, Recommendation Strength: Recommendation.)

TABLE 4 Risks of Adenotonsillectomy

Minor
Pain
Dehydration attributable to postoperative nausea/vomiting and poor oral intake
Major
Anesthetic complications
Acute upper airway obstruction during induction or emergence from anesthesia
Postoperative respiratory compromise
Hemorrhage
Velopharyngeal incompetence
Nasopharyngeal stenosis
Death

TABLE 5 Risk Factors for Postoperative Respiratory Complications in Children With OSAS Undergoing Adenotonsillectomy

Younger than 3 y of age
Severe OSAS on polysomnography ^a
Cardiac complications of OSAS
Failure to thrive
Obesity
Craniofacial anomalies ^b
Neuromuscular disorders ^b
Current respiratory infection

^a It is difficult to provide exact polysomnographic criteria for severity, because these criteria will vary depending on the age of the child; additional comorbidities, such as obesity, asthma, or cardiac complications of OSAS; and other polysomnographic criteria that have not been evaluated in the literature, such as the level of hypercapnia and the frequency of desaturation (as compared with lowest oxygen saturation). Nevertheless, on the basis of published studies (primarily Level III, see Technical Report), it is recommended that all patients with a lowest oxygen saturation <80% (either on preoperative polysomnography or during observation in the recovery room postoperatively) or an AHI ≥ 24 /h be observed as inpatients postoperatively as they are at increased risk for postoperative respiratory compromise. Additionally, on the basis of expert consensus, it is recommended that patients with significant hypercapnia on polysomnography (peak $P_{CO_2} \geq 60$ mm Hg) be admitted postoperatively. The committee noted that that most published studies were retrospective and not comprehensive, and therefore these recommendations may change if higher-level studies are published. Clinicians may decide to admit patients with less severe polysomnographic abnormalities based on a constellation of risk factors (age, comorbidities, and additional polysomnographic factors) for a particular individual.

^b Not discussed in these guidelines.

Evidence Profile KAS 4

- Aggregate evidence quality: B
- Benefit: Effectively manage severe respiratory compromise and avoid death.
- Harm: Expense, time, anxiety.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: The panel believes that early recognition of any serious adverse events is critically important.
- Role of patient preferences: Minimal; this is an important safety issue.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Recommendation.

Patients with OSAS may develop respiratory complications, such as worsening

of OSAS or pulmonary edema, in the immediate postoperative period. Death attributable to respiratory complications in the immediate postoperative period has been reported in patients with severe OSAS. Identified risk factors are shown in Table 5. High-risk patients should undergo surgery in a center capable of treating complex pediatric patients. They should be hospitalized overnight for close monitoring postoperatively. Children with an acute respiratory infection on the day of surgery, as documented by fever, cough, and/or wheezing, are at increased risk of postoperative complications and, therefore, should be rescheduled or monitored closely postoperatively. Clinicians should decide on an individual basis whether these patients should be rescheduled, taking into consideration the severity of OSAS in the particular patient and keeping in mind that many children with adenotonsillar hypertrophy have chronic rhinorrhea and nasal congestion, even in the absence of viral infections.

Key Action Statement 5: Reevaluation

Clinicians should clinically reassess all patients with OSAS for persisting signs and symptoms after therapy to determine whether further treatment is required. (Evidence Quality: Grade B, Recommendation Strength: Recommendation.)

Evidence Profile KAS 5A

- Aggregate evidence quality: B
- Benefit: Determine effects of treatment.
- Harm: Expense, time.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: Data show that a significant proportion of children continue to have abnormalities postoperatively; therefore, the panel deter-

mined that the benefits of follow-up outweigh the minor inconveniences.

- Role of patient preferences: Minimal; follow-up is good clinical practice.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Recommendation.

Clinicians should reassess OSAS-related symptoms and signs (Table 2) after 6 to 8 weeks of therapy to determine whether further evaluation and treatment are indicated. Objective data regarding the timing of the postoperative evaluation are not available. Most clinicians recommend reevaluation 6 to 8 weeks after treatment to allow for healing of the operative site and to allow time for upper airway, cardiac, and central nervous system recovery. Patients who remain symptomatic should undergo objective testing (see Key Action Statement 2) or be referred to a sleep specialist for further evaluation.

Key Action Statement 5B: Reevaluation of High-Risk Patients

Clinicians should reevaluate high-risk patients for persistent OSAS after adenotonsillectomy, including those who had a significantly abnormal baseline polysomnogram, have sequelae of OSAS, are obese, or remain symptomatic after treatment, with an objective test (see Key Action Statement 2) or refer such patients to a sleep specialist. (Evidence Quality: Grade B, Recommendation Strength: Recommendation.)

Evidence Profile KAS 5B

- Aggregate evidence quality: B
- Benefit: Determine effects of treatment.
- Harm: Expense, time, anxiety/discomfort.
- Benefits-harms assessment: Preponderance of benefit over harm.

- Value judgments: Given the panel's concerns about the consequences of OSAS and the frequency of postoperative persistence in high-risk groups, the panel believes that the follow-up costs are outweighed by benefits of recognition of persistent OSAS. A minority of panelists believed that all children with OSAS should have follow-up polysomnography because of the high prevalence of persistent postoperative abnormalities on polysomnography, but most panelists believed that persistent polysomnographic abnormalities in uncomplicated children with mild OSAS were usually mild in patients who were asymptomatic after surgery.
- Role of patient preferences: Minimal. Further evaluation is needed to determine the need for further treatment.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Recommendation.

Numerous studies have shown that a large proportion of children at high risk continue to have some degree of OSAS postoperatively^{10,13,14}; thus, objective evidence is required to determine whether further treatment is necessary.

Key Action Statement 6: CPAP

Clinicians should refer patients for CPAP management if symptoms/signs (Table 2) or objective evidence of OSAS persists after adenotonsillectomy or if adenotonsillectomy is not performed. (Evidence Quality: Grade B, Recommendation Strength: Recommendation.)

Evidence Profile KAS 6

- Aggregate evidence quality: B
- Benefit: Improve OSAS and accompanying symptoms and sequelae.

- Harm: Expense, time, anxiety; parental sleep disruption; nasal and skin adverse effects; possible midface remodeling; extremely rare serious pressure-related complications, such as pneumothorax; poor adherence.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: Panelists believe that CPAP is the most effective treatment of OSAS that persists postoperatively and that the benefits of treatment outweigh the adverse effects. Other treatments (eg, rapid maxillary expansion) may be effective in specially selected patients.
- Role of patient preferences: Other treatments may be effective in specially selected patients.
- Exclusions: Rare patients at increased risk of severe pressure complications.
- Intentional vagueness: None.
- Policy level: Recommendation.

CPAP therapy is delivered by using an electronic device that delivers air at positive pressure via a nasal mask, leading to mechanical stenting of the airway and improved functional residual capacity in the lungs. There is no clear advantage of using bilevel pressure over CPAP.¹⁵ CPAP should be managed by an experienced and skilled clinician with expertise in its use in children. CPAP pressure requirements vary among individuals and change over time; thus, CPAP must be titrated in the sleep laboratory before prescribing the device and periodically readjusted thereafter. Behavioral modification therapy may be required, especially for young children or those with developmental delays. Objective monitoring of adherence, by using the equipment software, is important. If adherence is suboptimal, the clinician should institute measures to improve adherence (such as behavioral modification, or treating side effects of

CPAP) and institute alternative treatments if these measures are ineffective.

Key Action Statement 7: Weight Loss

Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSAS is overweight or obese. (Evidence Quality: Grade C, Recommendation Strength: Recommendation.)

Evidence Profile KAS 7

- Aggregate evidence quality: C
- Benefit: Improve OSAS and accompanying symptoms and sequelae; non-OSAS-related benefits of weight loss.
- Harm: Hard to achieve and maintain weight loss.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: The panel agreed that weight loss is beneficial for both OSAS and other health issues, but clinical experience suggests that weight loss is difficult to achieve and maintain, and even effective weight loss regimens take time; therefore, additional treatment is required in the interim.
- Role of patient preferences: Strong role for patient and family preference regarding nutrition and exercise.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Recommendation.

Weight loss has been shown to improve OSAS,^{16,17} although the degree of weight loss required has not been determined. Because weight loss is a slow and unreliable process, other treatment modalities (such as adenotonsillectomy or CPAP therapy) should be instituted until sufficient weight loss has been achieved and maintained.

Key Action Statement 8: Intranasal Corticosteroids

Clinicians may prescribe topical intranasal corticosteroids for children with mild OSAS in whom adenotonsillectomy is contraindicated or for children with mild post-operative OSAS. (Evidence Quality: Grade B, Recommendation Strength: Option.)

Evidence Profile KAS 8

- Aggregate evidence quality: B
- Benefit: Improves mild OSAS and accompanying symptoms and sequelae.
- Harm: Some subjects may not have an adequate response. It is not known whether therapeutic effect persists long-term; therefore, long-term observation is required. Low risk of steroid-related adverse effects.
- Benefits-harms assessment: Preponderance of benefit over harm.
- Value judgments: The panel agreed that intranasal steroids provide a less invasive treatment than surgery or CPAP and, therefore, may be preferred in some cases despite lower efficacy and lack of data on long-term efficacy.
- Role of patient preferences: Moderate role for patient and family preference if OSAS is mild.
- Exclusions: None.
- Intentional vagueness: None.
- Strength: Option.

Mild OSAS is defined, for this indication, as an AHI <5 per hour, on the basis of studies on intranasal corticosteroids described in the accompanying technical report.² Several studies have shown that the use of intranasal steroids decreases the degree of OSAS; however, although

OSAS improves, residual OSAS may remain. Furthermore, there is individual variability in response to treatment, and long-term studies have not been performed to determine the duration of improvement. Therefore, nasal steroids are not recommended as a first-line therapy. The response to treatment should be measured objectively after a course of treatment of approximately 6 weeks. Because the long-term effect of this treatment is unknown, the clinician should continue to observe the patient for symptoms of recurrence and adverse effects of corticosteroids.

AREAS FOR FUTURE RESEARCH

A detailed list of research recommendations is provided in the accompanying technical report.² There is a great need for further research into the prevalence of OSAS, sequelae of OSAS, best treatment methods, and the role of obesity. In particular, well-controlled, blinded studies, including randomized controlled trials of treatment, are needed to determine the best care for children and adolescents with OSAS.

SUBCOMMITTEE ON OBSTRUCTIVE SLEEP APNEA SYNDROME*

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Oversight from the Steering Committee on Quality Improvement and Management, 2009–2012

STAFF

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REFERENCES

1. Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. American Academy of Pediatrics. Clinical

practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2002;109(4):704–712

2. Marcus CL, Brooks LJ, Davidson C, et al; American Academy of Pediatrics, Subcommittee on Obstructive Sleep Apnea

- Syndrome. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012; 130(3):In press
3. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114(3):874–877
 4. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med*. 1996;153(2):866–878
 5. Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep*. 2009;32(6):731–736
 6. Li AM, So HK, Au CT, et al. Epidemiology of obstructive sleep apnoea syndrome in Chinese children: a two-phase community study. *Thorax*. 2010;65(11):991–997
 7. O'Brien LM, Holbrook CR, Mervis CB, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics*. 2003; 111(3):554–563
 8. Himes JH, Dietz WH; The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. *Am J Clin Nutr*. 1994;59(2):307–316
 9. Mitchell RB. Adenotonsillectomy for obstructive sleep apnea in children: outcome evaluated by pre- and postoperative polysomnography. *Laryngoscope*. 2007;117(10):1844–1854
 10. Suen JS, Arnold JE, Brooks LJ. Adenotonsillectomy for treatment of obstructive sleep apnea in children. *Arch Otolaryngol Head Neck Surg*. 1995;121(5):525–530
 11. Nieminen P, Tolonen U, Löppönen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg*. 2000;126(4):481–486
 12. Blunden S, Lushington K, Lorenzen B, Wong J, Balendran R, Kennedy D. Symptoms of sleep breathing disorders in children are underreported by parents at general practice visits. *Sleep Breath*. 2003;7(4):167–176
 13. Apostolidou MT, Alexopoulos EI, Chaidas K, et al. Obesity and persisting sleep apnea after adenotonsillectomy in Greek children. *Chest*. 2008;134(6):1149–1155
 14. Mitchell RB, Kelly J. Outcome of adenotonsillectomy for severe obstructive sleep apnea in children. *Int J Pediatr Otorhinolaryngol*. 2004;68(11):1375–1379
 15. Marcus CL, Rosen G, Ward SL, et al. Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics*. 2006; 117(3). Available at: www.pediatrics.org/cgi/content/full/117/3/e442
 16. Verhulst SL, Franckx H, Van Gaal L, De Backer W, Desager K. The effect of weight loss on sleep-disordered breathing in obese teenagers. *Obesity (Silver Spring)*. 2009;17(6):1178–1183
 17. Kalra M, Inge T. Effect of bariatric surgery on obstructive sleep apnoea in adolescents. *Paediatr Respir Rev*. 2006;7(4):260–267

Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome

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RSV prophylaxis (palivizumab) Guideline Note 19 Revision

Question: Should the guideline on Respiratory Syncytial Virus prophylaxis be revised?

Question source: Pharmacy and Therapeutics; FamilyCare CCO

Issue: It was brought to HERC's attention that there is updated July 2014 guidance on the use of Palivizumab (Synagis) which is inconsistent with (and significantly more restrictive than) the current Prioritized List guideline. The Pharmacy & Therapeutics committee is reviewing this and planning to update the Prior Authorization criteria in September 2014 prior to the upcoming RSV season.

Prioritized List Status

GUIDELINE NOTE 69, SYNAGIS

Line 3

CPT code 90378, Synagis (palivizumab), is covered for infants meeting one of the criteria given below (A-E), according to the treatment guidelines for each criterion:

- A) Infants younger than 24 months who have congenital heart disease (CHD) or chronic lung disease of prematurity (CLD, formerly called bronchopulmonary dysplasia) AND require medical therapy
 - 1) Therapy is initiated within 6 months before the start of the RSV season
 - 2) Maximum 5 doses
- B) Infants younger than 12 months with congenital abnormalities of the airway or neuromuscular disease
 - 1) Maximum 5 doses
- C) Had a gestation age of 28 weeks or less
 - 1) Initiated during the RSV season before the infant reaches 12 months
 - 2) Maximum 5 doses
- D) Had a gestation age of 29 weeks and 0 days to 31 weeks and 6 days
 - 1) Initiated during the RSV season before the infant reaches 6 months
 - 2) Maximum 5 doses
- E) Had a gestational age of 32 weeks 0 days to 34 weeks 6 days
 - 1) Born within 3 months before the start of RSV season or at any time throughout the RSV season
 - 2) Have at least 1 of these 2 risk factors
 - a) Infant attends child care; or
 - b) One or more siblings or other children younger than 5 years live permanently in the child's household.
 - 3) Should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first).

CPT code 90378 *Respiratory syncytial virus, monoclonal antibody, recombinant, for intramuscular use, 50 mg, each*

Updated Evidence Summary

American Academy of Pediatrics, July 2014, Technical Report

- 1) 2 RCTs total
 - a. One in 1996–1997 describing an overall reduction in RSV hospitalization rate from 10.6% among placebo recipients to 4.8% among children who received prophylaxis.

RSV prophylaxis (palivizumab) Guideline Note 19 Revision

- b. Second in 2003 in children with hemodynamically significant heart disease revealing a reduction in RSV hospitalization rate from 9.7% in control subjects to 5.3% among prophylaxis recipients.
- 2) No new trials
- 3) New information on seasonality of RSV circulation, palivizumab pharmacokinetics, the changing incidence of bronchiolitis hospitalizations, the effects of gestational age and other risk factors on RSV hospitalization rates, the mortality of children hospitalized with RSV infection, and the effect of prophylaxis on wheezing and palivizumab-resistant RSV isolates.
- 4) In their assessment of cost-effectiveness they conclude, "Because the high cost of palivizumab prophylaxis is associated with minimal health benefit, this intervention cannot be considered as high-value health care for any group of infants."

Updated Guideline

American Academy of Pediatrics, July 2014, Guidance

1. American Academy of Pediatrics Committee on Infectious Diseases
2. Performed a systematic review
3. Updated their guidelines

SUMMARY OF GUIDANCE

- In the first year of life, palivizumab prophylaxis is recommended for infants born before 29 weeks, 0 days' gestation.
- Palivizumab prophylaxis is not recommended for otherwise healthy infants born at or after 29 weeks, 0 days' gestation.
- In the first year of life, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at <32 weeks, 0 days' gestation and a requirement for >21% oxygen for at least 28 days after birth.
- Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease.
- Clinicians may administer up to a maximum of 5 monthly doses of palivizumab (15 mg/kg per dose) during the RSV season to infants who qualify for prophylaxis in the first year of life. Qualifying infants born during the RSV season may require fewer doses. For example, infants born in January would receive their last dose in March.
- Palivizumab prophylaxis is not recommended in the second year of life except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy).
- Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.
- Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year of life.
- Children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.
- Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.

RSV prophylaxis (palivizumab) Guideline Note 19 Revision

- The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native populations and possibly in selected other American Indian populations.
- Palivizumab prophylaxis is not recommended for prevention of health care-associated RSV disease.

HERC Staff Recommendations:

1) Delete the current guideline note

GUIDELINE NOTE 69, SYNAGIS

Line 3

~~CPT code 90378, Synagis (palivizumab), is covered for infants meeting one of the criteria given below (A-E), according to the treatment guidelines for each criterion:~~

- ~~F) Infants younger than 24 months who have congenital heart disease (CHD) or chronic lung disease of prematurity (CLD, formerly called bronchopulmonary dysplasia) AND require medical therapy~~
 - ~~1) Therapy is initiated within 6 months before the start of the RSV season~~
 - ~~2) Maximum 5 doses~~
- ~~G) Infants younger than 12 months with congenital abnormalities of the airway or neuromuscular disease~~
 - ~~1) Maximum 5 doses~~
- ~~H) Had a gestation age of 28 weeks or less~~
 - ~~1) Initiated during the RSV season before the infant reaches 12 months~~
 - ~~2) Maximum 5 doses~~
- ~~I) Had a gestation age of 29 weeks and 0 days to 31 weeks and 6 days~~
 - ~~1) Initiated during the RSV season before the infant reaches 6 months~~
 - ~~2) Maximum 5 doses~~
- ~~J) Had a gestational age of 32 weeks 0 days to 34 weeks 6 days~~
 - ~~1) Born within 3 months before the start of RSV season or at any time throughout the RSV season~~
 - ~~2) Have at least 1 of these 2 risk factors~~
 - ~~a) Infant attends child care; or~~
 - ~~b) One or more siblings or other children younger than 5 years live permanently in the child's household.~~
 - ~~3) Should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first).~~

2) Replace with:

GUIDELINE NOTE 69, RESPIRATORY SYNCYTIAL VIRAL PROPHYLAXIS

Line 3

Prophylaxis with palivizumab (CPT code 90378) is included on this line when meeting criteria developed by the Pharmacy and Therapeutics Committee according to OAR 410-121-0040 as found in Prior Authorization Approval Criteria Guide on palivizumab

<http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pa-criteria.pdf>.

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Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

COMMITTEE ON INFECTIOUS DISEASES and BRONCHIOLITIS GUIDELINES COMMITTEE

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<http://pediatrics.aappublications.org/content/134/2/e620.full.html>

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TECHNICAL REPORT

Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

abstract

FREE

Guidance from the American Academy of Pediatrics (AAP) for the use of palivizumab prophylaxis against respiratory syncytial virus (RSV) was first published in a policy statement in 1998. Guidance initially was based on the result from a single randomized, placebo-controlled clinical trial conducted in 1996–1997 describing an overall reduction in RSV hospitalization rate from 10.6% among placebo recipients to 4.8% among children who received prophylaxis. The results of a second randomized, placebo-controlled trial of children with hemodynamically significant heart disease were published in 2003 and revealed a reduction in RSV hospitalization rate from 9.7% in control subjects to 5.3% among prophylaxis recipients. Because no additional controlled trials regarding efficacy were published, AAP guidance has been updated periodically to reflect the most recent literature regarding children at greatest risk of severe disease. Since the last update in 2012, new data have become available regarding the seasonality of RSV circulation, palivizumab pharmacokinetics, the changing incidence of bronchiolitis hospitalizations, the effects of gestational age and other risk factors on RSV hospitalization rates, the mortality of children hospitalized with RSV infection, and the effect of prophylaxis on wheezing and palivizumab-resistant RSV isolates. These data enable further refinement of AAP guidance to most clearly focus on those children at greatest risk. *Pediatrics* 2014;134:e620–e638

Palivizumab is a humanized mouse immunoglobulin (IgG1) monoclonal antibody produced by recombinant DNA technology. The antibody is directed against a conserved epitope of the A antigenic site of the fusion (F) protein of respiratory syncytial virus (RSV) and demonstrates both neutralizing and fusion inhibitory activity.¹ The antibody consists of 2 heavy chains and 2 light chains; 95% of the amino acid sequences (framework) are of human origin, and 5% (antigen binding sites) are of mouse origin. After intramuscular administration, palivizumab is distributed hematogenously throughout the body, including the lower respiratory tract. When RSV encounters palivizumab in the lower respiratory tract, antibody binds to F protein and prevents the structural

COMMITTEE ON INFECTIOUS DISEASES and BRONCHIOLITIS
GUIDELINES COMMITTEE**KEY WORDS**

RSV, respiratory syncytial virus, palivizumab, bronchiolitis, infants and young children, chronic lung disease, congenital heart disease

ABBREVIATIONS

AAP—American Academy of Pediatrics
CDC—Centers for Disease Control and Prevention
CHD—congenital heart disease
CI—confidence interval
CLD—chronic lung disease
COID—Committee on Infectious Diseases
FDA—US Food and Drug Administration
HSCT—hematopoietic stem cell transplant
KID—Kids' Inpatient Database
NVSN—New Vaccine Surveillance Network
PHIS—Pediatric Health Information System
QALY—quality-adjusted life year
RSV—respiratory syncytial virus
SOT—solid organ transplant

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Technical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, technical reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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(Continued on last page)

conformational change that is necessary for fusion of the viral RSV envelope with the plasma membrane of the respiratory epithelial cell.² Without fusion, the virus is unable to enter the cell and unable to replicate. In addition, palivizumab prevents cell-to-cell fusion of RSV-infected cells.²

BACKGROUND

Palivizumab was licensed by the US Food and Drug Administration (FDA) in June 1998, largely on the basis of results of the IMpact-RSV trial conducted during the 1996–1997 RSV season. This randomized, placebo-controlled, double-blind trial involved 1501 infants and young children born preterm (at or before 35 weeks' gestation), some of whom had chronic lung disease (CLD) of prematurity.³ The IMpact-RSV trial demonstrated an RSV hospitalization rate of 10.6% in the placebo arm and 4.8% among high-risk infants who received prophylaxis, a reduction of 5.8% in RSV hospitalizations ($P < .001$).³ A second randomized, double-blind, placebo-controlled trial conducted from 1998 to 2002 enrolled 1287 children with hemodynamically significant congenital heart disease (CHD).⁴ This cardiac trial evaluated both the safety and efficacy of palivizumab prophylaxis and demonstrated an RSV hospitalization rate of 9.7% in the placebo arm and 5.3% among recipients of palivizumab prophylaxis, a reduction in the RSV hospitalization rate of 4.4% ($P < .003$). No additional placebo-controlled trials regarding the efficacy of palivizumab prophylaxis in any other subgroup have been published.

Palivizumab was licensed for the prevention of severe lower respiratory tract disease in pediatric patients at increased risk of severe RSV disease.¹ Recommendations from the American Academy of Pediatrics (AAP) for use of prophylaxis have evolved since licensure

of palivizumab as additional information has become available.

In addition, peer-reviewed data have been published since preparation of the most recent guidance in 2012.⁵ This technical report reviews the newer and older scientific literature to offer guidance on the most appropriate use of palivizumab prophylaxis, as published in the accompanying policy statement.⁶ Current guidance is risk stratified, targeting infants at greatest risk of severe disease and most likely to benefit from prophylaxis on the basis of evaluation of the published literature. Therefore, not all infants enrolled in the 2 randomized trials are included in the current guidance. Twenty-one AAP sections and committees plus groups outside the AAP have contributed to and concur with the updated guidance presented in the accompanying policy statement.

AAP guidance regarding the use of palivizumab was first published in a policy statement⁷ in 1998 and subsequently was revised in a 2003 policy statement,⁸ the 2006 *Red Book*,⁹ a 2009 policy statement,¹⁰ and most recently in the 2012 *Red Book*.⁵ The AAP guidance for palivizumab prophylaxis is being updated at this time to reflect the ongoing assessment by the Committee on Infectious Diseases (COID) of peer-reviewed publications, as exemplified in the following areas:

- Data regarding palivizumab pharmacokinetics¹¹;
- Data on the seasonality of RSV circulation^{12,13};
- Data on overall declining incidence of hospitalizations for bronchiolitis in the United States¹⁴;
- Data demonstrating that mortality rates in children hospitalized with laboratory-confirmed RSV are lower than previously estimated¹⁵;
- Data demonstrating a statistically significant but clinically minimal

reduction of wheezing episodes among recipients of palivizumab prophylaxis^{16,17};

- Reports indicating little benefit of palivizumab prophylaxis among patients with cystic fibrosis or Down syndrome^{18–20};
- Reports describing palivizumab resistant RSV isolates from hospitalized patients who receive prophylaxis^{21–23}; and
- Independently conducted cost analyses demonstrating a high cost versus limited benefit from palivizumab prophylaxis.^{24,25}

In addition, the complexity of the current guidance has resulted in lack of prophylaxis for some children who qualify, whereas other children who do not qualify receive prophylaxis that may not be indicated.^{26,27} The goal of this updated guidance is to present more clearly the COID recommendations for palivizumab use for infants and young children who are most likely to derive benefit from prophylaxis and, in the process, to simplify guidance for pediatricians and other clinicians.

It is important to note that using the same aggregate data, prophylaxis guidelines from other countries such as the United Kingdom are more restrictive than AAP guidance for the United States, and no evidence of excess morbidity has been observed.^{28,29}

Indications contained in a package label reflect data from clinical trials conducted by the sponsor and submitted to the FDA for drug licensure. The FDA does not issue guidelines or recommendations for drug use. The palivizumab package inserts states "Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease."¹ In the absence of a specific definition of "high risk" by the FDA, the AAP has endeavored since palivizumab was

first licensed to provide more precise guidance for determining those at increased risk.^{5,7,8,10} The same is true with this revision.

ADMINISTRATION

Palivizumab is administered intramuscularly at a dosage of 15 mg/kg once a month. The drug is packaged in single-dose liquid solution vials at 50 mg/0.5 mL and 100 mg/1.0 mL and does not contain preservative. A vial cannot be stored once it is opened, so a vial-sharing scheme is important to minimize waste. Anaphylaxis has occurred after palivizumab administration after initial exposure or reexposure, with some cases of severe hypersensitivity reactions reported.¹

RSV IMMUNOPROPHYLAXIS AND VACCINE ADMINISTRATION

Palivizumab does not interfere with the immune response to live or inactivated vaccines. The childhood immunization schedule should be followed for all children, regardless of palivizumab use.¹

GUIDANCE FOR PALIVIZUMAB PROPHYLAXIS

Burden of RSV Disease

In the United States, RSV remains an important cause of hospitalization in the first months of life. Retrospective analyses using national databases and *International Classification of Diseases, Ninth Revision* discharge diagnoses have shown considerable variation in estimates of annual hospitalization rates attributable to RSV for infants.^{30–33} More recent prospective population-based studies of laboratory confirmed cases demonstrate that RSV hospitalization rates are approximately half the rates reported in retrospective studies, yet rates remain high.^{14,34–36} It is estimated that approximately 2.1 million children younger than 5 years

require medical care as inpatients or as outpatients for RSV infection annually. Among outpatients, 60% (1.3 million) are 2 through 5 years of age, and the remaining 40% are between birth and 2 years of age.³⁵ Approximately 25% of RSV-infected children younger than 5 years are assessed and treated in an emergency department, and approximately 70% are assessed and treated in a pediatric office. It is estimated that each year, nearly 58 000 children in the first few years of life are hospitalized because of RSV infection.³⁵ Infants in the second month after birth have the highest RSV hospitalization rate, a rate that is almost twice that of the next highest risk group (infants in the first month after birth).³⁴

Preterm Infants Without CLD

In 2012, 3.95 million births were reported in the United States. Preterm infants (singleton and multiple births) born at less than 37 weeks' gestation represented 11.6% of all births.³⁷ Preterm births of infants at less than 28 weeks' gestation accounted for 0.7% of the annual birth cohort.³⁷ Infants born from 32 weeks to 35 weeks' gestation represented approximately 9% of the birth cohort.

Beginning with the first AAP statement in 1998,⁷ the high cost of palivizumab influenced recommendations for use by the COID, leading to attempts to identify risk factors for RSV hospitalization among the large number of moderately preterm infants. The New Vaccine Surveillance Network (NVSN), sponsored by the Centers for Disease Control and Prevention (CDC) was a prospective population-based surveillance program from 3 geographically diverse locations in the United States for young children hospitalized with laboratory-confirmed RSV respiratory illness. Several studies were published summarizing data from the NVSN. One

conducted during the RSV seasons from 2000 through 2005 using multiple logistic-regression analyses of data revealed that some of the previously reported potential risk factors, including siblings in the household and child care attendance, were not associated with a significantly increased risk of RSV hospitalization.³⁴ In this study, only young chronologic age was significantly correlated with risk of hospitalization for RSV illness. The association between preterm birth and increased risk of severe illness was not specific for RSV.³⁵

In addition, data from the NVSN study revealed that for all preterm infants (<37 weeks' gestation), the RSV hospitalization rate was 4.6/1000 children, which was not significantly different from the hospitalization rate for term infants, which was 5.3/1000 children (Table 1).³⁴ Rates were derived from 132 085 children born during the study period, among whom 2149 were hospitalized with acute respiratory illness, and 559 of the hospitalized children had laboratory-confirmed RSV (Table 1). Infants born at <30 weeks' gestation experienced a higher RSV hospitalization rate (18.7/1000 children) than early preterm infants (30–33 weeks),³⁴ although the small number of infants born before 30 weeks' gestation limits the generalizability of this data. Late preterm infants were hospitalized significantly less often than term infants for RSV infection.³⁴

An analysis of Tennessee Medicaid data for children younger than 3 years conducted from July 1989 to June 1993 (preimmunoprophylaxis era) included 248 652 child-years of follow-up. The retrospective cohort analysis was conducted to determine RSV hospitalization rates among infants with different degrees of prematurity and other comorbidities.³⁸ Within each age group, preterm infants had similar

TABLE 1 Average RSV Hospitalization Rates Among Children Younger Than 24 Months (2000–2005)³⁴

Children <24 mo	N ^a	RSV Hospitalization Rate/1000	95% CI
All infants regardless of gestational age	559 ^b	5.2	4.8–5.7
All term infants (≥37 wk gestation)	479	5.3	4.9–5.8
All preterm infants (<37 wk gestation)	56	4.6	3.4–5.8
≥35 wk gestation	494	5.1	4.7–5.5
32–34 wk gestation	23	6.9	4.3–10.1
29–31 wk gestation	6	6.3	2.0–12.4
<29 wk gestation	12	19.3	8.4–34.0
All very preterm (<30 wk gestation)	15 ^c	18.7	10.0–30.0

^a Among 2149 enrolled hospitalized children from a birth cohort of 132 085 children.

^b The total of 559 children hospitalized with RSV includes 24 whose gestational age could not be verified.

^c Personal communication, Geoffrey A. Weinberg, MD.

rates of RSV hospitalization, regardless of the degree of prematurity (Table 2). In this analysis, preterm infants with CLD were categorized separately to reduce confounding.

A historical cohort analysis from Rochester, New York, reported on RSV hospitalization rates among 1029 consecutive preterm infants born before or at 32 weeks' gestation during a 5-year period.³⁹ The RSV hospitalization rate increased with decreasing gestational age, with a breakpoint at ≤28 weeks' gestation (Table 3). Among infants born at or before 26 weeks' gestation, the risk of RSV-associated hospitalization was 13.9% vs 4.4% among children hospitalized at >30 to 32 weeks' gestation. There was not a statistically significant difference in RSV hospitalization rates between infants with gestational ages of >28 to 30 weeks and infants with gestational ages of >30 to 32 weeks.

A retrospective cohort study of infants enrolled in Medicaid in Texas and

Florida between 1999 and 2004 examined RSV hospitalization rates in moderately preterm infants 32 to 34 weeks' gestation⁴⁰ Less than 20% of each cohort received palivizumab prophylaxis. In Florida, 71 (3.1%) of the moderately preterm infants were hospitalized compared with 1246 (1.5%) of term infants, and in Texas 164 (4.5%) of the preterm infants were hospitalized compared with 3815 (2.5%) of term infants. Palivizumab prophylaxis was associated with decreased hospitalization in moderately preterm infants in Texas but not in Florida. The risk of RSV hospitalization in moderately preterm infants was similar to 1-month-old term infants by 4.2 months in Florida (95% confidence interval [CI], 2.5–5.7) and by 4.5 months in Texas (95% CI, 2.8–6.4).⁴⁰

Choosing an appropriate cutoff for gestational age for which palivizumab prophylaxis may be considered for preterm infants without other indications is challenging. Data consistently

demonstrate the greatest increase in risk for hospitalization is in preterm infants born before 29 weeks' gestation. These infants have hospitalization rates 2 to 4 times higher than later preterm infants (Tables 1, 2, and 3). The consensus of the COLD and the Bronchiolitis Guidelines Committee is that palivizumab prophylaxis may be considered for infants, without other indications, whose gestational age is less than 29 weeks (28 weeks, 6 days or fewer). The available data do not support universal recommendations for palivizumab prophylaxis for preterm infants born at or after 29 weeks' gestation.

Data regarding the risk of RSV hospitalization for most preterm infants do not support a benefit from prophylaxis. In recent large cohort studies of moderately preterm infants, the majority of whom did not receive palivizumab, 2.5% to 4.9% required hospitalization for RSV infection during the RSV season indicating that more than 95% did not require hospitalization.⁴⁰ The rate of hospitalization among infants ≥35 weeks' gestation (5.1/1000) was no different than the rate for term infants (5.3/1000; Table 1). The hospitalization rate of infants ≥30 weeks to 35 weeks' gestation indicate only a slight increase in risk (less than twofold; Tables 1, 2, and 3). Data concerning host or environmental risk factors for hospitalization in preterm infants without CLD or CHD are inconsistent, with the exception of age

TABLE 2 RSV Hospitalizations per 1000 Children From >248 000 Child-Years of Follow-up³⁸

Age Stratum/Risk Group	0 to <6 mo	6 to <12 mo	12 to <24 mo	IRR (95% CI) for 0 to <6 mo	Adjusted IRR (95% CI) for first 12 mo
Low-risk infants	44.1	15.0	3.7	Comparator	Comparator
Infants with CHD	120.8	63.5	18.2	2.7 (2.2–3.4)	2.8 (2.3–3.3)
Infants with CLD	562.5	214.3	73.4	12.8 (9.3–17.2)	10.7 (8.4–13.6)
≤28 wk gestation	93.8	46.1	30.0	2.1 (1.4–3.1)	2.4 (1.8–3.3)
29 to <33 wk gestation	81.8	50.0	8.4	1.9 (1.4–2.4)	2.2 (1.8–2.7)
33 to <36 wk gestation	79.8	34.5	10.8	1.8 (1.5–2.1)	1.8 (1.6–2.1)
Other condition ^a	122.3	55.2	24.1	2.8 (2.5–3.1)	2.3 (2.1–2.6)

IRR, incidence rate ratio.

^a Asthma, cystic fibrosis, cancer, HIV infection, immunodeficiency, steroid therapy, chronic renal disease, diabetes mellitus, congenital anomalies of the respiratory tract, or respiratory distress syndrome.

TABLE 3 RSV Hospitalizations Among 1029 Infants Born at or Before 32 Weeks' Gestation³⁹

Gestational Age, wk	No. of Infants	No. of RSV Admissions	% Admitted	<i>P</i> vs 30–32 Weeks' Gestation
≤26	165	23	13.9	<.001
27–28	171	17	9.9	.007
>28–30	240	18	7.5	.12
>30–32	453	20	4.4	Comparator
Total	1029	78	7.6	Not applicable

younger than 3 months at the start of the RSV season, which has been associated with an increased risk of hospitalization.³⁴

For all infants, particularly those who are preterm, the environment should be optimized to prevent RSV and other viral respiratory infections by offering breast milk feeds, immunizing household contacts with influenza vaccine, practicing hand and cough hygiene, and by avoiding tobacco or other smoke exposure and attendance in large group child care during the first winter season, whenever possible.

Preterm Infants With CLD

Studies have documented that infants and young children with CLD have increased rates of RSV hospitalization.^{38,39} Results from the IMpact-RSV trial evaluating all preterm infants with CLD (*n* = 762 randomized preterm infants) demonstrated that the RSV hospitalization rate among placebo recipients was 12.8% and 7.9% among palivizumab recipients (*P* = .038).³

Infants With Hemodynamically Significant CHD

The results of an industry-funded multicenter, randomized, double-blind, placebo-controlled trial of palivizumab prophylaxis among 1287 children (639 palivizumab recipients, 648 placebo recipients) younger than 24 months with hemodynamically significant CHD was published in 2003.⁴ Results from this study demonstrated a reduction in RSV hospitalization rates of 4.4% (9.7% among placebo recipients and 5.3% among palivizumab recipients;

P = .003).⁴ The reduction in the number of RSV hospitalizations between the 2 study groups was 29 fewer RSV hospitalizations among palivizumab recipients during the 4 years of the study.⁴ Prophylaxis with palivizumab appeared to have less benefit among cyanotic children than among acyanotic children. Among children in the cyanotic group, there were 23 fewer RSV hospitalizations per 1000 palivizumab recipients (7.9% vs 5.6%, *P* = .285). Among children in the acyanotic group, there were 68 fewer RSV hospitalizations per 1000 prophylaxis recipients (11.8% vs 5.0%; *P* = .003). Despite enrolling 1287 subjects, the trial did not have sufficient power to detect statistically significant differences among subgroups of children with different cardiac lesions.

A retrospective analysis of the effect of palivizumab prophylaxis on RSV hospitalizations among children with hemodynamically significant CHD was conducted in California. The authors estimated a statewide 19% reduction in RSV hospitalization between 2000 and 2002 (preprophylaxis era) and 2004 and 2006 (prophylaxis era) after the licensure of palivizumab for children with CHD. The authors concluded that in the state of California, 7 fewer RSV hospitalizations per year occurred among children younger than 2 years with hemodynamically significant CHD following recommendations for palivizumab prophylaxis in this group.⁴¹

Other investigators describe rates of RSV hospitalizations among patients with hemodynamically significant CHD (2%–3%) who do not receive pro-

phylaxis as lower than the 9.7% rate reported in the placebo arm of the cardiac study.^{42–46} As the rate of RSV hospitalization decreases among children who do not receive prophylaxis, the cost to prevent 1 hospitalization with prophylaxis increases.

A retrospective analysis of children younger than 3 years (248 652 children-years) in the Tennessee Medicaid program revealed that the RSV hospitalization rate for children with CHD in the second year of life (18.2/1000) was less than half the hospitalization rate for low-risk infants in the first 5 months after birth (44.1/1000), a group for whom palivizumab prophylaxis is not recommended³⁸ (Table 2). Thus, prophylaxis is not recommended during the second year of life.

Children With Anatomic Pulmonary Abnormalities or Neuromuscular Disorder

The risk of RSV hospitalization is not well defined in children with neuromuscular disorders that impair the ability to clear secretions from the upper airway because of ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy.

Studies suggest children and infants with neuromuscular disease who are hospitalized with RSV infection tend to be older compared with other groups of patients hospitalized with RSV infection and are more likely to have preexisting immunity to RSV.^{47,48} This may reflect the progressive nature of neuromuscular disease, with susceptibility to respiratory disease tract increasing with age.

Immunocompromised Children

Population-based data are not available on the incidence or severity of RSV disease among children who receive

solid organ transplants (SOTs) or hematopoietic stem cell transplants (HSCTs), children who receive chemotherapy, or children who are immunocompromised because of other conditions. Progression of RSV infection from upper to lower respiratory tract disease depends on the virulence of the RSV strain, as well as specific abnormalities in the immunocompromised host's immune response attributable to the underlying disease or to chemotherapy.

RSV infection in immunocompromised children and adults can progress to respiratory failure and death.^{49,50} Lymphopenia has been recognized as a risk factor for disease progression in several studies of immunocompromised patients. One study in adults noted that progression of RSV to lower respiratory tract disease did not occur in patients with a lymphocyte count greater than 1000 cells/mm³ at time of onset of upper respiratory tract infection.⁵¹ An absolute lymphocyte count of 100 cells/mm³ or less at the time of RSV upper tract infection was associated with progression to lower respiratory tract disease. In contrast to lymphopenia, analysis of antibody concentration in these adult HSCT recipients indicated no correlation between preexisting anti-RSV antibody concentration and progression from upper to lower respiratory tract disease.⁵¹

A retrospective report from 1 institution described 58 immunocompromised children with RSV infection between 1997 and 2005.⁵² Sixty-five percent of the RSV-infected children were managed as outpatients. No deaths occurred among 28 children infected with RSV who were receiving chemotherapy for acute lymphoblastic leukemia or among 11 immunosuppressed SOT recipients. Five of 58 patients with lower respiratory tract infection died (8.6%), including 4 children who were allogeneic HSCT recipients and

1 child with severe combined immune deficiency. One of the deaths occurred in a 10-year-old child, and a second death occurred in a child with *Aspergillus* species coinfection. Profound lymphopenia (<100 cells/mm³) was associated with progression to lower respiratory tract disease.⁵²

Another retrospective report from 1 institution noted 5 deaths among 117 RSV-infected, immunocompromised patients between 2006 and 2011 (2 with severe combined immunodeficiency, 1 with uncharacterized immunodeficiency, 1 with chronic granulomatous disease, and 1 SOT recipient).⁵³ The deaths occurred in children who presented with community-acquired RSV lower respiratory tract infection. No deaths occurred among children who were HSCT recipients or those with leukemia or lymphoma.

A third retrospective review of RSV infections in children with cancer was conducted from 1998 to 2009.⁵⁴ Among 57 patients, 37% experienced progression to lower respiratory tract disease. Three patients died of respiratory failure within 60 days of RSV diagnosis (1 had concomitant bacteremia and fungemia and 1 had concomitant herpes simplex pneumonia).

In a review of 208 viral respiratory infections among 166 patients over a 13-year period who received HSCTs, SOTs, or chemotherapy for malignancy, RSV infection accounted for 43% of the infections.⁵⁵ The mean and median ages of patients at the time of infection were 6.1 years and 4.3 years, with a range of 2 months to 21 years of age. Death occurred in 17 (8%) of patients with viral respiratory infection, including 6 of 88 (7%) RSV-infected children who received allogeneic HSCTs or SOTs. No infection resulted in death among patients who received chemotherapy, despite being severely immunosuppressed. Mortality and morbidity

did not have a statistically significant correlation with the degree of immune suppression.

Risk factors for a poor outcome after RSV infection in an immunosuppressed host include age younger than 2 years, presence of lower respiratory tract symptoms at presentation (particularly in the absence of symptoms of upper respiratory infection), corticosteroid therapy, and varying degrees of lymphopenia. Underlying diagnosis, degree of immune suppression, RSV load in bronchoalveolar lavage, or specific humoral immunity to RSV have not been found to correlate with outcome.⁵⁶ This inability to correlate degree of immunosuppression with disease severity indicates an incomplete understanding of the immune response to viral respiratory infections in an immunocompromised host.

Antibody-based treatments, including immune globulin and palivizumab, have not been associated with improved outcome in HSCT recipients.⁵⁷ No data are available to suggest benefit from immunoprophylaxis among immunocompromised patients, and practices vary nationwide.^{58,59} Further research is required before definitive recommendations can be made for the use of palivizumab in this heterogeneous group of children.

Children With Down Syndrome

Several factors appear to place children with Down syndrome at increased risk of RSV lower respiratory tract disease than children without Down syndrome.^{18,19,60,61} CHD, with or without pulmonary hypertension, occurs in approximately 45% of children with Down syndrome, and lesions include atrioventricular canal, ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot. Anatomic abnormalities of the upper or lower respiratory tract, muscle dystonia, and intrinsic immune dysfunction may

contribute to viral respiratory disease in this population.

One population-based cohort study over an 11-year period in Colorado revealed a statewide total of 85 RSV hospitalizations among 680 children with Down syndrome during their first 2 years of life. Concurrent risk factors were present in 35 of the 85 (41%) hospitalized children, indicating they would have qualified for prophylaxis for other reasons. RSV hospitalization rates were 67/1000 child-years for children with Down syndrome and other risk factors, 42/1000 child-years for children with Down syndrome without cardiopulmonary disease, and 12/1000 child-years for children in a control group.⁶¹ These data suggest an estimated overall 7.7 RSV admissions per year (85 admissions per 11 years) in the state of Colorado for children with Down syndrome. Using these figures, 4.6 RSV hospitalizations per year occur among children with Down syndrome without concurrent factors (50 admissions per 11 years) in Colorado. Assuming a 55% reduction in hospitalization, approximately 2 to 3 hospitalizations per year might have been avoided from prophylaxis administered to 680 children. Although children with Down syndrome were more likely to experience a temperature >38°C, the median duration of stay for children younger than 1 year of age with Down syndrome was 4 days, and for children without Down syndrome the median was 3 days. No deaths were reported in this study.⁶¹ These data suggest children with Down syndrome have a slightly higher hospitalization rate, but the absolute number of RSV hospitalizations is small, and a number of children with Down syndrome are at increased risk because of qualifying heart disease or other factors.

Another report described 39 of 395 (9.9%) children with Down syndrome hospitalized because of RSV infection

in the first 2 years of life.⁶⁰ Among hospitalized children, 38% had hemodynamically significant heart disease. This study had insufficient power to differentiate among subgroups, meaning the increased RSV hospitalization rate may have been explained by concurrent risk factors and not Down syndrome.⁶⁰ Another study of 41 children with Down syndrome hospitalized with RSV infection noted that 51% had underlying CHD.¹⁸ An additional report of 222 children with Down syndrome hospitalized with RSV infection noted the mean age of hospitalized children (1.3 years; range, 0–6.1 years) was significantly older than the age of children hospitalized with RSV who did not have Down syndrome. A similar finding was noted in the Colorado report, with a mean age of 9.6 months at admission for RSV infected patients with Down syndrome and no other risk factors. In this study, the age range for hospitalization extended through 17 years.⁶¹ RSV prophylaxis for the first year of life would have limited effect on RSV hospitalization for children with Down syndrome without other risk factors for RSV.^{19,61}

Children With Cystic Fibrosis

Available studies indicate the incidence of RSV hospitalization in children with cystic fibrosis is uncommon and unlikely to be different from children without cystic fibrosis. Evidence to support a benefit from palivizumab prophylaxis in patients with cystic fibrosis is not available.^{20,62,63}

A randomized clinical trial with palivizumab prophylaxis included 186 children with cystic fibrosis from 40 centers. One subject in the untreated group and 1 subject in the palivizumab group were hospitalized for RSV infection.⁶⁴ Although this study was not powered for efficacy, no clinically meaningful differences in outcome between the 2 groups were reported.

At the 12-month follow-up, there was no significant difference between the treated and untreated groups in number of *Pseudomonas* colonizations or change in weight-to height ratio. A case-control study of palivizumab in 75 children with cystic fibrosis noted a possible trend toward a potential clinical benefit of palivizumab prophylaxis, but the difference was not statistically significant.⁶²

A large study of RSV hospitalizations occurring between 1997 and 2003 in Danish children with chronic medical conditions identified 72 children with cystic fibrosis.⁶⁵ There were 13 RSV-related hospitalizations, which resulted in an adjusted incidence rate ratio for risk of RSV hospitalization of 4.32 (95% CI, 2.42–7.71). The geometric mean ratio for duration of RSV hospitalization in these children with cystic fibrosis was 1.3 days (95% CI, 0.81–2.11 days).

Two recent reviews^{20,66} of RSV infection in infants with cystic fibrosis acknowledged that infants with cystic fibrosis may have a slightly increased risk for hospitalization with RSV. However, they both stated that there is insufficient evidence related to safety and efficacy in infants with cystic fibrosis to support a recommendation of palivizumab prophylaxis.^{20,66} A survey of cystic fibrosis center directors published in 2008 noted that palivizumab prophylaxis is not the standard of care for patients with cystic fibrosis.⁶⁷

Discontinuation of Palivizumab Prophylaxis Among Children Who Experience Breakthrough RSV Hospitalization

RSV is classified into subgroups A and B, based on antigenic differences in the surface G glycoprotein. Subgroups are classified further into genotypes based on genetic analysis. The ability of RSV to cause reinfections throughout life likely

is attributable both to strain variability and to an immune response that does not fully protect against subsequent infection. Reinfections with both heterologous and homologous strains occur. More than 1 RSV strain may circulate concurrently in a community. However, repeat RSV hospitalizations during 1 season are rare.

One study identified 726 RSV lower respiratory tract infections among 1560 children younger than 5 years over 8 successive RSV seasons in an outpatient setting.⁶⁸ Only 1 instance of repeat RSV infection occurred during the same season. Furthermore, it is well established that repeat RSV infections are associated with less severe clinical illness than the initial RSV infection.^{69,70}

In the blinded and randomized cardiac trial that involved 1287 children younger than 24 months with hemodynamically significant CHD, a total of 5 readmissions for a second RSV hospitalization occurred (a rate of less than 0.5%). Three of 648 children in the placebo group and 2 of 639 children who received palivizumab had more than 1 RSV hospitalization over 4 years.⁴ In the Dutch trial of 429 preterm infants randomly assigned to receive either palivizumab prophylaxis or placebo between April 2008 and December 2010, infants were followed for recurrent wheezing. No RSV reinfections were detected in either group, again indicating that repeat RSV infections in the same year seldom occur.¹⁶

Use of Palivizumab in the Second Year of Life

A prospective population-based surveillance study of 5067 children younger than 5 years evaluated 564 children hospitalized with laboratory-confirmed RSV infection. Among the children hospitalized with RSV infection, 75% were younger than 12 months. Less than 20% of all pediatric RSV hospitalizations

occurred during the second year of life.³⁵

Limited safety data and no efficacy data are available regarding palivizumab prophylaxis in the second year of life.^{71,72} Regardless of the presence or absence of comorbidities, RSV hospitalization rates decline during the second RSV season for all children.^{34,38} In a retrospective cohort study conducted over 4 years and involving 248 652 child-years, RSV hospitalization rates in the second year of life for children with comorbidities were lower than the rate for healthy term infants in the first 12 months of life, a group for whom prophylaxis is not recommended³⁸ (Table 2).

Lack of Therapeutic Efficacy of Palivizumab

Controlled studies have demonstrated that monoclonal antibodies have no therapeutic benefit in the treatment of RSV infected children. One randomized study determined that intravenous palivizumab administered to RSV-infected, intubated infants reduced the RSV viral load in the lower respiratory tract but had no effect on RSV concentration in the upper respiratory tract.⁷³ Despite a reduction in viral load in the lower respiratory tract, no difference in disease severity was found between palivizumab recipients and placebo recipients. A phase 2 therapeutic trial involving 118 hospitalized, RSV infected infants evaluated the outcome among recipients of intravenous motavizumab at 30 mg/kg or at 100 mg/kg compared with placebo.⁷⁴ Motavizumab is an investigational monoclonal antibody with enhanced potency relative to palivizumab. No significant effect on RSV viral load in the upper respiratory tract was detected among motavizumab recipients. No difference in duration of hospitalization, requirement for supplemental oxygen, ICU admission, or need for mechanical ventilation between groups was detected.

Prevention of Health Care-Associated RSV Disease

Strict infection-control practices, including restriction of visitors to the neonatal ICU during respiratory virus season, will decrease health care-associated RSV disease. Evidence does not support the use of palivizumab among hospitalized preterm infants to prevent health care-associated spread of RSV.^{75,76} If an RSV outbreak occurs in a high-risk unit (eg, pediatric or neonatal ICU or HSCT unit), primary emphasis should be placed on proper infection-control practices, especially hand hygiene. No rigorous data exist to support palivizumab use in controlling outbreaks of health care-associated disease. Further, hospitalization rates for RSV infection do not differ among infants who receive inpatient palivizumab prophylaxis while in the neonatal ICU compared with those who initiate prophylaxis at hospital discharge.⁷⁷

CONSIDERATIONS AFFECTING REVISION OF GUIDANCE

Risk Factors for RSV Hospitalization

Overall, approximately 2% to 3% of infants in the first 12 months of life are hospitalized with RSV infection each year in the United States. Children with certain comorbidities are at increased risk of severe RSV disease relative to children without these comorbidities.^{35,38} Chronologic age is the single most important risk factor for RSV hospitalization on the basis of the observation that more than 58% to 64% of pediatric RSV hospitalizations occur in the first 5 months after birth.^{34,35,38} Most of these hospitalizations occur in the first 90 days after birth.^{22,34,40} Certain subgroups of infants with comorbidities such as prematurity, CLD, or hemodynamically significant CHD have increased risks for RSV hospitalization, although the

degree of risk varies among studies.^{30,78} The risk of RSV hospitalization associated with most other risk factors has been difficult to determine because of low rates of occurrence. Most host and environmental factors increase the risk for RSV hospitalization by only a small magnitude, so their contribution to overall disease burden is limited.⁷⁹ In addition, these factors are not identified consistently from study to study. These inconsistencies likely reflect variation in practice patterns in different countries, variation in living conditions and climate, variation in health care coverage, yearly variation in disease severity, and incompletely understood genetic factors. Differences in study design may contribute to these differences.

Reported host risk factors of limited (inconsistent) impact include the following: congenital malformations, congenital airway anomaly, neuromuscular impairment, birth weight, gender, lack of breastfeeding, duration of breastfeeding, cord serum anti-RSV antibody concentration, small for gestational age, Down syndrome, epilepsy, cord blood vitamin D concentration, family history of atopy, viral load, malnutrition, multiple births, and singletons versus multiple birth subjects. Environmental risk factors of limited (variable) impact include the following: environmental pollution, crowded living conditions, living at increased altitude, meteorological conditions, low parental education, low socioeconomic status, child care attendance, size of child care facility, month of birth, smoke exposure, maternal smoking during pregnancy, and proximity to hospital care.^{30,35,38,47,48,60,65,78,80–94} One publication suggested that malformations of the urinary tract increase the risk of RSV hospitalization.⁶⁵

Multiple logistic-regression analyses of data from the 4-year population-based prospective study revealed that

of the evaluated risk factors (male gender, child care attendance, smoke exposure, lack of breastfeeding, and other children in the house), only preterm birth and young chronologic age independently correlated with more severe RSV disease after adjusting for other covariates.³⁵

RSV Seasonality

During the 6 RSV seasons from July 2007 to January 2013, the median duration of the RSV season ranged from 13 to 23 weeks, with median peak activity from mid-December to early February, with the exception of Florida and Alaska (see later discussions for each).^{12,13} Within the 10 Health and Human Services Regions, in the few regions when the RSV season began in October, the season ended in March or early April. In regions where the RSV season began in November or December, the season ended by April or early May. Because 5 monthly doses of palivizumab at 15 mg/kg per dose will provide more than 6 months of serum palivizumab concentrations above the desired serum concentration for most infants, administration of more than 5 monthly doses is not recommended within the continental United States.¹¹ Children who qualify for 5 monthly doses of palivizumab prophylaxis should receive the first dose at the time of onset of the RSV season. For qualifying infants born during the RSV season, fewer than 5 doses will be needed to provide protection until the RSV season ends in their region (maximum of 5 doses).

A small number of sporadic RSV hospitalizations occur before or after the main season in many areas of the United States,^{79,95} but maximum benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low.

Prophylaxis for Alaska Native/American Indian Children and Timing of Palivizumab Initiation

Hospitalization rates for all causes of bronchiolitis as high as 484 to 590/1000 infants have been described in isolated Inuit populations.^{96–99} Alaska Native infants in southwestern Alaska experience higher RSV hospitalization rates and a longer RSV season. On the basis of the epidemiology of RSV in Alaska, particularly in remote regions, the selection of infants eligible for prophylaxis may differ from the remainder of the United States. Clinicians may wish to use RSV surveillance data generated by the state of Alaska to assist in determining onset and end of the RSV season for appropriate timing of palivizumab administration.¹⁰⁰

Two published studies have documented a bronchiolitis hospitalization rate in Navajo populations that was 91.3 to 96.3/1000 infants younger than 1 year.^{101,102} This rate was similar to those seen with high-risk groups, such as infants born preterm and those with CLD. There are no data on efficacy of palivizumab in this population. However, if local data support a high burden of RSV disease in select American Indian populations, selection of infants eligible for prophylaxis may differ from the remainder of the United States for infants in the first year of life.

Timing of Prophylaxis for the State of Florida

Variation in the onset and offset of the RSV season in different regions of Florida may affect the timing of palivizumab administration. Florida Department of Health data may be used to determine the appropriate timing for administration of the first dose of palivizumab for qualifying infants. Despite varying onset and offset dates of the RSV season in different regions of Florida, a maximum of 5 monthly

doses of palivizumab will be adequate for qualifying infants for most RSV seasons in Florida. Even if the first of 5 monthly doses is administered in July, protective serum concentrations of palivizumab will be present for most infants and young children for at least 6 months and likely into February. More than 5 monthly doses are not recommended, despite the detection of a small number of cases of RSV infection outside this time window. A small number of sporadic RSV hospitalizations occur before or after the main season in many areas of the United States, but maximum benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low.

Pharmacokinetics of Palivizumab

A threshold protective serum palivizumab concentration in humans has not been established. On the basis of studies of palivizumab prophylaxis with the cotton rat, serum concentrations of 25 to 30 mcg/mL produced a mean reduction in pulmonary RSV concentrations of 99% (2 log₁₀).^{103,104} Because of the reliability of the cotton rat model to predict results in humans, this serum concentration became the target trough concentration in the randomized clinical trials.^{3,4} The package label states “palivizumab serum concentrations of greater than or equal to 40 mcg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100 fold.”¹

Palivizumab pharmacokinetic data published by the manufacturer in 2012 demonstrate that after 5 monthly doses, serum concentrations of palivizumab remain at or above protective levels for most children for at least 6 months (>24 weeks).¹¹ There is seldom justification to administer more than 5 doses within the continental United States. These data were derived from

a computer model based on 22 clinical trials.

Weight dosing at 15 mg/kg resulted in similar palivizumab concentrations in healthy term infants as well as preterm infants.¹¹

Race and Sex

Data from the NVSN demonstrate that the overall rate of RSV hospitalization does not differ between African American and white children younger than 24 months of age (5.4/1000 for African American children and 4.7/1000 for white children).³⁴ Among infants younger than 6 months, RSV hospitalization rates for African American and white children were not significantly different.³⁴ Another report from NVSN evaluated 564 children hospitalized with RSV infection. Neither race nor ethnic group was found to be an independent risk factor for hospitalization.³⁵ A third CDC report revealed rates of RSV coded illness in African American and white children to be similar at 5.3/1000 (95% CI, 3.7–6.9/1000) and 5.3/1000 (95% CI, 4.3–6.3/1000), respectively.³³ Hospitalization rates did not differ during the years of this study (1997–1999 and 2004–2006) by African American or white race. In this study, hospitalization rates for RSV-coded illness were 7.5/1000 boys (95% CI, 5.9–9.1) and 5.9/1000 girls (95% CI, 4.5–7.3).

Another population-based study evaluated racial disparities between African American and white children who were hospitalized because of RSV infection in 3 large United States counties.¹⁰⁵ No disparity was found in any county for any of the 7 years studied among children in the first 12 months of life or between infants 0 to 2 months or infants 3 to 5 months of age. Because of small numbers, reliable estimates for other race groups are not available.³³ RSV hospitalization

rates among boys exceed that of girls in some, but not all studies.^{34,35}

Mortality Rates Among Hospitalized Children With RSV Infection

Using 2 national databases (the Pediatric Health Information System [PHIS] data for 2004–2011 and the Health Cost and Utilization Project Kids' Inpatient Database [KID] for 2009), mortality rates associated with hospitalized infants with RSV infection were lower than previously estimated. The PHIS data set from 44 children's hospitals identified 33 deaths per year (13.7 deaths/10 000 RSV admissions during the RSV season), but only 8.5 deaths/10 000 admissions were coded with RSV as the primary diagnosis, suggesting that other comorbidities were involved. In the KID data set from more than 4000 hospitals in 44 states, RSV was estimated to account for 121 deaths annually in the United States (9/10 000 RSV admissions) with 84 deaths per year occurring during the typical RSV season. In addition, as suggested by the PHIS database, nearly 80% of deaths occurred in children with complex chronic medical conditions. The mean age at time of death was 7.5 months for infants in the PHIS data set and 6.2 months in the KID data set.¹⁵

An industry-sponsored meta-analysis of published reports of fatality rates attributable to RSV infection in children suggested higher rates of death based on estimates from earlier years, likely because supportive care received in intensive care units was less effective in earlier years.¹⁰⁶

A statistically significant reduction in RSV mortality has not been demonstrated in any randomized clinical trial with palivizumab or motavizumab. Thus, inclusion of mortality reduction or life years saved is difficult to justify in a cost analysis of palivizumab prophylaxis.

Motavizumab

Motavizumab is a second-generation monoclonal antibody that differs from palivizumab by 13 amino acids. Motavizumab was developed by affinity maturation of the complementarity determining regions of palivizumab to improve binding affinity to F protein. In cell culture, motavizumab has approximately 10-fold greater neutralizing activity than palivizumab against RSV clinical isolates of both A and B subtypes.¹⁰⁷ Unlike palivizumab, motavizumab may reduce RSV viral load in the upper respiratory tract, as well as the lower respiratory tract.¹⁰⁸

Data from several clinical trials, including a noninferiority trial between palivizumab and motavizumab, were submitted to the FDA as part of the licensing application for motavizumab.^{109–111} In August 2010, the FDA rejected the license application for motavizumab. Among a number of concerns noted by the FDA was lack of greater clinical efficacy from motavizumab and a threefold increase in hypersensitivity reactions among motavizumab recipients relative to palivizumab recipients.^{107,109,112} Methodologic concerns were raised by the FDA in regard to laboratory testing procedures and geographic variation in results from the noninferiority trial. Specifically, the generalizability of the main study finding was uncertain, because the results of the primary end point differed when stratified by geographic location. The results did not reach the noninferiority threshold for the northern hemisphere, where approximately 90% of subjects were enrolled.¹⁰⁷

The overall RSV hospitalization rate was 4.8% among palivizumab recipients in the IMPact-RSV trial compared with a 1.9% RSV hospitalization rate among palivizumab recipients in the palivizumab-motavizumab noninferiority trial. It was concluded that the non-

inferiority trial may have been conducted in a population with less comorbidity than the IMPact-RSV study. The FDA requested an additional clinical trial to support a satisfactory risk–benefit profile in populations for which prophylaxis is being considered.¹⁰⁷

RSV-specific outpatient medically attended lower respiratory tract infections were reported to be significantly lower among motavizumab recipients relative to palivizumab recipients in the noninferiority trial. However, this outcome was determined in a subset of patients from selected study sites, making the risk of bias high, as noted in the FDA report.¹⁰⁷

Outpatient visits among RSV-infected children exceed the number of outpatient visits attributable to influenza infection by more than twofold.¹¹³ One study of acute respiratory infection in children younger than 8 years estimated children from birth through 23 months of age experienced overall emergency department visits attributable to RSV infection at a rate of 64.4/1000 (95% CI, 45.4–91.3) compared with a rate of 15.0/1000 (95% CI, 4.4–50.6) among influenza-infected children (27% had received influenza vaccine) during 2 respiratory virus seasons between 2003 and 2005.¹¹³ The impact of immunoprophylaxis on outpatient medically attended events attributable to RSV infection is an important consideration but remains unknown because of lack of evaluation in a rigorous, controlled fashion.

Palivizumab-Resistant Isolates

Palivizumab and motavizumab bind to a highly conserved epitope (antigenic site A) on the extracellular domain of the mature F protein that encompasses amino acids 262 to 275. After antibody binding, viral entry into the respiratory epithelial cell is blocked, as is cell-to-cell fusion of infected cells.² RSV escape mutants resistant

to palivizumab have been isolated from approximately 5% of children hospitalized with breakthrough RSV infection while receiving monthly palivizumab prophylaxis.^{1, 21,22,23,114} RSV isolates resistant to palivizumab contain mutations in codons encoding the amino acids between 262 and 275 of the F protein. Amino acid sequence variations outside antigenic site A do not appear to confer palivizumab resistance.

Effect of Palivizumab Prophylaxis on Subsequent Wheezing

Numerous studies have documented that infants hospitalized with viral lower airway disease are more likely to experience recurrent wheezing compared with infants who do not experience severe bronchiolitis.^{68,115–119} The possible effect of avoidance of RSV lower respiratory tract infection early in life with palivizumab prophylaxis on recurrent wheezing was addressed in 3 industry-sponsored studies.^{16,17,120}

One trial among preterm infants without CLD describes physician-diagnosed recurrent wheezing in 8% of prophylaxis recipients and in 16% of the control group. This trial was conducted at 27 sites, and the patients were followed for up to 24 months. Participants were not prospectively randomized, the groups were not balanced for birth weight, degree of prematurity or known RSV risk factors, and families were not blinded to study medication, making the results of uncertain significance.¹²⁰

A nonrandomized observational report from Japan compared the incidence of wheezing between 349 preterm infants (33–35 weeks' gestation) who received palivizumab prophylaxis in the first 6 months of life with 95 infants who did not receive prophylaxis. The primary end point of the study was physician-diagnosed wheezing during

a 3-year follow-up. Twenty-two of 345 infants (6.4%) who received immunoprophylaxis experienced wheezing, whereas 18 of 95 infants (18.9%) who did not receive prophylaxis developed recurrent wheezing ($P < .001$) during the 3-year follow-up period.¹⁷ No difference in hospitalization rates attributable to respiratory disease between the 2 groups was found. Concerns with this study design include the lack of randomization and blinding and the absence of standardized enrollment criteria at the 52 participating sites, each of which may have led to enrollment bias, and no information was provided on the severity of the wheezing episodes. In addition, a history of smokers in the household and family history of allergy was significantly more common in the untreated group.

A double-blind placebo-controlled trial conducted in the Netherlands addressed palivizumab prophylaxis and recurrent wheezing using a different study design.¹⁶ Parent-reported wheezing in 429 otherwise healthy late preterm infants during the first year of life was evaluated in 214 infants who received monthly prophylaxis with palivizumab compared with 215 infants who received placebo. During the first year of life, infants and young children in the placebo group experienced 2309 days with wheezing from a total 51 726 patient days (4.5%), whereas those in the palivizumab group had 930 days of wheezing of 53 075 patient days (1.8%; $P = .01$). This represents an absolute 2.7 fewer days of wheezing per 100 patient days (17.5 wheezing days/1000 days vs 44.6 wheezing days/1000 days or 27.1 fewer wheezing days/1000 days) among infants who received monthly palivizumab in contrast to those who did not receive prophylaxis.¹⁶ Reliance on parent reporting of wheezing was identified as a potential limitation. The wheezing episodes were not

medically attended events but parent-reported wheezing of unknown severity.¹⁶ The proportion of infants using bronchodilators in the placebo group was 23% and 13% among palivizumab recipients.

Cost Analyses

Financial stewardship is a concept that acknowledges a physician's responsibility to advocate "for a just and cost-effective distribution of finite resources."^{121,122} Use of noncost-effective interventions contribute to maladies within the health care system, including huge deficits, lower quality of care, and inequitable access to health care.¹²³ Financial stewardship has become an essential component of successful reform of the existing health care system.

A number of economic analyses from different countries have evaluated immunoprophylaxis use in different age groups, among children with varying comorbidities and from both the payer and the societal perspective.²⁴ Economic evaluations sponsored by the manufacturer of palivizumab suggest cost neutrality or even cost savings.^{124–134} In contrast, analyses conducted by independent investigators consistently demonstrate the cost of palivizumab prophylaxis far exceeds the economic benefit of hospital avoidance, even among infants at highest risk.^{24,25,39–42,46,90,135–143} Variation in results are explained by differences in study methodology and different base case assumptions used in the model, such as incidence of RSV hospitalization for different risk groups, effectiveness of prophylaxis in reducing hospitalization rate by risk group, estimates of cost of prophylaxis and RSV hospitalizations avoided, number of doses administered, estimated age and weight of infants, and inclusion of a theoretical benefit on mortality reduction.

The CDC has recommended quality-adjusted life years (QALYs) saved as an optimal approach to evaluate the benefit of an intervention. One analysis using this methodology for hypothetical cohorts of infants without CLD born at 26 to 32 weeks' gestation revealed the incremental cost-effectiveness ratio to be greater than \$200 000 per QALY saved for all gestational ages, a figure not considered to be cost-effective.¹³⁵

An economic analysis funded by the manufacturer of palivizumab and published in the *Journal of Medical Economics* also examined incremental cost-effectiveness ratios per QALY gained in 4 groups of preterm infants without CLD and revealed the cost of treatment with palivizumab for infants 32 to 35 weeks' gestation with ≤ 1 risk factor was \$464 476, using an average cost for palivizumab for private and public payers. Medicaid discounts were reported to have resulted in an "approximate 40% reduction in palivizumab cost for approximately 60% of palivizumab recipients."¹²⁹ Nonetheless, in most state Medicaid programs, palivizumab is one of the most costly medication expenditures.

Cost was considered during deliberations by the COID and the Bronchiolitis Guidelines Committee, but the final guidance as presented in the accompanying Policy Statement is driven by the limited clinical benefit derived from palivizumab prophylaxis.

The American College of Physicians Clinical Guidelines Committee outlines principles to help clinicians define high-value health care by considering key concepts: benefits, harms and cost of the intervention, downstream costs that occur as a result of the intervention, and finally, the incremental cost-effectiveness ratio.¹⁴⁴ On the basis of these principles, the minimal clinical reduction in RSV hospitalizations and reduction in wheezing

episodes associated with palivizumab prophylaxis are not of sufficient clinical and societal importance to justify the cost. Although some RSV hospitalizations may be severe and prolonged, the majority of hospitalizations generally last 2 to 3 days. The high cost of palivizumab prophylaxis becomes a cost-inefficient way to prevent a few short hospitalization stays and a small number of longer hospital stays, especially in the absence of evidence of significant long-term benefit and no measurable effect on mortality.¹⁴⁴

Health expenditures should not be based only on cost and benefit but rather on the assessment of the benefit of the intervention relative to the expenditure. High-cost interventions may be appropriate if highly beneficial.¹⁴⁴ Because the high cost of palivizumab prophylaxis is associated with minimal health benefit, this intervention cannot be considered as high-value health care for any group of infants.

Control Measures

A critical aspect of RSV prevention among all infants is education of parents and other caregivers about the importance of decreasing exposure to and transmission of RSV. Preventive measures include limiting, where feasible, exposure to contagious settings (eg, child care centers) and emphasis on hand hygiene in all settings, including the home and the neonatal ICU, especially during periods when contacts of children at high risk have respiratory tract infections. For all children, the importance of breastfeeding, avoidance of crowds, and absence of exposure to tobacco smoke, including second-hand and third-hand exposure, should be emphasized.

Future Possibilities

Continued evaluation of the impact of palivizumab prophylaxis should include other groups considered to be

at increased risk of disease to evaluate reductions in RSV hospitalizations, as well as the effect of prophylaxis on medically attended outpatient visits.

Investigation of other types of passive immunoprophylaxis including anti-G monoclonal antibodies, should continue not only in prophylaxis but in treatment studies to modulate RSV disease severity.¹⁴⁵ Modification of the Fc fragment of the motavizumab molecule appears to prolong the half-life and theoretically may enable administration of fewer doses of motavizumab per season, although an increased risk of adverse effects remains a concern.^{107,146} Nanobodies are antibody-derived proteins consisting of functional heavy-chain antibodies that lack light chains and were initially found in camels and llamas. Nanobodies directed against the RSV fusion protein have demonstrated RSV-neutralizing activity in experimental models.¹⁴⁷

Ribavirin was licensed in 1986 and remains the only FDA-licensed antiviral agent for therapy but seldom is used because of limited efficacy, cumbersome delivery (aerosol), and high cost.⁵ Interest continues in developing more broadly effective antiviral agents including fusion inhibitors and small interfering RNA.^{148,149}

Development of a safe and effective RSV vaccine remains a high priority.^{150–153} Progress has been achieved with live-attenuated intranasal vaccines,¹⁵⁴ but ensuring adequate attenuation while maintaining immunogenicity remains a challenge. Early experience with a formalin-inactivated whole virus vaccine resulted in enhanced RSV disease in young children in the 1960s, which has complicated development of inactivated RSV vaccines.^{150,155} The demonstration of the effectiveness of passive prophylaxis with an anti-F monoclonal provides reassurance that antibody to the F protein is protective. New

subunit vaccines and particularly vaccines directed against the F protein administered intramuscularly or intranasally continue to be explored.^{150,155} A vaccine against a “prefusion” configuration of the F protein may offer increased efficacy with less risk of disease enhancement.¹⁵⁶ F protein viral-like particle vaccines administered during the latter half of pregnancy might offer passive protection for young children through the first months of life.^{157,158}

SUMMARY

The vast majority of RSV hospitalizations occur among healthy term infants. Immunoprophylaxis remains an option for a very small number of children, but palivizumab immunoprophylaxis will continue to have only a minimal effect on the burden of RSV disease. Effort should be made to avoid prophylaxis among infants and young children who do not qualify for prophylaxis, as outlined in the accompanying AAP policy statement.⁶

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REFERENCES

1. Synagis Package Insert. Gaithersburg, MD: MedImmune; April 2013. Available at: www.medimmune.com/docs/default-source/pdfs/prescribing-information-for-synagis.pdf. Accessed April 24, 2014
2. Huang K, Incognito L, Cheng X, Ulbrandt ND, Wu H. Respiratory syncytial virus-neutralizing monoclonal antibodies motavizumab and palivizumab inhibit fusion. *J Virol*. 2010;84(16):8132–8140
3. IMPact-RSV study group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102(3):531–537
4. Feltes TF, Cabalka AK, Meissner HC, et al; Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143(4):532–540
5. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2012:609–618
6. American Academy of Pediatrics. Policy statement: updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014; (in press)
7. American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics*. 1998;102(5):1211–1216
8. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics*. 2003;112(6 pt 1):1442–1446
9. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2006:560–566
10. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements—Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6):1694–1701
11. Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. *Antimicrob Agents Chemother*. 2012;56(9):4927–4936
12. Centers for Disease Control and Prevention (CDC). Respiratory syncytial virus activity—United States, July 2011–January 2013. *MMWR Morb Mortal Wkly Rep*. 2013; 62(8):141–144
13. Centers for Disease Control and Prevention (CDC). Respiratory syncytial virus—United States, July 2007–June 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(35):1203–1206

14. Hasegawa K, Tsugawa Y, Brown DFM, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. *Pediatrics*. 2013;132(1):28-36
15. Byington CL, Wilkes J, Sheng X, Korgenski K. Respiratory syncytial virus associated mortality in hospitalized United States infants and children less than 2 years of age. Presented at the Pediatric Academic Societies Annual Meeting; May 4-7, 2013; Washington, DC. Abstract 2915.181
16. Blanken MO, Rovers MM, Molenaar JM, et al; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013;368(19):1791-1799
17. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA; C-CREW Investigators. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics*. 2013;132(5):811-818
18. Bloemers BL, van Furth AM, Weijerman ME, et al. High incidence of recurrent wheeze in children with Down syndrome with and without previous respiratory syncytial virus lower respiratory tract infection. *Pediatr Infect Dis J*. 2010;29(1):39-42
19. Megged O, Schlesinger Y. Down syndrome and respiratory syncytial virus infection. *Pediatr Infect Dis J*. 2010;29(7):672-673
20. Robinson KA, Odelola OA, Saldanha IJ, McKoy NA. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. *Cochrane Database Syst Rev*. 2012;2(2):CD007743
21. Zhu Q, McAuliffe JM, Patel NK, et al. Analysis of respiratory syncytial virus pre-clinical and clinical variants resistant to neutralization by monoclonal antibodies palivizumab and/or motavizumab. *J Infect Dis*. 2011;203(5):674-682
22. Zhu Q, Patel NK, McAuliffe JM, et al. Natural polymorphisms and resistance-associated mutations in the fusion protein of respiratory syncytial virus (RSV): effects on RSV susceptibility to palivizumab. *J Infect Dis*. 2012;205(4):635-638
23. Boivin G, Caouette G, Frenette L, Carbonneau J, Ouakki M, De Serres G. Human respiratory syncytial virus and other viral infections in infants receiving palivizumab. *J Clin Virol*. 2008;42(1):52-57
24. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane Database Syst Rev*. 2013;4(4):CD006602
25. Hamp C, Kauf TL, Saidi AS, Winterstein AG. Cost-effectiveness of respiratory syncytial virus prophylaxis in various indications. *Arch Pediatr Adolesc Med*. 2011;165(6):498-505
26. Carroll KN, Griffin MR, Edwards KM, et al. Adherence to guidelines for respiratory syncytial virus immunoprophylaxis among infants with prematurity or chronic lung disease in three United States counties. *Pediatr Infect Dis J*. 2012;31(11):e229-e231
27. Hamp C, Saidi AS, Winterstein AG. Palivizumab utilization and compliance: trends in respiratory syncytial virus prophylaxis in Florida. *J Pediatr*. 2010;156(6):953-959, e1
28. Public Health England. Respiratory syncytial virus. In: *Green Book*. London, England: Public Health England; 2013:1-13. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/148494/Green-Book-Chapter-27a-dh_130131.pdf. Accessed April 24, 2014
29. Fitzgerald DA. Preventing RSV bronchiolitis in vulnerable infants: the role of palivizumab. *Paediatr Respir Rev*. 2009;10(3):143-147
30. Langley GF, Anderson LJ. Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. *Pediatr Infect Dis J*. 2011;30(6):510-517
31. Leader S, Kohlhasse K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143(suppl 5):S127-S132
32. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282(15):1440-1446
33. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langley G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997-2006. *Pediatr Infect Dis J*. 2012;31(1):5-9
34. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics*. 2013;132(2). Available at: www.pediatrics.org/cgi/content/full/132/2/e341
35. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588-598
36. Zhou H, Thompson WW, Viboud C, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. *Clin Infect Dis*. 2012;54(10):1427-1436
37. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. *Natl Vital Stat Rep*. 2013;62(3):1-20
38. Boyce TG, Mellen BG, Mitchel EF, Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr*. 2000;137(6):865-870
39. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. *Arch Pediatr Adolesc Med*. 2000;154(1):55-61
40. Winterstein AG, Knox CA, Kubilis P, Hamp C. Appropriateness of age thresholds for respiratory syncytial virus immunoprophylaxis in moderate-preterm infants: a cohort study. *JAMA Pediatr*. 2013;167(12):1118-1124
41. Chang RKR, Chen AY. Impact of palivizumab on RSV hospitalizations for children with hemodynamically significant congenital heart disease. *Pediatr Cardiol*. 2010;31(1):90-95
42. Yount LE, Mahle WT. Economic analysis of palivizumab in infants with congenital heart disease. *Pediatrics*. 2004;114(6):1606-1611
43. Meberg A, Bruu AL. Respiratory syncytial virus infections in congenital heart defects—hospitalizations and costs. *Acta Paediatr*. 2006;95(4):404-406
44. Duppenhaler A, Ammann RA, Gorgievski-Hrisoho M, Pfammatter JP, Aebi C. Low incidence of respiratory syncytial virus hospitalisations in haemodynamically significant congenital heart disease. *Arch Dis Child*. 2004;89(10):961-965
45. Geskey JM, Thomas NJ, Brummel GL. Palivizumab in congenital heart disease: should international guidelines be revised? *Expert Opin Biol Ther*. 2007;7(11):1615-1620
46. Harris KC, Anis AH, Crosby MC, Gender LM, Potts JE, Human DG. Economic evaluation of palivizumab in children with congenital heart disease: a Canadian perspective. *Can J Cardiol*. 2011;27(4):523.e11-523.e15
47. Resch B, Manzoni P, Lanari M. Severe respiratory syncytial virus (RSV) infection in infants with neuromuscular diseases and immune deficiency syndromes. *Paediatr Respir Rev*. 2009;10(3):148-153
48. Wilkesmann A, Ammann RA, Schildgen O, et al; DSM RSV Ped Study Group. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. *Pediatr Infect Dis J*. 2007;26(6):485-491
49. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and

- treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis*. 2013;56(2):258–266
50. Shah DP, Ghantaji SS, Shah JN, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. *J Antimicrob Chemother*. 2013;68(8):1872–1880
 51. Kim YJ, Guthrie KA, Wagmare A, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. *J Infect Dis*. 2014;209(8):1195–1204
 52. El Saleeby CM, Somes GW, DeVincenzo JP, Gaur AH. Risk factors for severe respiratory syncytial virus disease in children with cancer: the importance of lymphopenia and young age. *Pediatrics*. 2008;121(2):235–243
 53. Asner S, Stephens D, Pedulla P, Richardson SE, Robinson J, Allen U. Risk factors and outcomes for respiratory syncytial virus-related infections in immunocompromised children. *Pediatr Infect Dis J*. 2013;32(10):1073–1076
 54. Chemaly RF, Ghantaji SS, Shah DP, et al. Respiratory syncytial virus infections in children with cancer. *J Pediatr Hematol Oncol*. 2013; doi:10.1097/MPH.0000000000000086
 55. Lo MS, Lee GM, Gunawardane N, Burchett SK, Lachenauer CS, Lehmann LE. The impact of RSV, adenovirus, influenza, and parainfluenza infection in pediatric patients receiving stem cell transplant, solid organ transplant, or cancer chemotherapy. *Pediatr Transplant*. 2013;17(2):133–143
 56. Renaud C, Xie H, Seo S, et al. Mortality rates of human metapneumovirus and respiratory syncytial virus lower respiratory tract infections in hematopoietic cell transplantation recipients. *Biol Blood Marrow Transplant*. 2013;19(8):1220–1226
 57. Seo S, Campbell AP, Xie H, et al. Outcome of respiratory syncytial virus lower respiratory tract disease in hematopoietic cell transplant recipients receiving aerosolized ribavirin: significance of stem cell source and oxygen requirement. *Biol Blood Marrow Transplant*. 2013;19(4):589–596
 58. Michaels MG, Fonseca-Aten M, Green M, et al. Respiratory syncytial virus prophylaxis: a survey of pediatric solid organ transplant centers. *Pediatr Transplant*. 2009;13(4):451–456
 59. Danziger-Isakov LA, Arslan D, Sweet S, Benden C, Goldfarb S, Wong J. RSV prevention and treatment in pediatric lung transplant patients: a survey of current practices among the International Pediatric Lung Transplant Collaborative. *Pediatr Transplant*. 2012;16(6):638–644
 60. Bloemers BL, van Furth AM, Weijerman ME, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis—a prospective birth-cohort study. *Pediatrics*. 2007;120(4). Available at: www.pediatrics.org/cgi/content/full/120/4/e1076
 61. Zachariah P, Rutenber M, Simões EA. Down syndrome and hospitalizations due to respiratory syncytial virus: a population-based study. *J Pediatr*. 2012;160(5):827–831, e1
 62. Giebels K, Marcotte JE, Podoba J, et al. Prophylaxis against respiratory syncytial virus in young children with cystic fibrosis. *Pediatr Pulmonol*. 2008;43(2):169–174
 63. Winterstein AG, Eworuke E, Xu D, Schuler P. Palivizumab immunoprophylaxis effectiveness in children with cystic fibrosis. *Pediatr Pulmonol*. 2013;48(9):874–884
 64. Cohen AH, Boron ML, Dingivan C. A phase IV study of the safety of palivizumab for prophylaxis of RSV disease in children with cystic fibrosis. [abstr] *Proc Am Thorac Soc*. 2005;2:A178
 65. Kristensen K, Hjulter T, Ravn H, Simões EAF, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. *Clin Infect Dis*. 2012;54(6):810–817
 66. Elnazir B, Oni O, Hassan T, Greally P, Paes B. Does prophylaxis with palivizumab reduce hospitalisation rates for respiratory-syncytial-virus-related infection in cystic fibrosis children less than 2 years of age? *J Paediatr Child Health*. 2012;48(11):1033–1038
 67. Giusti R. North American synagis prophylaxis survey. *Pediatr Pulmonol*. 2009;44(1):96–98
 68. Yamaguchi M, Sano Y, Daput IC, et al. High frequency of repeated infections due to emerging genotypes of human respiratory syncytial viruses among children during eight successive epidemic seasons in Japan. *J Clin Microbiol*. 2011;49(3):1034–1040
 69. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med*. 2001;344(25):1917–1928
 70. Henderson FW, Collier AM, Clyde WA, Jr, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. *N Engl J Med*. 1979;300(10):530–534
 71. Lacaze-Masmonteil T, Seidenberg J, Mitchell I, et al; Second Season Safety Study Group. Evaluation of the safety of palivizumab in the second season of exposure in young children at risk for severe respiratory syncytial virus infection. *Drug Saf*. 2003;26(4):283–291
 72. Null D, Jr, Pollara B, Dennehy PH, et al. Safety and immunogenicity of palivizumab (Synagis) administered for two seasons. *Pediatr Infect Dis J*. 2005;24(11):1021–1023
 73. Malley R, DeVincenzo J, Ramilo O, et al. Reduction of respiratory syncytial virus (RSV) in tracheal aspirates in intubated infants by use of humanized monoclonal antibody to RSV F protein. *J Infect Dis*. 1998;178(6):1555–1561
 74. Ramilo O, Sagos R, Saez-Llorens X, et al. Motavizumab treatment of infants hospitalized with respiratory syncytial virus infection does not decrease viral load or severity of illness. *Pediatr Infect Dis J*. 2014;33(7):703–709
 75. Berger A, Obwegeser E, Aberle SW, Langgartner M, Popow-Kraupp T. Nosocomial transmission of respiratory syncytial virus in neonatal intensive care and intermediate care units: a prospective epidemiologic study. *Pediatr Infect Dis J*. 2010;29(7):669–670
 76. Katz BZ, Sullivan C. Respiratory syncytial virus prophylaxis in a tertiary care neonatal intensive care unit. *Pediatr Infect Dis J*. 2009;28(9):842–844
 77. Ohler KH, Pham JT. Comparison of the timing of initial prophylactic palivizumab dosing on hospitalization of neonates for respiratory syncytial virus. *Am J Health Syst Pharm*. 2013;70(15):1342–1346
 78. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003;143(suppl 5):S118–S126
 79. Meissner HC, Bocchini JA, Jr, Brady MT, Hall CB, Kimberlin DW, Pickering LK. The role of immunoprophylaxis in the reduction of disease attributable to respiratory syncytial virus. *Pediatrics*. 2009;124(6):1676–1679
 80. Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics*. 2011;127(6). Available at: www.pediatrics.org/cgi/content/full/127/6/e1513
 81. Carbonell-Estrany X, Quero J, Bustos G, et al; IRIS Study Group. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. *Pediatr Infect Dis J*. 2000;19(7):592–597
 82. Carbonell-Estrany X, Quero J; IRIS Study Group. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. *Pediatr Infect Dis J*. 2001;20(9):874–879

83. Choudhuri JA, Ogden LG, Ruttenber AJ, Thomas DSK, Todd JK, Simoes EAF. Effect of altitude on hospitalizations for respiratory syncytial virus infection. *Pediatrics*. 2006; 117(2):349–356
84. Figueras-Aloy J, Carbonell-Estrany X, Quero J; IRIS Study Group. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain. *Pediatr Infect Dis J*. 2004;23(9):815–820
85. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J*. 2004;23(9):806–814
86. Meissner HC, Hall CB. Respiratory syncytial virus. In: Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ, eds. *Feigin & Cherry's Textbook of Pediatric Infectious Diseases*, 7th ed. Philadelphia, PA: Elsevier Saunders; 2013:2407–2434
87. Hervás D, Reina J, Hervás JA. Meteorologic conditions and respiratory syncytial virus activity. *Pediatr Infect Dis J*. 2012;31(10):e176–e181
88. Nielsen HE, Siersma V, Andersen S, et al. Respiratory syncytial virus infection—risk factors for hospital admission: a case-control study. *Acta Paediatr*. 2003;92(11):1314–1321
89. Paynter S, Ware RS, Lucero MG, et al. Malnutrition: a risk factor for severe respiratory syncytial virus infection and hospitalization. *Pediatr Infect Dis J*. 2014; 33(3):267–271
90. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. *Health Technol Assess*. 2011;15(5):iii–iv, 1–124
91. Wang EE, Law BJ, Robinson JL, et al. PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) study of the role of age and respiratory syncytial virus neutralizing antibody on respiratory syncytial virus illness in patients with underlying heart or lung disease. *Pediatrics*. 1997;99(3). Available at: www.pediatrics.org/cgi/content/full/99/3/e9 PubMed
92. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr*. 1995;126(2):212–219
93. Zachariah P, Ruttenber M, Simões EA. Hospitalizations due to respiratory syncytial virus in children with congenital malformations. *Pediatr Infect Dis J*. 2011; 30(5):442–445
94. Le Saux N, Gaboury I, MacDonald N. Maternal respiratory syncytial virus antibody titers: season and children matter. *Pediatr Infect Dis J*. 2003;22(6):563–564
95. Panozzo CA, Fowlkes AL, Anderson LJ. Variation in timing of respiratory syncytial virus outbreaks: lessons from national surveillance. *Pediatr Infect Dis J*. 2007;26(suppl 11):S41–S45
96. Banerji A, Bell A, Mills EL, et al. Lower respiratory tract infections in Inuit infants on Baffin Island. *CMAJ*. 2001;164(13):1847–1850
97. Singleton RJ, Bulkow LR, Miernyk K, et al. Viral respiratory infections in hospitalized and community control children in Alaska. *J Med Virol*. 2010;82(7):1282–1290
98. Tam DY, Banerji A, Paes BA, Hui C, Tarride JE, Lanctôt KL. The cost effectiveness of palivizumab in term Inuit infants in the Eastern Canadian Arctic. *J Med Econ*. 2009;12(4):361–370
99. Young M, Kandola K, Mitchell R, Leamon A. Hospital admission rates for lower respiratory tract infections in infants in the Northwest Territories and the Kitikmeot region of Nunavut between 2000 and 2004. *Paediatr Child Health (Oxford)*. 2007;12(7):563–566
100. Alaska State Virology Laboratory Weekly Report, April 12–19, 2004. Available at: http://dhss.alaska.gov/dph/labs/documents/pdfs/ASVL_WeeklyReport.pdf. Accessed April 24, 2014
101. Bockova J, O'Brien KL, Oski J, et al. Respiratory syncytial virus infection in Navajo and White Mountain Apache children. *Pediatrics*. 2002;110(2 pt 1). Available at: www.pediatrics.org/cgi/content/full/110/2/e20
102. Lowther SA, Shay DK, Holman RC, Clarke MJ, Kaufman SF, Anderson LJ. Bronchiolitis-associated hospitalizations among American Indian and Alaska Native children. *Pediatr Infect Dis J*. 2000;19(1):11–17
103. Subramanian KN, Weisman LE, Rhodes T, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. *Pediatr Infect Dis J*. 1998;17(2):110–115
104. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J Infect Dis*. 1997;176(5):1215–1224
105. Iwane MK, Chaves SS, Szilagyi PG, et al. Disparities between black and white children in hospitalizations associated with acute respiratory illness and laboratory-confirmed influenza and respiratory syncytial virus in 3 US counties—2002–2009. *Am J Epidemiol*. 2013;177(7):656–665
106. Welliver RC, Sr, Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, Hall CB. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. *Curr Med Res Opin*. 2010;26(9):2175–2181
107. US Food and Drug Administration. Memorandum. Background package for BLA 125283 motavizumab. 2010. Available at: www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/antiviraladvisorycommittee/ucm213825.pdf. Accessed April 24, 2014
108. Wu H, Pfarr DS, Johnson S, et al. Development of motavizumab, an ultrapotent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *J Mol Biol*. 2007;368(3):652–665
109. Carbonell-Estrany X, Simões EA, Dagan R, et al; Motavizumab Study Group. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a non-inferiority trial. *Pediatrics*. 2010;125(1). Available at: www.pediatrics.org/cgi/content/full/125/1/e35
110. Abarca K, Jung E, Fernández P, et al; Motavizumab Study Group. Safety, tolerability, pharmacokinetics, and immunogenicity of motavizumab, a humanized, enhanced-potency monoclonal antibody for the prevention of respiratory syncytial virus infection in at-risk children. *Pediatr Infect Dis J*. 2009;28(4):267–272
111. Fernández P, Trenholme A, Abarca K, et al; Motavizumab Study Group. A phase 2, randomized, double-blind safety and pharmacokinetic assessment of respiratory syncytial virus (RSV) prophylaxis with motavizumab and palivizumab administered in the same season. *BMC Pediatr*. 2010;10:38
112. Feltes TF, Sondheimer HM, Tulloh RM, et al; Motavizumab Cardiac Study Group. A randomized controlled trial of motavizumab versus palivizumab for the prophylaxis of serious respiratory syncytial virus disease in children with hemodynamically significant congenital heart disease. *Pediatr Res*. 2011; 70(2):186–191
113. Bourgeois FT, Valim C, McAdam AJ, Mandl KD. Relative impact of influenza and respiratory syncytial virus in young children. *Pediatrics*. 2009;124(6). Available at: www.pediatrics.org/cgi/content/full/124/6/e1072

114. Adams O, Bonzel L, Kovacevic A, Mayatepek E, Hoehn T, Vogel M. Palivizumab-resistant human respiratory syncytial virus infection in infancy. *Clin Infect Dis*. 2010;51(2):185–188
115. Galöşkan M, Bochkov YA, Kreiner-Møller E, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med*. 2013;368(15):1398–1407
116. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178(7):667–672
117. Poorisrisak P, Halkjaer LB, Thomsen SF, et al. Causal direction between respiratory syncytial virus bronchiolitis and asthma studied in monozygotic twins. *Chest*. 2010;138(2):338–344
118. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171(2):137–141
119. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354(9178):541–545
120. Simoes EA, Groothuis JR, Carbonell-Estrany X, et al; Palivizumab Long-Term Respiratory Outcomes Study Group. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr*. 2007;151(1):34–42, e1
121. Cassel CK, Guest JA. Choosing wisely: helping physicians and patients make smart decisions about their care. *JAMA*. 2012;307(17):1801–1802
122. ABIM Foundation. American Board of Internal Medicine; ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine; European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med*. 2002;136(3):243–246
123. Ubel PA, Jagsi R. Promoting population health through financial stewardship. *N Engl J Med*. 2014;370(14):1280–1281
124. Bentley A, Filipovic I, Gooch K, Buesch K. A cost-effectiveness analysis of respiratory syncytial virus (RSV) prophylaxis in infants in the UK. *Thorax*. 2011;66(suppl 4):A136
125. Bentley A, Filipovic I, Gooch K, Büsch K. A cost-effectiveness analysis of respiratory syncytial virus (RSV) prophylaxis in infants in the United Kingdom. *Health Econ Rev*. 2013;3(1):18
126. Chirico G, Ravasio R, Sbarigia U. Cost-utility analysis of palivizumab in Italy: results from a simulation model in the prophylaxis of respiratory syncytial virus infection (RSV) among high-risk preterm infants. *Ital J Pediatr*. 2009;35(1):4
127. Krilov LR, Weiner LB, Yögev R, et al. The 2009 COLD recommendations for RSV prophylaxis: issues of efficacy, cost, and evidence-based medicine. *Pediatrics*. 2009;124(6):1682–1684
128. Lanctôt KL, Masoud ST, Paes BA, et al. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32–35 weeks: a Canadian-based analysis. *Curr Med Res Opin*. 2008;24(11):3223–3237
129. Mahadevia PJ, Masaquel AS, Polak MJ, Weiner LB. Cost utility of palivizumab prophylaxis among pre-term infants in the United States: a national policy perspective. *J Med Econ*. 2012;15(5):987–996
130. Neovius K, Buesch K, Sandström K, Neovius M. Cost-effectiveness analysis of palivizumab as respiratory syncytial virus prophylaxis in preterm infants in Sweden. *Acta Paediatr*. 2011;100(10):1306–1314
131. Nuijten MJC, Wittenberg W, Lebmeier M. Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: a UK analysis. *Pharmacoeconomics*. 2007;25(1):55–71
132. Paes B, Mitchell I, Li A, Lanctôt KL; CARESS Investigators. A comparative study of respiratory syncytial virus (RSV) prophylaxis in premature infants within the Canadian Registry of Palivizumab (CARESS). *Eur J Clin Microbiol Infect Dis*. 2012;31(10):2703–2711
133. Smart KA, Lanctôt KL, Paes BA. The cost effectiveness of palivizumab: a systematic review of the evidence. *J Med Econ*. 2010;13(3):453–463
134. Weiner LB, Masaquel AS, Polak MJ, Mahadevia PJ. Cost-effectiveness analysis of palivizumab among pre-term infant populations covered by Medicaid in the United States. *J Med Econ*. 2012;15(5):997–1018
135. Elhassan NO, Sorbero MES, Hall CB, Stevens TP, Dick AW. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. *Arch Pediatr Adolesc Med*. 2006;160(10):1070–1076
136. Embleton ND, Dharmaraj ST, Deshpande S. Cost-effectiveness of palivizumab in infancy. *Expert Rev Pharmacoecon Outcomes Res*. 2007;7(5):445–458
137. Handforth J, Sharland M, Friedland JS. Prevention of respiratory syncytial virus infection in infants. *BMJ*. 2004;328(7447):1026–1027
138. Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics*. 1999;104(3 pt 1):419–427
139. Liese JG, Grill E, Fischer B, Roeckl-Wiedmann I, Carr D, Belohradsky BH; Munich RSV Study Group. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. *Eur J Pediatr*. 2003;162(4):230–236
140. Prescott WA, Jr, Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. *Pharmacoeconomics*. 2010;28(4):279–293
141. Prescott WA, Jr, Hutchinson DJ. Respiratory syncytial virus prophylaxis in special populations: Is it something worth considering in cystic fibrosis and immunosuppression? *J Pediatr Pharmacol Ther*. 2011;16(2):77–86
142. Rietveld E, Steyerberg EW, Polder JJ, et al. Passive immunisation against respiratory syncytial virus: a cost-effectiveness analysis. *Arch Dis Child*. 2010;95(7):493–498
143. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. *Pediatrics*. 2004;114(6):1612–1619
144. Owens DK, Qaseem A, Chou R, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. *Ann Intern Med*. 2011;154(3):174–180
145. Kauvar LM, Harcourt JL, Haynes LM, Tripp RA. Therapeutic targeting of respiratory syncytial virus G-protein. *Immunotherapy*. 2010;2(5):655–661
146. Robbie GJ, Criste R, Dall'acqua WF, et al. A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE, has an extended half-life in healthy adults. *Antimicrob Agents Chemother*. 2013;57(12):6147–6153
147. Schepens B, Ibañez LI, De Baets S, et al. Nanobodies® specific for respiratory syncytial virus fusion protein protect against infection by inhibition of fusion. *J Infect Dis*. 2011;204(11):1692–1701
148. DeVincenzo J, Lambkin-Williams R, Wilkinson T, et al. A randomized, double-blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus. *Proc Natl Acad Sci USA*. 2010;107(19):8800–8805
149. Empey KM, Peebles RS, Jr, Kolls JK. Pharmacologic advances in the treatment and prevention of respiratory syncytial virus. *Clin Infect Dis*. 2010;50(9):1258–1267

150. Graham BS. Biological challenges and technological opportunities for respiratory syncytial virus vaccine development. *Immunol Rev*. 2011;239(1):149–166
151. Haynes LM. Progress and challenges in RSV prophylaxis and vaccine development. *J Infect Dis*. 2013;208(suppl 3):S177–S183
152. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010;375(9725):1545–1555
153. Régnier SA. Respiratory syncytial virus immunization program for the United States: impact of performance determinants of a theoretical vaccine. *Vaccine*. 2013;31(40):4347–4354
154. Luongo C, Winter CC, Collins PL, Buchholz UJ. Respiratory syncytial virus modified by deletions of the NS2 gene and amino acid S1313 of the L polymerase protein is a temperature-sensitive, live-attenuated vaccine candidate that is phenotypically stable at physiological temperature. *J Virol*. 2013;87(4):1985–1996
155. Rigter A, Widjaja I, Versantvoort H, et al. A protective and safe intranasal RSV vaccine based on a recombinant prefusion-like form of the F protein bound to bacterium-like particles. *PLoS ONE*. 2013;8(8):e71072
156. Magro M, Mas V, Chappell K, et al. Neutralizing antibodies against the preactive form of respiratory syncytial virus fusion protein offer unique possibilities for clinical intervention. *Proc Natl Acad Sci USA*. 2012;109(8):3089–3094
157. Glenn GM, Smith G, Fries L, et al. Safety and immunogenicity of a Sf9 insect cell-derived respiratory syncytial virus fusion protein nanoparticle vaccine. *Vaccine*. 2013;31(3):524–532
158. McLellan JS, Chen M, Joyce MG, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. *Science*. 2013;342(6158):592–598

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COMMITTEE ON INFECTIOUS DISEASES AND BRONCHIOLITIS
GUIDELINES COMMITTEE**KEY WORDS**

RSV, respiratory syncytial virus, palivizumab, bronchiolitis, infants and young children, chronic lung disease, congenital heart disease

ABBREVIATIONSAAP—American Academy of Pediatrics
CHD—congenital heart disease
CLD—chronic lung disease
COID—Committee on Infectious Diseases
RSV—respiratory syncytial virus

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abstract

FREE

Palivizumab was licensed in June 1998 by the Food and Drug Administration for the reduction of serious lower respiratory tract infection caused by respiratory syncytial virus (RSV) in children at increased risk of severe disease. Since that time, the American Academy of Pediatrics has updated its guidance for the use of palivizumab 4 times as additional data became available to provide a better understanding of infants and young children at greatest risk of hospitalization attributable to RSV infection. The updated recommendations in this policy statement reflect new information regarding the seasonality of RSV circulation, palivizumab pharmacokinetics, the changing incidence of bronchiolitis hospitalizations, the effect of gestational age and other risk factors on RSV hospitalization rates, the mortality of children hospitalized with RSV infection, the effect of prophylaxis on wheezing, and palivizumab-resistant RSV isolates. This policy statement updates and replaces the recommendations found in the 2012 *Red Book. Pediatrics* 2014;134:415–420

Policy statements from the American Academy of Pediatrics (AAP) are designed to provide updated guidance for child health care topics, with an emphasis on evidence-based recommendations whenever possible. Policy statements are reviewed at least every 3 years and updated when appropriate. In following this procedure, the AAP Committee on Infectious Diseases (COID) has undertaken a systematic review of all recent and older peer-reviewed literature relating to the burden of respiratory syncytial virus (RSV) disease in infants and children, focusing on publications that delineate children at greatest risk of serious RSV disease and studies that define pharmacokinetics, safety, and efficacy. Detailed input regarding this guidance has been solicited from 21 committees, councils, sections, and advisory groups within the AAP, as well as organizations outside the AAP. Outside groups include the American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Emergency Nurses Association, National Association of Neonatal Nurses, National Association of Neonatal Nurse Practitioners, and Society of Hospital

Medicine. In addition, this review includes all data presented to the COID by the manufacturer of palivizumab.

As part of this deliberative review of palivizumab use, the COID judged the quality of the available data, as well as the impact of palivizumab prophylaxis to reach a unanimous consensus on guidance for the use of palivizumab in the United States. Cost was considered during deliberations by the COID and Bronchiolitis Guideline Committee, but the final guidance as presented here is driven by the limited clinical benefit derived from palivizumab prophylaxis.^{1–3}

As detailed in the accompanying technical report,⁴ the benefit resulting from this drug is limited. Palivizumab prophylaxis has limited effect on RSV hospitalizations on a population basis, no measurable effect on mortality, and a minimal effect on subsequent wheezing.

This policy statement updates and replaces the most recent AAP recommendations for the use of palivizumab prophylaxis published in 2012 in the 29th edition of the *Red Book*.⁵ This policy statement offers specific guidance for the use of palivizumab on the basis of available evidence, as well as expert opinion. A detailed discussion of the foundation of the updated guidance for each category as well as the references for each section may be found in the accompanying technical report,⁴ and AAP guidelines for the diagnosis and management of bronchiolitis, which were published in 2006⁶ (for which a revision is forthcoming).

The palivizumab package insert states: “Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.”⁷ In the absence of a specific definition of “high risk” by the US Food and Drug Administration, the AAP has endeavored to provide pediatricians and other health care providers with more

precise guidance for determining who is at increased risk since palivizumab was first licensed.^{5,8–11}

The informed opinion of the COID and the Bronchiolitis Guidelines Committee, as well as others participating in the current statement, is that palivizumab use should be restricted to the populations detailed below.

PRETERM INFANTS WITHOUT CHRONIC LUNG DISEASE OF PREMATURITY OR CONGENITAL HEART DISEASE

Palivizumab prophylaxis may be administered to infants born before 29 weeks, 0 days’ gestation who are younger than 12 months at the start of the RSV season. For infants born during the RSV season, fewer than 5 monthly doses will be needed.

Available data for infants born at 29 weeks, 0 days’ gestation or later do not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear. For this reason, infants born at 29 weeks, 0 days’ gestation or later are not universally recommended to receive palivizumab prophylaxis. Infants 29 weeks, 0 days’ gestation or later may qualify to receive prophylaxis on the basis of congenital heart disease (CHD), chronic lung disease (CLD), or another condition.

Palivizumab prophylaxis is not recommended in the second year of life on the basis of a history of prematurity alone.

Some experts believe that on the basis of the data quantifying a small increase in risk of hospitalization, even for infants born earlier than 29 weeks, 0 days’ gestation, palivizumab prophylaxis is not justified.

PRETERM INFANTS WITH CLD

Prophylaxis may be considered during the RSV season during the first year of life for preterm infants who develop

CLD of prematurity defined as gestational age <32 weeks, 0 days and a requirement for >21% oxygen for at least the first 28 days after birth.

During the second year of life, consideration of palivizumab prophylaxis is recommended only for infants who satisfy this definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life prophylaxis is not recommended.

INFANTS WITH HEMODYNAMICALLY SIGNIFICANT CHD

Certain children who are 12 months or younger with hemodynamically significant CHD may benefit from palivizumab prophylaxis. Children with hemodynamically significant CHD who are most likely to benefit from immunoprophylaxis include infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension.

Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist.

These recommendations apply to qualifying infants in the first year of life who are born within 12 months of onset of the RSV season.

The following groups of infants with CHD are not at increased risk of RSV infection and generally should not receive immunoprophylaxis:

- Infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal

defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus)

- Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
- Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
- Children in the second year of life

Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that involve cardiopulmonary bypass, for children who are receiving prophylaxis and who continue to require prophylaxis after a surgical procedure, a post-operative dose of palivizumab (15 mg/kg) should be considered after cardiac bypass or at the conclusion of extracorporeal membrane oxygenation for infants and children younger than 24 months.

Children younger than 2 years who undergo cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis.

CHILDREN WITH ANATOMIC PULMONARY ABNORMALITIES OR NEUROMUSCULAR DISORDER

No prospective studies or population-based data are available to define the risk of RSV hospitalization in children with pulmonary abnormalities or neuromuscular disease. Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough are known to be at risk for a prolonged hospitalization related to lower respiratory tract infection and, therefore, may be considered for prophylaxis during the first year of life.

IMMUNOCOMPROMISED CHILDREN

No population based data are available on the incidence of RSV hospitalization in children who undergo solid organ or hematopoietic stem cell transplantation. Severe and even fatal disease attributable to RSV is recognized in children receiving chemotherapy or who are immunocompromised because of other conditions, but the efficacy of prophylaxis in this cohort is not known. Prophylaxis may be considered for children younger than 24 months of age who are profoundly immunocompromised during the RSV season.

CHILDREN WITH DOWN SYNDROME

Limited data suggest a slight increase in RSV hospitalization rates among children with Down syndrome. However, data are insufficient to justify a recommendation for routine use of prophylaxis in children with Down syndrome unless qualifying heart disease, CLD, airway clearance issues, or prematurity (<29 weeks, 0 days' gestation) is present.

CHILDREN WITH CYSTIC FIBROSIS

Routine use of palivizumab prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present. An infant with cystic fibrosis with clinical evidence of CLD and/or nutritional compromise in the first year of life may be considered for prophylaxis. Continued use of palivizumab prophylaxis in the second year may be considered for infants with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persist when stable) or weight for length less than the 10th percentile.

RECOMMENDATIONS FOR TIMING OF PROPHYLAXIS FOR ALASKA NATIVE AND AMERICAN INDIAN INFANTS

On the basis of the epidemiology of RSV in Alaska, particularly in remote regions where the burden of RSV disease is significantly greater than the general US population, the selection of Alaska Native infants eligible for prophylaxis may differ from the remainder of the United States. Clinicians may wish to use RSV surveillance data generated by the state of Alaska to assist in determining onset and end of the RSV season for qualifying infants.

Limited information is available concerning the burden of RSV disease among American Indian populations. However, special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life.

DISCONTINUATION OF PALIVIZUMAB PROPHYLAXIS AMONG CHILDREN WHO EXPERIENCE BREAKTHROUGH RSV HOSPITALIZATION

If any infant or young child receiving monthly palivizumab prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization in the same season (<0.5%).

USE OF PALIVIZUMAB IN THE SECOND YEAR OF LIFE

Hospitalization rates attributable to RSV decrease during the second RSV season for all children. A second season of palivizumab prophylaxis is recommended only for preterm infants born at <32 weeks, 0 days' gestation who required at least 28 days of oxygen after birth and who continue to require

supplemental oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of the start of the second RSV season.

LACK OF THERAPEUTIC EFFICACY OF PALIVIZUMAB

Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.

PREVENTION OF HEALTH CARE-ASSOCIATED RSV DISEASE

No rigorous data exist to support palivizumab use in controlling outbreaks of health care-associated disease, and palivizumab use is not recommended for this purpose. Infants in a neonatal unit who qualify for prophylaxis because of CLD, prematurity, or CHD may receive the first dose 48 to 72 hours before discharge to home or promptly after discharge.

Strict adherence to infection-control practices is the basis for reducing health care-associated RSV disease.

RSV SEASONALITY

Because 5 monthly doses of palivizumab at 15 mg/kg per dose will provide more than 6 months (>24 weeks) of serum palivizumab concentrations above the desired level for most children, administration of more than 5 monthly doses is not recommended within the continental United States. For qualifying infants who require 5 doses, a dose beginning in November and continuation for a total of 5 monthly doses will provide protection for most infants through April and is recommended for most areas of the United States. If prophylaxis is initiated in October, the fifth and final dose should be administered in February, which will provide protection for most infants through March. If

prophylaxis is initiated in December, the fifth and final dose should be administered in April, which will provide protection for most infants through May.

Variation in the onset and offset of the RSV season in different regions of Florida may affect the timing of palivizumab administration. Data from the Florida Department of Health may be used to determine the appropriate timing for administration of the first dose of palivizumab for qualifying infants. Despite varying onset and offset dates of the RSV season in different regions of Florida, a maximum of 5 monthly doses of palivizumab should be adequate for qualifying infants for most RSV seasons in Florida.

Sporadic RSV infections occur throughout the year in most geographic locations. During times of low RSV prevalence (regardless of proportion of positive results), prophylaxis with palivizumab provides the least benefit because of the large number of children who must receive prophylaxis to prevent 1 RSV hospitalization.

EFFECT OF PALIVIZUMAB PROPHYLAXIS ON SUBSEQUENT WHEEZING

Prophylaxis is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.

SUMMARY OF GUIDANCE

- In the first year of life, palivizumab prophylaxis is recommended for infants born before 29 weeks, 0 days' gestation.
- Palivizumab prophylaxis is not recommended for otherwise healthy infants born at or after 29 weeks, 0 days' gestation.
- In the first year of life, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at <32 weeks, 0 days'

gestation and a requirement for >21% oxygen for at least 28 days after birth.

- Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease.
- Clinicians may administer up to a maximum of 5 monthly doses of palivizumab (15 mg/kg per dose) during the RSV season to infants who qualify for prophylaxis in the first year of life. Qualifying infants born during the RSV season may require fewer doses. For example, infants born in January would receive their last dose in March.
- Palivizumab prophylaxis is not recommended in the second year of life except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy).
- Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.
- Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year of life.
- Children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.
- Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.
- The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native

populations and possibly in selected other American Indian populations.

- Palivizumab prophylaxis is not recommended for prevention of health care-associated RSV disease.

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REFERENCES

1. Cassel CK, Guest JA. Choosing wisely: helping physicians and patients make smart decisions about their care. *JAMA*. 2012;307(17):1801–1802
2. ABIM Foundation. American Board of Internal Medicine; ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine; European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med*. 2002;136(3):243–246
3. Ubel PA, Jagsi R. Promoting population health through financial stewardship. *N Engl J Med*. 2014;370(14):1280–1281

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- syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics*. 2003;112(6 pt 1):1442–1446
9. American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics*. 1998;102(5):1211–1216
10. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2006:560–566
11. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements—Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6):1694–1701

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Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

COMMITTEE ON INFECTIOUS DISEASES AND BRONCHIOLITIS
GUIDELINES COMMITTEE

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Section 7.0

Previously Discussed Items

Botulinum Toxin

Questions:

- 1) What conditions should be paired with botulinum toxin injection on the Prioritized List?
- 2) What restrictions should be placed on use of botulinum toxin?

Question source: HERC staff, P&T Committee

Issue: Botulinum toxin was recently reviewed by the Pharmacy and Therapeutics Committee. P&T issued prior authorization guidance on what conditions should be treated with botulinum toxin and the types of restrictions that should be put in place for use. Previously, HSC/HERC has reviewed the use of botulinum toxin for particular conditions. This is the first class review done for HERC use.

Botox use for migraines was reviewed at the March, 2014 VBBS meeting and “model” guideline wording was approved. HERC staff was charged with bringing a more specific guideline back to HERC when P&T recommendations were available.

Model guideline note language for Line 435

Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine) only when the patient meets [insert here the criteria for use as defined by the Pharmacy and Therapeutics Committee at its May, 2014 meeting].

One guideline regarding use of botulinum toxin for bladder indications is presently on the List.

GUIDELINE NOTE 103, CHEMODENERVATION OF THE BLADDER

Line 331

Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of overactive bladder caused by spinal cord injury, multiple sclerosis and other spinal cord diseases in patients in whom appropriate pharmacologic therapy has proven to be ineffective or poorly tolerated.

Botulinum Toxin

Summary of Conclusions/Recommendations from P&T

Conclusions:

- There is moderate quality evidence and support from clinical guidelines that BoNT A is recommended first line for cervical dystonias due to increased efficacy compared to standard therapies. BoNT B is recommended for BoNT A resistant dystonias. There is low quality evidence of no difference between abobotulinumtoxinA (ABO) and onabotulinumtoxinA (ONA) in the treatment of cervical dystonia.
- There is low quality evidence demonstrating efficacy of BoNT A for the treatment of blepharospasm. However, open-label studies have demonstrated a significant effect size and clinical guidelines recommend BoNT should be a treatment option for blepharospasm. There is low quality evidence of no difference between ABO and ONA and no difference between ABO and incobotulinumtoxinA (INC) in the treatment of blepharospasm.
- There is moderate quality evidence that ABO, ONA and rimabotulinumtoxinB (RIM) reduces muscle tone and improves passive function for upper limb spasticity and low quality evidence for lower limb spasticity. There is insufficient evidence for an effect on active function.
- There is low quality evidence that unspecified BoNT A products may be associated with benefit in the prophylaxis of chronic migraine headaches (≥ 15 days a month), but results are inconsistent. In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headache per month.³ There is moderate quality evidence of no benefit of prophylaxis with BoNT A in patients with intermittent migraine attacks (less than 15 headache days per month) or chronic tension type headache.
- There is high quality evidence of no difference between BoNT injections and placebo in neck pain.⁸ There is insufficient evidence to support the use of BoNT injections to improve pain or function in patients with lower back pain.
- There is low quality and inconsistent evidence for the use of BoNT for increasing healing of anal fissure and appears less effective than sphincterotomy.
- In the treatment of strabismus, there is very low quality evidence, based on a systematic review with limited data that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia, but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus.
- There is low quality evidence of clinical efficacy of BoNT in the treatment of axillary hyperhidrosis and palmar hyperhidrosis. There is insufficient comparative evidence. Aluminum chloride preparations are the most widely used first line agents.

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- There is moderate quality evidence that BoNT A injections in the detrusor are the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity that is unresponsive to more conservative therapies
- There is moderate to high quality evidence that pneumatic dilation (PD) and surgical myotomy are more effective on long term remission than BoNT for the treatment of achalasia. BoNT is effective short term, but response diminishes at 2 years. It is a reasonable treatment approach for patients who are not candidates for surgical therapy.

Recommendations:

- Prior Authorize BoNT agents to ensure it is only used where there is evidence to support its use (for all FDA-approved indications, when used in a manner consistent with the evidence) and limit in appropriate patient populations.
- For the prophylaxis of migraine, limit use to patients that meet the following criteria:
 - o The patient has chronic migraines (at least 15 days per month with headache lasting 4 hours per day or longer)
 - o In consultation with a neurologist or headache specialist
 - o An inadequate response with a 3 month trial or contraindication to least two prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, or antiepileptic agents)
 - o Do not approve for chronic tension type headaches or for prophylaxis of intermittent migraine attacks.
 - o Approve for two injections (given 3 months apart) and then require additional documentation regarding migraines after therapy
- Limit BoNT for the treatment of urinary incontinence to patients' refractory to behavioral modification and antimuscarinic therapy.
- Limit BoNT for the treatment of chronic anal fissure for those unresponsive to conservative therapy with topical nitroglycerin or calcium channel blockers.
- Limit BoNT for hyperhidrosis to patients who have failed topical aluminum chloride.
- Limit BoNT for achalasia to patients who have failed or are not candidates for pneumatic dilation and surgical myotomy.

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CPT code	Code description	Current Location	Relevant diagnosis(es)	P&T diagnosis	Comments
43201	Esophagoscopy, rigid or flexible; with directed submucosal injection(s), any substance	382 ESOPHAGEAL STRICTURE; ACHALASIA Also on 60,319,384	530.0 Achalasia	Achalasia	CPT code used for more than Botox. No current restrictions on use. See P&T recommended restriction
46505	Chemodenervation of internal anal sphincter	532 CHRONIC ANAL FISSURE	565.0 Anal fissure	Chronic anal fissure	Add CPT code to line No current restrictions on use. See P&T recommended restriction
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder	331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION		Neurogenic detrusor overactivity	Delete current guideline 103 See P&T recommended restrictions and evidence statement
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)	364 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS	333.81 Blepharospasm	Blepharospasm	Delete coding specification
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)	414 MIGRAINE HEADACHES	346.x	Migraine	See P&T recommended restrictions. “Model” guideline adopted with addition of CPT code.
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the	364 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND	333.6 Genetic torsion dystonia 333.79 Other	Cervical dystonia	Delete coding specification

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	larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)	STENOSIS	acquired torsion dystonia 333.83 Spasmodic torticollis		
64642-64647	Chemodenervation of extremity or trunk muscle(s)	297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS		Upper and lower limb spasticity	Limit pairings to only upper and lower limb spasticity (many possible diagnostic codes). No current restrictions on line 297
64650	Chemodenervation of eccrine glands; both axillae	523 DISORDERS OF SWEAT GLANDS	705.2 focal hyperhidrosis 780.8 Generalized hyperhidrosis	Hyperhidrosis	Narrow to just treatment of axillary hyperhidrosis and palmar hyperhidrosis. No current restrictions on use. See P&T recommended restriction
64653	Chemodenervation of eccrine glands; other area(s) (eg, scalp, face, neck), per day	523 DISORDERS OF SWEAT GLANDS	See above	See above	See above
67345	Chemodenervation of extraocular muscle	354 STRABISMUS DUE TO NEUROLOGIC DISORDER 372 AMBLYOPIA 398 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN		Strabismus	Remove from line 372 Multiple diagnostic codes used for strabismus depending on type, cause, etc. No current restrictions on lines

Botulinum Toxin

HERC staff recommendations (October 1, 2014 List/January 1, 2015 List)

- 1) Add 46505 (Chemodenervation of internal anal sphincter) to line 506/532
CHRONIC ANAL FISSURE
- 2) Remove 67345 (Chemodenervation of extraocular muscle) from line 397/372
AMBLYOPIA
 - a. On the two strabismus lines; not approved for amblyopia
- 3) Do not add coverage for botulinum toxin injections for treatment of neck or lower back pain or chronic daily headaches
 - a. Lack of evidence of effectiveness
- 4) Keep the coding specification shown below on line 388/364 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS
 - a. "Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-9 333.81/ICD-10-CM G24.5), spasmodic torticollis (ICD-9 333.83/ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-9 333.89/ICD-10-CM G24.9)."
- 5) Add the coding specification shown below to line 318/297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
 - a. "Chemodenervation with botulinum toxin injection (CPT 64642-64647) is included on this line for treatment of upper and lower limb spasticity (ICD-9 333.6x, 333.7x, 340.xx, 341.0, 342.xx, 343.xx, 344.0x, 344.1, 344.2, 344.3x, 344.4x, 344.5, 344.89, 344.9, 359.0-359.2, 438.2x-438.5x/ICD-10 G24.02, G24.1, G35, G36.0, G71.xx, G80-G83, I69.03-I69.06).
 - b. Note: these codes were identified from claims data for use of botulinum toxin. There may be other appropriate codes on line 318/297. An alternate strategy would be to have no coding specification for line 318/297 and let all diagnoses pair.
- 6) Add the coding specification shown below to lines 452 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE/354 STRABISMUS DUE TO NEUROLOGIC DISORDER and 398 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
 - a. "Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-9 378.73 /ICD-10 H50.89)."
- 7) Add the coding specification shown below to line 421 ACHALASIA, NON-NEONATAL/382 ESOPHAGEAL STRICTURE; ACHALASIA
 - a. "Chemodenervation with botulinum toxin injection (CPT 43201) is included on this line for treatment of achalasia (ICD-9 530.0/ICD-10 K22.0)."
- 8) Add the coding specification shown below to line 542/523 DISORDERS OF SWEAT GLANDS

Botulinum Toxin

- b. "Chemodenervation with botulinum toxin injection (CPT 64650, 64653) is included on this line for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-9 705.2 and 780.8/ICD-10 L74.52, R61).
- 9) Delete GUIDELINE NOTE 103, CHEMODENERVATION OF THE BLADDER
 - a. Apply new guideline below to line 351/331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
- 10) Apply new guideline to line 435,414 MIGRAINE
- 11) Add the guideline shown below for use of botulinum toxin

GUIDELINE NOTE XXX BOTULINUM TOXIN

Lines 318,351,388,397,421,435,452,506,542 (October 1, 2014 List)

Lines 297,331,354,364,382,398,414,523,532 (January 1, 2015 List)

Chemodenervation with botulinum toxin injection is included on these lines only when the patient meets criteria for use as defined by the Pharmacy and Therapeutics Committee (P&T) according to OAR 410-121-0400 as found in the Botulinum Prior Authorization Criteria, at [web link].

Botulinum Toxins (BoNT)

Goal(s):

- Approve BoNT only for funded OHP diagnoses which are supported by the medical literature (e.g. various dystonias and spasticity associated with certain neurological diseases).

Length of Authorization:

- 90 days up to lifetime

Requires PA:

Use of BoNT without associated dystonia or neurological disease diagnosis in last 12 months (i.e. 333.6x, 333.7x, 333.81, 333.83, 333.89, 340.xx, 341.0, 342.xx, 343.xx, 344.0x, 344.1, 344.2, 344.3x, 344.4x, 344.5, 344.89, 359.0-2, 438.2x-5x or 378.73)

HSN	Generic Drug Name
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)
036477	ABOBOTULINUMTOXINA (DYSPORE)
021869	RIMABOTULINUMTOXINB (MYOBLOC)
036687	INCOBULINUMTOXINA (XEOMIN)

ProcCode	Descriptions
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria

1. What diagnosis is being treated?

Record ICD-9 Code

Approval Criteria

2. Does client have diagnosis of certain dystonias or spasticity associated with other neurological diseases that make BoNT a first-line treatment option? Examples: 333.6x (genetic torsion dystonia) 333.7x (acquired torsion dystonia), 333.81 (blepharospasm) 333.83 (spasmodic torticollis) 333.89 (other fragments of torsion dystonia) 438.2x – 432.5x (paralysis associated with CVD) 340.xx (multiple sclerosis) 341.0 (neuromyelitis optica) 342.xx (spastic hemiplegia, other specified hemiplegia), 343.xx (cerebral palsy), 344.0x (quadriplegia and quadraparesis), 344.1 (paraplegia), 344.2 (diplegia of upper limbs) 344.3x (monoplegia of lower limb) 344.4x (monoplegia of upper limb) 344.5 (unspecified monoplegia) 344.89 (other specified paralytic syndrome) 359.0x – 359.2x (muscular dystrophies) 378.73 (strabismus in other neuromuscular disorders)	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3
3. Does client have diagnosis of chronic migraine based on clinical symptoms; at least 15 headache days per month, of which, at least 8 of those days are considered migraine days?	Yes: Go to #6	No: Go to #4
4. Does client have diagnosis of overactive bladder related to neurological causes? Document neurological cause	Yes: Go to #7	No: Go to #5

Approval Criteria

5. Does client have any of the following diagnoses?

Insufficient evidence of benefit:

787.2x (dysphagia)
 333.xx (other extrapyramidal disease and abnormal movement disorders excluding 333.6x, 333.7x, 333.81, 333.83, 333.89 and 333.82, 333.84, 333.94-333.99)
 378 excluding 378.73 (other disorders of binocular eye movements (e.g. esotropia, exotropia, mechanical strabismus, sixth nerve palsy)
 307.2x (tics)
 478.75 (laryngeal spasm),
 723.0 and 723.4 (Spinal stenosis in cervical region or Brachial neuritis or radiculitis NOS)
 728.85 (spasm of muscle [in absence of neurological diagnoses]),
 727.81 (contracture of tendon – sheath [in absence of neurological diagnoses])
 335.20 (amyotrophic sclerosis),
 724.00-724.09, 724.4 (clinically significant spinal deformity or disorders of spine with neurological impairment)
 600.xx (hyperplasia of prostate),

Unfunded OHP condition:

333.82, 333.84, 333.94-333.99 (neurologic conditions with no or minimally effective treatment or not treatment is necessary)
 351.xx (facial nerve disorders),
 478.79 (spastic dysphonia)
 565.0 (anal fissure),
 705.xx (disorders of sweat glands e.g. focal hyperhidrosis),
 723.xx except 723.4 (other disorders of cervical region),
 705.0-705.1, 705.21-705.9, 780.8 (disorders of sweat glands)
 724.1, 724.2, 724.4-724.6, 727.70-724.9 (acute and chronic disorders of the spine without neurologic impairment)
 729.0-729.2 (disorders of soft tissue)
 307.81, 339.10-339.89, 784. (tension headaches)
 536.3 (gastroparesis),

Yes: Pass to RPH; Deny

(Medical Appropriateness)

(Condition not funded by OHP)

No: Go to #8

Approval Criteria

6. Has the client not responded or are they contraindicated to at least one drug in three of the following drug classes? • B-blocker (metoprolol, atenolol, nadolol, propranolol, timolol) • Tricyclic antidepressant (nortriptyline, amitriptyline) • Anticonvulsant (valproic acid, divalproate, carbamazepine, topiramate, gabapentin) • Calcium Channel Blocker (verapamil, diltiazem, nimodipine)	Yes: Approve for 180 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (www.orpdl.org).
7. Has the client tried or are they contraindicated to at least two of the following urinary incontinence antimuscarinic therapies? (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium)	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (www.orpdl.org).
8. Pass to pharmacist to evaluate for evidence support and OHP funding level.	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness)

P&T / DUR Action: 7/31/2014

Revision(s):

Initiated:



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Oregon State
UNIVERSITY

Drug Use Research & Management Program

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Abbreviated Class Review: Botulinum toxins

Month/Year of Review: May 2014

End date of literature search: March 2014

Current PDL Class: None

Drugs included in review

Drug	FDA approved indications*	Evidence available from clinical trials
OnabotulinumtoxinA (Botox®)	Prophylaxis of chronic migraines (≥ 15 days/month) in adults, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, bladder dysfunction (detrusor overactivity associated with a neurologic condition or overactive bladder), blepharospasm, strabismus,	Pharyngoesophageal segment spasm, achalasia
AbobotulinumtoxinA (Dysport®)	Cervical dystonia	Blepharospasm, Neurogenic detrusor overactivity, urinary incontinence, upper limb spasticity, pharyngoesophageal segment spasm
RimabotulinumtoxinB (Myobloc®)	Cervical dystonia	Urinary incontinence, upper limb spasticity
IncobotulinumtoxinA (Xeomin®)	Cervical dystonia, blepharospasm	Upper limb spasticity

*Non-cosmetic indications only

Research Questions:

- For what indications is there evidence to support the use of botulinum toxin (BoNT)?
- Are there differences in efficacy/effectiveness between the agents and is there evidence to support choosing a specific BoNT based on indication?
- Is BoNT safe for indications with evidence to support its use?
- Are there subpopulations that certain BoNT preparations are more effective or safer than others?

Conclusions:

- There is moderate quality evidence and support from clinical guidelines that BoNT A is recommended first line for cervical dystonias due to increased efficacy compared to standard therapies.^{1,2} BoNT B is recommended for BoNT A resistant dystonias. There is low quality evidence of no difference between abobotulinumtoxinA (ABO) and onabotulinumtoxinA (ONA) in the treatment of cervical dystonia.
- There is low quality evidence demonstrating efficacy of BoNT A for the treatment of blepharospasm. However, open-label studies have demonstrated a significant effect size and clinical guidelines recommend BoNT should be a treatment option for blepharospasm.¹ There is low quality evidence of no difference between ABO and ONA and no difference between ABO and incobotulinumtoxinA (INC) in the treatment of blepharospasm.¹
- There is moderate quality evidence that ABO, ONA and rimabotulinumtoxinB (RIM) reduces muscle tone and improves passive function for upper limb spasticity and low quality evidence for lower limb spasticity.¹⁰ There is insufficient evidence for an effect on active function.¹¹
- There is low quality evidence that unspecified BoNT A products may be associated with benefit in the prophylaxis of chronic daily headaches (≥15 days a month), but results are inconsistent.^{3,4,5} In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headache per month.³ There is moderate quality evidence of no benefit of prophylaxis with BoNT A in patients with intermittent migraine attacks (less than 15 headache days per month) or chronic tension type headache.^{6,5,7}
- There is high quality evidence of no difference between BoNT injections and placebo in neck pain.⁸ There is insufficient evidence to support the use of BoNT injections to improve pain or function in patients with lower back pain.^{7,9}
- There is low quality and inconsistent evidence for the use of BoNT for increasing healing of anal fissure and appears less effective than sphincterotomy.
- In the treatment of strabismus, there is very low quality evidence, based on a systematic review with limited data that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia, but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus.
- There is low quality evidence of clinical efficacy of BoNT in the treatment of axillary hyperhidrosis and palmar hyperhidrosis. There is insufficient comparative evidence. Aluminum chloride preparations are the most widely used first line agents.
- There is moderate quality evidence that BoNT A injections in the detrusor are the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity that is unresponsive to more conservative therapies
- There is moderate to high quality evidence that pneumatic dilation (PD) and surgical myotomy are more effective on long term remission than BoNT for the treatment of achalasia. BoNT is effective short term, but response diminishes at 2 years. It is a reasonable treatment approach for patients who are not candidates for surgical therapy.

Recommendations:

- Prior Authorize BoNT agents to ensure it is only used where there is evidence to support its use (for all FDA-approved indications, when used in a manner consistent with the evidence) and limit in appropriate patient populations.
- For the prophylaxis of migraine, limit use to patients that meet the following criteria:
 - The patient has chronic migraines (at least 15 days per month with headache lasting 4 hours per day or longer)
 - In consultation with a neurologist or headache specialist
 - An inadequate response with a 3 month trial or contraindication to least two prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, or antiepileptic agents)
 - Do not approve for chronic tension type headaches or for prophylaxis of intermittent migraine attacks.

- Approve for two injections (given 3 months apart) and then require additional documentation regarding migraines after therapy
- Limit BoNT for the treatment of urinary incontinence to patients' refractory to behavioral modification and antimuscarinic therapy.
- Limit BoNT for the treatment of chronic anal fissure for those unresponsive to conservative therapy with topical nitroglycerin or calcium channel blockers.
- Limit BoNT for hyperhidrosis to patients who have failed topical aluminum chloride.
- Limit BoNT for achalasia to patients who have failed or are not candidates for pneumatic dilation and surgical myotomy.

Background:

There are seven serologically distinct forms of botulinum toxin (BoNT), A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain.¹⁰ All serotypes interfere with neural transmission by blocking acetylcholine release at the neuromuscular junction, causing muscle paralysis.¹¹ Each neurotoxin works at a distinct site.¹⁰ Botulinum toxins now play a role in the management of a variety of medical conditions. Three distinct serotype A botulinum toxin (BoNT A) products, abobotulinumtoxinA (ABO), incobotulinumtoxinA (INC), onabotulinumtoxinA (ONA), and one serotype B botulinum toxin (BoNT B) product, rimabotulinumtoxinB (RIM), have been approved by the U.S. Food and Drug Administration (FDA). The most recent preparation approved is INC in 2010. Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each BoNT product and cannot be compared or converted into units of another product. In addition, there are no universally accepted safe dose conversion ratios.¹⁰ BoNTs are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, where the goal of therapy is to reduce contraction of striated or smooth muscle. All of the products have a black box warning in their labeling regarding the risk of BoNT spreading beyond the site of injection, resulting in adverse events and death in some cases. BoNT A has become first line therapy for cervical dystonia.¹² Not all patients respond well to BoNT A though, and 5 to 10% become resistant to it.¹³ In these cases, BoNT B is an alternative to BoNT A.¹² Head to head studies comparing the efficacy and safety of different BoNT formulations are limited.¹⁴

The use of BoNT has also been evaluated for prophylaxis treatment of migraines. Prophylactic treatment for migraines is often considered for patients who have two or more migraines with three or more days of disability per month or use of acute medication more than twice per week. Common prophylactic treatments for migraines include beta-blockers, tricyclic antidepressants, calcium channel blockers, antiepileptic drugs, and lifestyle management. The reported range of efficacy for these drugs varies from modest (effect size, 0.5-0.8) for most drugs to large (effect size, >0.8) for amitriptyline and valproate.³ Due to the lack of proven differences in efficacy between different prophylactic medications, a medication is often selected based potential side effects, the presence of other disorders which may be coexistent with migraine, patient disability, and patient preferences in a given patient. OnabotulinumtoxinA is the only BoNT approved by the FDA for the prophylactic treatment of chronic migraine. None of the BoNT formulations are approved for the prophylactic treatment of chronic tension-type headache.

Methods:

A Medline literature search ending March 2014 for new systematic reviews, clinical guidelines, and head to head randomized controlled trials (RCTs) for all of the BoNT products was conducted. Cosmetic indications were excluded, as they are not covered by the Oregon Health Plan (OHP). The focus of the review is on non-cosmetic indications only. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts,

and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Cervical Dystonia and Blepharospasm:

Cervical dystonia is the most common form of focal dystonia and also referred to as spasmodic torticollis. It is a neurologic condition that causes abnormal movements and/or postures of the neck.¹⁵ Botulinum toxin is considered first-line therapy for cervical dystonia to decrease the severity of associated abnormal head position and neck pain.¹⁶ According to DynaMed, there is level 1 evidence that BoNT (6 trials used ONA, 4 trials used abobotulinumtoxinA and 3 trials used RIM) reduced pain in patients with cervical dystonia and is effective and safe. There is level 2 evidence that abobotulinumtoxinA may be more effective than anticholinergic drugs and that unspecified BoNT A may have fewer adverse events than BoNT B with similar efficacy.¹⁶ BoNT B may be useful for patients refractory to BoNT A. Blepharospasm is a focal dystonia involving the periocular muscles. Clinical signs include increased blinking and spasms of involuntary eye closure. BoNT A is the current first line medication therapy for blepharospasm.¹⁷ Other treatments include surgery, psychological support, and biofeedback.

Systematic Reviews:

A Cochrane Collaboration systematic review of all blinded RCTs of BoNT A versus placebo evaluated the effectiveness and safety of BoNT for cervical dystonia.¹⁸ A literature search up to June 2003 identified 13 studies for inclusion; most of which were published in the early 1990s and included only small numbers of participants. Eight trials evaluated ONA and five evaluated abobotulinumtoxinA. Techniques and administration methods varied significantly between the studies. In general, the quality of the studies was good. There was limited data on objective outcomes. Data from 3 studies (n=121) demonstrated a significant improvement of at least one point (OR 8.16; 95% CI 4.03-16.5) and at least 3 points (OR 4.25; 95% CI 2.00-9.05) in the Tsui scale (demonstrating improvement) compared to placebo. The patient subjective assessment of any improvement was also significantly better with treatment than placebo (OR 6.58; 95% CI 4.55-9.54; 11 studies; n=510). Adverse effects were transient and either mild to moderate or intermittent. Events that occurred more frequently with BoNT than placebo were neck weakness, dysphagia, dry mouth, voice changes, and local pain. There did not appear to be any significant differences between ONA and ABO in efficacy or safety.

In addition, the authors of the Cochrane systematic reviews compared the clinical efficacy and safety of BoNT A versus BoNT B in cervical dystonia.¹² However, at the time of the literature search, only two ongoing trials were identified and there were no preliminary results or interim analysis available for them. The authors were able to make any conclusions on the comparative efficacy or safety of BoNT A versus BoNT B. Since this systematic review, two randomized trials have been published comparing BoNT types A and B.^{19,20} The first study was a randomized, double-blind, noninferiority trial in patients cervical dystonia who were toxin-naïve (n=111).¹⁹ The primary outcome was change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), which is a summation of motor severity, pain, and disability. Results demonstrated that BoNT B was noninferior to BoNT A in change in baseline in TWSTRS score (mean difference 0.2 points; 90% CI -4.9 to 0.6), with no difference in duration of effect or adverse events. The second trial was a randomized, double-blind, parallel-arm study in subjects with cervical dystonia who had a previous response from BoNT A (n=139).²⁰ Both serotypes of BoNT were found to be equivalent at week 4 in terms of efficacy. The BoNT B group had an increase in frequency and severity of dysphagia and dry mouth after treatment compared to BoNT A (dysphagia: ONA 19% vs. RIM 48%; dry mouth: ONA 41% vs. RIM 80%). In clinical responders, BoNT A was associated with a slightly longer duration of benefit than BoNT B (ONA 14 weeks, RIM 12.1 weeks; p=0.033).²⁰

Another Cochrane systematic review evaluated RCTs to determine how effective and safe BoNT A is for the treatment of blepharospasm.¹⁷ Overall, the authors found no high quality, randomized, controlled efficacy data to support the use of BoNT A for blepharospasm. Because none of the studies met their inclusion criteria, only a descriptive analysis was provided for the trials excluded that were controlled. However, open-label studies demonstrate a significant effect size (90% of patients benefit), making it difficult to justify new placebo-controlled trials and it appears that BoNT A is indeed effective and safe in blepharospasm. Most of the trials evaluated ONA; two trials included ABO.

An evidence-based review and meta-analysis attempted to evaluate which treatments for dystonia have proven efficacy and which of them have unproven results.²¹ A literature search was performed through 2003 and all types of articles were comprised, including case reports. A random effects meta-analysis confirmed positive results for BoNTA efficacy in patients with cervical dystonia (RD 0.46; 95% CI 0.25-0.67; $p < 0.0001$; $I^2 = 82.1\%$) based on 6 double-blind, placebo-controlled trials, all comparing ONA to placebo. Similar results were seen in one RCT evaluating ABO in 75 patients. Two RCTs compared ONA to ABO and one found no differences in degree of improvements between the two preparations, while the second study showed abobotulinumtoxinA to be superior to ONA for impairment and pain, but with a higher incidence of minor side effects. Three double-blind and one single-blind study ($n = 73$) showed a positive effect of BoNT A (nonspecific) on blepharospasm lasting more than 2-3 months (Level A data). A meta-analysis included two placebo controlled studies using BoNT A to treat writer's cramp that resulted in C-level data (RD 0.31; 95% CI 0.10-0.52; $p = 0.004$; $I^2 = 0\%$). The authors concluded that BoNT is possibly effective for writer's cramp. Treatment efficacy was found to be unproven for the following indications: Oromandibular dystonia and laryngeal dystonia. No controlled studies were found in laryngeal dystonia and a single placebo-controlled study showed improvement in only 37.5% of a total of 8 patients with oromandibular dystonia with BoNTA injections.

Clinical Guidelines:

The American Academy of Neurology performed an evidence-based review of the safety and efficacy of BoNT in the treatment of movement disorders.¹ They concluded that BoNT is established as safe and effective for the treatment of cervical dystonia based on seven Class 1 (RCT with masked or objective outcome assessment in a representative population) rated studies. Due to no effective alternative medical therapies, the academy concludes the following:

- BoNT should be offered as a treatment option to patients with cervical dystonia (Level A).
- BoNT is probably more efficacious and better tolerated in patients with cervical dystonia than treatment with trihexyphenidyl (Level B).
- There are no data to compare BoNT with surgical treatment of cervical dystonia.
- From the available evidence there is no proven superiority for a single BoNT product.

Recommendations for additional movement disorders are also included:

- BoNT injection should be considered as a treatment option for blepharospasm (Level B).
 - This is based on two studies demonstrating that BoNT is probably effective with minimal side effects. OnabotulinumtoxinA and INC have been shown to be probably equivalent, and ONA and ABO as possibly equivalent.
- BoNT may be considered as a treatment option for hemifacial spasm (Level C).
- BoNT should be considered as a treatment option for focal upper extremity dystonia (Level B). However, the data are insufficient to provide a recommendation for lower extremity dystonia.
- BoNT should be considered as a treatment option for adductor spasmodic dysphonia (Level B).
- There is insufficient evidence to support or refute the use of BoNT in abductor spasmodic dysphonia (Level U).
- BoNT may be considered as a treatment option for motor tics (Level C). There are insufficient data to determine the effectiveness of BoNT in phonic tics.

- BoNT should be considered as a treatment option for essential hand tremor in those patients who fail treatment with oral agents (Level B).

The European Federation of Neurological Societies also recommend botulin toxin as a treatment option for patients with cervical dystonia.² Based on a systematic review from the American Academy of Neurology that established botulinum toxin as an effective treatment for cervical dystonia, blepharospasm, focal upper extremity dystonia, and laryngeal dystonia (probably effective). A lower level of evidence was found for focal lower limb dystonia (possibly effective). The following recommendations are provided:

- BoNT A (or BoNT B if there is resistance to BoNT A) is recommended as first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia (Level A).
- BoNT A is probably effective for adductor-type laryngeal dystonia, but there is insufficient evidence to support efficacy in abductor-type laryngeal dystonia and in muscular tension dysphonia.

Spasticity:

Spasticity results from many etiologies including stroke, trauma, multiple sclerosis, cerebral palsy and neoplasm involving the CNS. Reduction in function is related to at least muscle weakness, soft tissue contracture, and muscle overactivity. A recent systematic review and meta-analysis evaluated the efficacy of any preparation of BoNT A for spasticity and pain in adults.²² Trials including both ONA and ABO were included, although the comparative efficacy and safety of the different BoNT A preparations was not addressed. Specifically, data was evaluated for spasticity and spasticity-related pain in the upper and lower limbs in adults. Results showed that BoNT A may improve spasticity but may not reduce spasticity-related pain in adults.²² A literature review through April 2013 identified 27 studies and 10 were used for quantitative analysis of pain. Significant heterogeneity was found ($I^2=83\%$) for the studies evaluating spasticity-related pain in the upper limb. There was a non-significant effect slightly in favor of BoNT A (standardized mean difference [SMD] 0.44; 95% CI -0.02 to 0.90; $p=0.06$). Removing the two studies that were thought to cause significant heterogeneity due to different patient populations confirmed a non-significant result ($p=0.35$). Three studies evaluated pain in the lower limb and also showed no significant effect with BoNT A (RR 1.01; 95% CI 0.19-5.36; $p=0.99$) with significant heterogeneity ($I^2=87\%$). There was moderate quality evidence that BoNT A did demonstrate a statistically significant improvement of spasticity of the upper limb with compared to placebo (RR 1.30; 95% CI 1.11-1.52; $p=0.001$). There was moderate quality evidence of a significant effect on spasticity in the lower limb as well (RR 2.42; 95% CI 1.60-3.65; $p<0.0001$).

The American Academy of Neurology also performed an evidence-based review of the safety and efficacy of BoNT (serotypes A and B) in the treatment of adult and childhood spasticity.²³ The review evaluated the use in the following indications: adult spasticity and spasticity in pediatric cerebral palsy. A literature search identified 11 class I efficacy trials in adult upper extremity spasticity, 6 of which used ABO, 4 used ONA and 1 used RIM. All of these studies showed that BoNT is safe and reduced tone in a dose-dependent manner. There was insufficient evidence to evaluate the outcome of active functional gains. Three trials evaluated lower extremity spasticity, most of which focused on reduction in muscle tone with demonstrated efficacy. The authors concluded that BoNT is established as effective in the treatment of adult spasticity in the upper and lower limb in reducing muscle tone and improving passive function. However, few studies examined active function. There were no RCTS comparing BoNT to other treatments for spasticity. In addition, BoNT is established as effective in the treatment of spastic equinus in patients with cerebral palsy. The AAN recommends that:

- BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (level A), and should be considered to improve active function (Level B).
- There is insufficient information to recommend an optimum technique for muscle localization at the time of injection (Level U).

- BoNT injections of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy (level A).
- BoNT should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery (Level B).
- BoNT should be considered as a treatment option in children with upper extremity spasticity (level B).

The Royal College of Physicians developed national guidelines on the management of BoNT in spasticity in adults.²⁴ The guideline panel notes that local intramuscular injection of BoNT is an established, well-tolerated treatment in the pharmacological management of focal spasticity and there is a strong body of evidence for its effectiveness in the management of upper and lower limb spasticity. The guideline recommends that it be used for focal or multi-focal spasticity in demonstrable muscle overactivity.

The international cerebral palsy institute released a consensus statement for lower limb spasticity in children with cerebral palsy.²⁵ Based on a literature review and appraisal, the committee recommends the following:

- BoNT A is established as effective in the treatment of spastic equinus to improve gait (level A).
- BoNT A is probably effective to improve goal attainment and function in the management of spastic equinus (level B).
- BoNT A injections to the adductor muscles do not improve gross motor function (level A).
- BoNT A injections to the adductor muscles may delay hip displacement, but does not affect long-term outcomes (level A).
- BoNT A injections to multiple lower limb muscles have inadequate and conflicting data in respect of gait, goal attainment and function (level U).

Migraine:

DynaMed reports that BoNT injections appear ineffective for patients with episode migraine headache (< 15 days/month) based on level 2 evidence, but they may reduce frequency in adults with chronic migraine headache (≥15 days/month).²⁶

Systematic Reviews:

A systematic review of trials was conducted through 2012 to assess BoNT A (specific products were not reported) for the prophylactic treatment of headaches in adults.³ Only RCTs that evaluated BoNT A in association with the reduction in frequency or severity of headaches that were at least 4 weeks induration were included. The Cochrane Risk of Bias tool was used to assess study quality and disagreements were resolved by consensus. A total of 27 placebo-controlled RCTs and 4 active comparator trials were included. Among the placebo controlled trials, 10 evaluated episodic migraines, 5 assessed chronic migraines, 8 evaluated patients with chronic tension-type headaches, and 3 studied chronic daily headaches. Different protocols were followed for botulinum injections, including fixed injection plans and follow-the-pain approached. BoNT A was associated with a reduction in headaches per month for both chronic daily headaches (-2.06 headaches per month; 95% CI -3.56 to -0.56; $I^2=28.2\%$; $p=0.25$) and chronic migraine (-2.30 headaches per month; 95% CI -3.66 to -0.94; $I^2=32.2\%$; $p=0.21$). There was no association of BoNT A with a reduction in the number of episodic migraine headaches per month or chronic tension-type headaches. Eight studies reported on the likelihood of achieving 50% improvement in headache and BoNT A was associated with improvement in chronic migraine headaches (2 studies; RR 2.21; 95% CI 1.30-3.78). Compared with placebo, there was no association of BoNT A with improvement in chronic daily headaches, episodic migraine headaches, or chronic tension-type headaches.³

Only 4 trials compared BoNT A with other treatments. In single trials, BoNT A was not associated with a reduction in headache frequency compared with topiramate (1.4 headaches per month; 95% CI -2.5 to 1.3) or amitriptyline (2.1 headaches per month; 95% CI -1.2 to 5.4) for prophylaxis against chronic migraine

headaches. It was also not associated with reduction in headache frequency compared to valproate in patients with chronic and episodic migraines or in patients with episodic migraines.³ These trials were not designed as equivalence trials and all were underpowered to show even modest differences. Overall, there was moderate heterogeneity between trials and variability in overall study quality. There was also evidence of a favorable improvement in headaches in the placebo-treated groups, with patients reporting a substantial improvement in headaches over time. The authors concluded that there may be an association between BoNT A and improvement in the frequency of chronic migraine and chronic daily headaches, but not with improvement in the frequency of episodic migraine, chronic tension-type headaches, or episodic tension-type headaches. Also, the effect size was small with a reduction seen in number of headaches per month from 19.5 to 17.2 for chronic migraine and from 17.5 to 15.4 for chronic daily headaches. Although there is insufficient direct evidence to make definitive conclusions comparing BoNT A to other medications, it appears that BoNT A may be associated with less benefit than other common prophylactic medications for migraine headaches.

A 2011 systematic review evaluated the evidence from double-blind, RCTs that had at least 100 patients from a literature search through August 2011.⁴ Studies including both BoNT A and BoNT B in the treatment of migraine were included in the search criteria; however, all 10 trials identified evaluated BoNT A (eight with ONA and 2 with ABO). One trial compared BoNT A to histamine and the other nine versus placebo. The primary outcome included the difference in the number of headache episodes and the mean change in number of headache days or headache-free days. The largest available study evaluated ONA and found a small but statistically significant decrease in the mean number of headache days per month (-8.4 vs. -6.6; $p < 0.001$) and in mean number of migraine days per month (-8.2 versus -6.2, $p < 0.001$) in the treatment group. The small effect size suggests that this may not be clinically significant. Eight additional trials reported on migraine frequency. With the exception of one trial, there were no significant differences in migraine medication use or migraine severity or duration in any of these 8 trials. Only one trial compared BoNT A to another active treatment (histamine), and found no statistical difference between the two groups in the number of headache attacks, or in any of the secondary outcome measures. Common adverse events occurred in 20% to 67% of patients, and included muscular weakness, headache, pain, neck rigidity, blepharoptosis, skin tightness, hypertonia, dysphagia, asthenia, and eyelid edema or ptosis. Overall, the evidence for the effectiveness of BoNT A is inconsistent, and suggests that if there is a benefit, it is small and the clinical significance is unknown. In addition, it does not appear effective for improving quality of life. There was insufficient evidence to evaluate if there was a difference in efficacy among serotypes and the various products. In addition, this review combines the results of trials in chronic migraine and episodic migraine.

Another systematic review evaluated BoNT A use in chronic tension-type headache.⁴ A literature search identified 9 RCTs with outcome measures including headache severity and/or intensity, headache frequency, medication use, measures of mood, and quality of life. Six trials evaluated ONA and three evaluated ABO. Seven of the nine found no significant difference in most or all headache outcomes compared to placebo. One trial ($n=300$) found significantly more headache free days in the placebo group compared to the highest dose of ONA (150U), but no differences in any of the lower dose groups (50U-100U). The only trial to show a statistically significant improvement in multiple headache symptoms was small ($n=28$) and found fewer headache days, lower headache severity, and shorter duration in the treatment group (ONA) compared to placebo. There were no studies comparing BoNT A to another active treatment for chronic tension-type headache. Overall, the evidence suggests that BoNT is ineffective for the use in chronic tension-type headache.

Clinical Guidelines:

The Canadian Headache Society released high quality clinical guidelines for migraine prophylaxis in March 2012 with an overall goal to assist the practitioner in choosing an appropriate prophylactic medication for an individual with episodic migraine (headache on ≤ 14 days a month), based on current evidence and expert consensus.⁶ A comprehensive literature search and systematic review was done by the guideline panel to inform the recommendations regarding medications for migraine prophylaxis. The initial review found eight studies on the use of BoNT A for the prophylaxis of migraine and five fair-quality trials were negative with respect to the primary outcome on migraine frequency. The following are the main recommendations included:

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Starting and stopping prophylactic therapy (Based on Expert Consensus only)

- Migraine prophylactic therapy should be considered in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management (Expert Consensus)
- Migraine prophylactic therapy should be considered when the frequency of migraine attacks is such that reliance on acute medications alone puts patients at risk of medication overuse headache. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, NSAIDs) on 15 days a month or more (Expert Consensus).
- Migraine prophylaxis should be considered for patients with greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective.
- Migraine prophylaxis may be considered according to patient preference and physician judgment, for example in patients with hemiplegic migraine.
- A prophylactic medication trial should consist of at least two months at the target or optimal dose before it is considered ineffective.
- A prophylactic medication is usually considered effective if migraine attack frequency or the number of days with headache per month is reduced by 50% or more.
- After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the medication in many patients, although others may benefit from a much longer duration of therapy.

Botulinum Toxin Type A

- A strong recommendation based on high quality evidence against BoNT A for the prophylaxis of episodic migraine in patients with less than 15 headache days per month. The evidence indicates that BoNT A is no better than placebo for prophylaxis of migraine in such patients.

Other medications (for the treatment of episodic migraine)

- A strong recommendation based on high quality evidence supports the use of topiramate, propranolol, metoprolol, and amitriptyline for migraine prophylaxis.
- A strong recommendation based on moderate quality evidence supports the use of nadolol, gabapentin, candesartan, and butterbur.
- A strong recommendation based on low quality evidence and minimal side effects for riboflavin, coenzyme Q10, and magnesium citrate.
- A weak recommendation based on high quality evidence for efficacy of divalproex sodium, flunarizine, and pizotifen primarily because of frequent and significant side effects.
- Propranolol, nadolol, and metoprolol are good initial prophylactic drug choices for many patients with migraine. (Expert Consensus)
- Amitriptyline is a good initial drug and may be particularly useful in patients with insomnia or associated tension-type headache. (Expert Consensus)
- Magnesium is considered the safest migraine prophylactic during pregnancy.

The National Institute for Health and Clinical Excellence (NICE) produced a technology appraisal guidance for BoTN A for the prevention of headaches in adults with chronic migraine.⁵ Efficacy was established based on a systematic review of RCTs comparing BoTN A with placebo. Although the clinical trial evidence demonstrated statistically significant benefits of BoTN A compared with placebo for a number of outcomes, the absolute numerical differences were small. Further, there was a large placebo effect seen in trials. The guidance includes the following:

- BoTN A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):
 - That has not responded to at least three prior pharmacological prophylaxis therapies
 - AND**
 - Whose condition is appropriately managed for medication overuse
- Treatment with BoTN A that is recommended should be stopped in people whose condition:
 - Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles)
 - OR**
 - Has changed to episodic migraine (fewer than 15 headache days per month) for three consecutive months.

The American Academy of Neurology evaluated the evidence for using BoNT in episodic migraine, tension-type headache, and chronic daily headache.⁷ Analysis of data resulted in conclusions that BoNT is probably ineffective for episodic migraine and tension-type headache (Grade B Recommendation) and that there is insufficient evidence for use in chronic daily headache. However, this was performed before the FDA approval of ONA for the use of prophylaxis of headaches in adult patients with chronic migraine.

Chronic Neck/Back Pain:

A Cochrane Database systemic review of BoNT A for subacute/chronic neck pain did not find a statistically or clinically difference between BoNT A and placebo injections.⁸ Randomized and quasi-randomized controlled trials were included. Nine trials with 503 participants were included; only BoNT type A was used in these studies. High quality evidence showed little or no difference in pain between BoNT A and saline injections at 4 weeks (standardized mean difference [SMD] -0.07; 95% CI -0.36 to 0.21) and six months for chronic neck pain. Very low quality evidence suggests no difference in pain in those with cervicogenic headache (SMD 0.16; 95% CI -0.53 to 0.86; NNT 264). There was also no benefit seen for disability and quality of life at four weeks and six months.

Another Cochrane Database systematic review evaluated BoNT for treating non-specific lower back pain and did not find sufficient evidence to reach a conclusion regarding its effectiveness.⁹ Only 3 trials met inclusion criteria, but only one had a low risk of bias and evaluated patients with non-specific lower back pain (N=31). The two other studies examined specific subpopulations. Heterogeneity of the studies prevented meta-analysis. The one study with a low risk of bias did demonstrate that BoNT A injections were significantly better than control injections on pain intensity and improved function. There is no evidence for long-term improvement in pain intensity. The authors concluded that the evidence in favor of BoNT injections is only of low or very low quality and further research is very likely to change the estimate of effect.

The American Academy of Neurology found only one class II study that demonstrated that BoNT is possibly effective for the treatment of chronic predominantly unilateral low back pain.⁷ Although they give a Level C recommendation that it may be considered as a treatment option for patients with chronic predominantly unilateral low back pain, it is difficult to diagnose the precise origin of pain.

Hyperhidrosis:

Hyperhidrosis is a chronic idiopathic disorder of excessive sweating which usually affects the axillae, palms, soles, and forehead. Overall, there is a lack of high quality evidence and clinical guidelines to guide management of the disease.²⁷ Aluminum chloride topical preparations are the most widely used first line agent. When topical agents have not worked, BoNT (most commonly BoNT A) is often recommended. Effects are reported to last for 6 to 9 months with high reported

levels of patient satisfaction.²⁷ However, treatment is potentially lifelong. A small quasi-randomized trial (n=10) found ONA and ABO to be equally effective in reducing sweat rate and no difference in duration of benefit.²⁸ Patients were randomized based on date of birth which adds a significant risk of bias. Another double-blind trial compared ONA and INC in 46 patients with axillary hyperhidrosis using patient reported outcomes.²⁹ Both groups were equally effective, with a total of 89% reported the overall therapeutic effect as excellent. According to DynaMed, BoNT A intradermal injections are effective for up to 16 weeks and for improving quality of life (level 1 evidence) and BoNT B is reported to reduce sweating and improve quality of life based on poor quality evidence (level 3 evidence).³⁰

In the American Academy of Neurology (AAN) assessment of BoNT for the treatment of autonomic disorders and pain, a subcommittee recommended that BoNT should be offered as a treatment option to patients with axillary hyperhidrosis (Level A; Established as effective).⁷ Two Class I studies were identified in axillary hyperhidrosis. A RCT double-blind study showed that patients receiving BoNT had a higher response rate (more than 50% reduction of sweat production) at all time points than those receiving placebo (P<0.001). The panel also recommended it should be considered as a treatment option for palmar hyperhidrosis and drooling (Level B; Probably effective). There are no head to head comparisons of BoNT with other treatment options in hyperhidrosis or drooling.

The Canadian Hyperhidrosis Advisory Committee created guidelines for the treatment of primary focal hyperhidrosis.³¹ These guidelines recommend using the Hyperhidrosis Disease Severity Scale (HDSS) to measure disease severity before evaluating for treatment. A HDSS score of 2 is defined as underarm sweating is tolerable but sometimes interferes with daily activities. A score of 3 and 4 correlates with underarm sweating frequently interferes with daily activities to always interferes with daily activities. The following recommendations are provided:

Axillary Hyperhidrosis

HDSS Score of 2:

- For mild or moderate axillary hyperhidrosis, topical aluminum chloride is the first choice of therapy. An initial concentration of 10-2% may be tried to minimize irritation. Euhidrosis may not be achieved until a 35% solution is used.
- If a patient fails to respond to topical therapy after 1 month, intradermal injection of BoNT A may be administered. Treatment is repeated on average every 4 to 6 months when the patient has a change in HDSS score that warrants treatment.

HDSS Score of 3 or 4:

- For severe axillary hyperhidrosis, aluminum chloride or BoNT A is first line therapy.
- If a patient fails to respond, consider using both in combination.

Palmer and Plantar Hyperhidrosis

HDSS Score of 2:

- For mild or moderate axillary hyperhidrosis, aluminum chloride hexahydrate in absolute ethanol or in a salicylic acid gel is the therapy of first choice of therapy.
- If a patient fails to respond to topical therapy, intradermal injection of BoNT A may be administered or iontophoresis therapy initiated.

HDSS Score of 3 or 4:

- For severe palmer hyperhidrosis, aluminum chloride, iontophoresis or BoNT A are considered first line therapy.
- If a patient fails to respond, consider using both in combination.

Neurogenic Bladder Dysfunction and Overactive Bladder Syndrome:

Urinary symptoms can arise due to neurological disease in the brain, the spinal cord, or the peripheral nervous system. Damage within these areas can produce characteristic patterns of bladder and sphincter dysfunction. Conditions such as cerebral palsy, stroke, multiple sclerosis, Parkinson's disease, dementia, spinal cord injury, and peripheral neuropathy can cause dysfunction of the lower urinary tract system.³² Detrusor overactivity is defined as an urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. Detrusor overactivity is subdivided into idiopathic detrusor overactivity (IDO), or overactive bladder syndrome, and neurogenic detrusor overactivity (NDO). Overactive bladder syndrome is a symptom complex of urgency with or without urge incontinence. Overactive bladder symptoms may occur with or without NDO.³³ There are limited high quality systematic reviews evaluating BoNT for NDO. Oral antimuscarinic agents are recommended as first line treatment for neurogenic bladder dysfunction.³³ There is evidence that ONA reduces urinary incontinence but increases urinary tract infections in patients with NDO.^{33,34} A prospective, double-blind study demonstrated that ONA injection was associated with decreased incontinence episodes in patients with NDO due to multiple sclerosis.³⁵

A 2011 systematic review from the Cochrane Collaboration evaluated BoNT injections for adults with overactive bladder syndrome, both NDO and IDO.³⁶ A total of 19 unique studies met the inclusion criteria. The majority of studies included participants with NDO, often due to spinal cord injury or multiple sclerosis (MS). The majority also had symptoms refractory to antimuscarinics or did not tolerate the medication as an inclusion criteria. Two studies used BoNT B and the other 8 used BoNT A (two used ABO). Three studies compared intravesical BoNT A versus placebo in change in urinary frequency. At 4-6 weeks results favored BoNT A in reducing episodes per day (mean difference [MD] -6.50; 95% CI -8.92 to -4.07; $p < 0.001$; I²=0%). The meta-analysis for incontinence episodes also favored BoNT A at both 4-6 weeks (MC -1.58; 95% CI -2.16 to -1.01; $p = 0.00001$) and 12 weeks (MD -2.74; 95% CI -4.47 to -1.01; $p = 0.002$) of follow-up. However, the results for post-void residual volume (PVR) favored placebo with an increase of PVR of 10.22 ml (95% CI 30.63 to 109.81) in the BoNT group ($p = 0.00005$). Due to different tools used, no pooling of quality of life data could be performed. There were no trials that looked at if one formulation of BoNT is better than another, but it seems that BoNT A has a more durable effect than BoNT B which seems to be limited to less than 10 weeks. In addition, the optimally safe and effective dose is still undetermined. One small study suggested that a lower dose may have comparable efficacy to and improved safety over high doses. The authors concluded that BoNT injections appear to have an effective effect on refractory overactive bladder symptoms, but little controlled data exist on benefits and safety compared with other interventions, or with placebo. Further data is needed on long term outcomes, safety, and optimal dose.

Another systematic review evaluated the evidence of ONA and ABO in the treatment of NDO, including IDO, painful bladder syndrome, bladder outflow obstruction and detrusor sphincter dyssynergia.³⁷ The authors reviewed articles between 1985 and December 2010 and the results were compiled into high level and low level data. High level data were RCTs or well-designed quasi-experimental studies. Low level data included non-experimental, correlation or comparative studies. A total of 43 articles met the inclusion criteria. The authors noted that ONA has been studied more widely than ABO or the other preparations. ONA had high level data to support its use in all 5 conditions included; while ABO only had high level data for use in NDO. The evidence for use in detrusor sphincter dyssynergia is very limited, with most of the data coming from open label studies. There are no head to head comparisons of the two preparations.

Guidelines:

The American Urological Association (AUA) provides guidelines for the diagnosis and treatment of non-neurogenic overactive bladder, or IDO.³⁸ The primary evidence source was an AHRQ review of the treatment of overactive bladder in women.³⁹ Studies focusing on males were added to the database. The AUA performed its own analysis of the data. The panel notes that overactive bladder is not a disease but a symptom complex that generally is not life-threatening.

Based on expert opinion, no treatment is an acceptable choice made by some patients and caregivers. Treatment is focused on quality of life and symptom improvements. Further recommendations are as followed:

- First line therapy is behavioral therapies including bladder training, bladder control strategies, pelvic floor muscle training, and fluid management. (Grade B Evidence)
 - The literature indicates that behavioral treatments are generally either equivalent to or superior to medications in reducing incontinence episodes, improving frequency, and improving quality of life
- Oral anti-muscarinics, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium, are recommended as second-line therapy (Grade B Evidence), followed by transdermal oxybutynin (Grade C Evidence)
- If patients experience inadequate symptom control or adverse events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried.
- Third line treatment includes sacral neuromodulation or ONA to the carefully selected patient who has failed behavioral and anti-muscarinic therapy or who is not a candidate for these therapies (Grade C Evidence)
 - If prescribed ONA, the patient must be able and willing to return for frequent PVR evaluation and to perform self-catheterization.

The Obstetricians and Gynecologists of Canada also released guidelines for the treatment of unspecified overactive bladder.⁴⁰ These guidelines are consistent with AUA guidelines in recommending behavioral therapy as first line treatment, followed by anti-muscarinics as second line. BoNT A is only recommended for refractory overactive bladder due to the high rate of urinary retention. Studies have shown that up to 43% of patients needed clean intermittent self-catheterization. The guidelines recommend that intravesical BoNT A is a clinically effective option for patients unresponsive to conservative options, anticholinergics, or vaginal estrogen.

The European Association of Urology guidelines on neurogenic lower urinary tract dysfunction recommends that the mainstay of treatment for NDO anticholinergic drug therapy (Grade A recommendation), which is a non-invasive conservative treatment.⁴¹ In regards to minimal invasive treatments, the guidelines state that BoNT injection in the detrusor is most effective minimally invasive treatment to reduce NDO.⁴¹ BoNT causes a long-lasting but reversible chemical denervation that lasts for about 9 months. Generalized muscular weakness is an occasional adverse effect. The Consortium for Spinal Cord Medicine clinical practice guidelines recommend considering ONA injections into detrusor for patients with intermittent catheterization with detrusor overactivity.⁴² A NICE clinical guideline for NDO was published in August 2012 based on the best available evidence.³² BoNT injections are not included in the recommendations for stress incontinence or for the treatment to improve bladder emptying. The following recommendations are given to improve bladder storage:

- Offer bladder wall injection with BoNT A to adults and consider in children:
 - With spinal cord disease AND
 - Symptoms of an overactive bladder or urodynamic investigations showing impaired bladder storage AND
 - In whom antimuscarinic drugs have proven to be ineffective or poorly tolerated
- Before offering bladder wall injection with BoNT A:
 - Explain that a catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, AND
 - That they are able and willing to manage such a regimen should urinary retention develop after the treatment.

The American Academy of Neurology evaluated the literature for the treatment of neurogenic bladder from detrusor overactivity and detrusor sphincter dyssynergia with BoNT.⁷ The review found that BoNT is established as safe and effective for the treatment of NDO in adults (3 studies) and data on the use of BoNT for detrusor sphincter dyssynergia are conflicting. BoNT is probably safe and effective for the treatment in patients with spinal cord injury. However, one class I study did not show significant benefit in the treatment of detrusor sphincter dyssynergia in patients with MS. The following recommendations are provided:

- BoNT should be offered as a treatment option for NDO (Level A).
- BoNT should be considered for detrusor sphincter dyssynergia in patients with spinal cord injury (Level B).

A NICE clinical guideline for the management of urinary incontinence in women was issued in September 2013.⁴³ These guidelines recommend injection of BoNT A to women with overactive bladder caused by proven detrusor overactivity that has not responded to conservative management (including drug therapy with antimuscarinics). They also recommend discussing the risk and benefits, including the risk of intermittent catheterization and the increased risk of urinary tract infection. Treatment should only be started in women who have been trained in clean intermittent catheterization and have performed the technique successfully, and are able and willing to perform this on a regular basis for as long as needed. The recommended dose is 200 units of BoNT-A, or 100 units for women who would prefer a lower dose. BoNT-B should not be offered to women with proven NDO

Anal Fissure: Chronic Anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter, and is treated surgically with an internal sphincterotomy. According to DynaMed, BoNT has inconsistent evidence for increasing healing of anal fissure but appears less effective than sphincterotomy.⁴⁴

Based on a Cochrane Collaboration systematic review limited by heterogeneity, authors concluded that medical therapy for chronic anal fissure, including topical glyceryl trinitrate, BoNT (unspecified serotype) or topical calcium channel blockers for fissure in children may be applied with a chance of cure that is marginally better than placebo.⁴⁵ For chronic fissure in adults, all medical therapies were found to be far less effective than surgery. Glyceryl trinitrate was found to be marginally but significantly better than placebo in healing anal fissure (48.9% vs. 35.5%/ $p<0.0009$). Studies identified showed that BoNT injection was found in combined analysis to be no better or worse than topical glyceryl trinitrate (OR 0.56; 95% CI 0.20-1.57; $p=0.27$; $I^2=71\%$), and also no better than placebo (OR 0.29; 95% CI 0.02-3.61; $p=0.34$; $I^2=89\%$). BoNT has also not been shown to do as well as surgery in curing fissure (OR 7.20; 95% CI 3.97-13.07; $p<0.001$; $I^2=47\%$). There was no difference seen in one study between ONA and ABO in non-healing of fissure (OR 1.36; 95% CI 0.29-6.43; $p=0.70$), and the authors concluded that the type of BoNT has not been found to affect healing rates. Overall, there was high quality evidence of a significantly higher risk of non-healing (persistence or recurrence) in any medical therapy compared to any surgery (OR 0.11; 95% CI 0.06 to 0.23; $p<0.001$; $I^2=62\%$).

The American Society of Colon and Rectal Surgeons released practice guidelines for the management of anal fissures based on a literature search and evidence grading.⁴⁶ The following recommendations are provided:

- Nonoperative measures including sitz baths, psyllium fiber and bulking agents with or without the addition of topical anesthetics or anti-inflammatory ointments is recommended first line (strong recommendations; moderate quality evidence).
- Topical nitrates may be used, although they are only marginally superior to placebo in regard to healing (strong recommendation; high quality evidence).
- Anal fissures may be treated with topical calcium blockers, which have a lower incidence of adverse effects than topical nitrates. There are insufficient data to conclude whether they are superior to placebo in healing anal fissures (strong recommendation; moderate quality evidence).

- BoNT has been associated with healing rates superior to placebo. There is inadequate consensus on dosage, site of administration, number of injections or efficacy (Strong recommendation; low quality evidence).
- Surgery is consistently superior to medical therapy and may be offered without a pharmacological treatment failure (Strong recommendation; high quality evidence).

Achalasia

Achalasia is enlargement of the esophagus. Treatment is focused on relieving the obstruction in the distal esophagus created by the incompletely relaxed lower esophageal sphincter. Pharmacological therapy, BoNT injection, pneumatic dilatation (PD), and surgical myotomy are the primary treatment strategies in management of achalasia. BoNT injections are recommended for patients who are poor candidates for other more effective treatment options, such as surgery or dilation.⁴⁷ BoNT has been shown to be effective in the short term, but has a high rate of relapse and efficacy quickly and dramatically decreases by 2 years.⁴⁸ A meta-analysis by Campos et al. evaluated 9 studies utilizing BoNT as the primary form of therapy. The percentage of patients with symptomatic improvement after one session of BoNT injection was 78.7% at 1 month, 7% at 3 months, 53.3% at 6 months, and 40.6% at over 12 months. However, at least a second injection was required in almost half of patients (46.6%).

A 2006 Cochrane Collaboration systematic review identified 6 studies comparing PD to BoNT (unspecified serotype), both endoscopic options, in patients with primary achalasia.⁴⁹ Results of a meta-analysis demonstrated no significant difference in remission between PD and BoNT treatment (RR 1.15; 95% CI 0.95 to 1.38; p=0.39). There was also no significant difference in the mean esophageal pressures between the groups. At 6 months, more patients were in remission in the PD group compared to the BoNT group (RR 2.90; 95% CI 1.48 to 5.67; p=0.00), as well as at 12 months (RR 2.67; 95% CI 1.58 to 4.52; p=0.0002). The authors concluded that PD is the more effective endoscopic treatment in the long term for patients with achalasia.

Another systematic review by Wang, et al. evaluated remission and relapse rate of BoNT compared to PD and surgical myotomy for the treatment of achalasia.⁵⁰ A total of 17 clinical studies were included in the analysis (n=761). Five of the studies compared unspecified BoNT injection with PD, 2 compared BoNT with myotomy. Results demonstrated significant differences in remission rate between PD and BoNT (65.8% vs. 36%; RR 2.20; 95% CI 1.51-3.20, p<0.0001) and relapse rate (16.7% vs. 50%; RR 0.36; 95% CI 0.22-0.58) favoring BoNT at 12 months. The authors concluded that PD remains more efficacious than BoNT for the treatment of achalasia. They also found that myotomy had superior efficacy to BoNT in remission rate (83.3% vs. 64.9%; RR 1.28; 95% CI 1.02-1.59; p=0.03). However, there were also more adverse events with BoNT compared to PD (4.5% vs. 18.8%). There was insufficient data to perform a meta-analysis on adverse events and withdrawals. The authors concluded that laparoscopic myotomy is the preferred method in the management of achalasia and BoNT can offer dysphagia control, but it is temporary and reversible.

The American College of Gastroenterology recommends PD or laparoscopic surgical myotomy as first line therapy (strong recommendation; moderate quality evidence).⁵¹ BoNT (ONA) is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy (strong recommendation, moderate quality evidence). Lastly, pharmacologic therapy (smooth muscle relaxants) is recommended for patients who have failed BoNT therapy. The primary disadvantage with BoNT for this use is that repeat injections after 6 to 12 months are commonly needed, and the long-term efficacy and safety are not well studied beyond 2 years. Although the initial response rate is high (>75%), the effect eventually wears off and repeat injection is required in a significant portion of the patients. Approximately 50% of patients relapse and require repeat treatments at 6-24 month intervals. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) conducted a literature search to also provide guidelines for the treatment of esophageal achalasia.⁵² They are consistent that a single injection of BoNT has been shown to be quite effective, but its long term effectiveness remains limited. They recommend that BoNT can

be administered safely, but its effectiveness is limited especially in the long-term. It should be reserved for patients who are poor candidates for other more effective treatment options, such as surgery or dilation (strong recommendation).

Under the rein of the International Society for Diseases of Esophagus, the Kagoshima consensus on esophageal achalasia was released in 2010.⁵³ The statement discusses that the clinical response at 2 years is only 3%, decreasing from 90% as an initial clinical response. However, the panel noted that because of its safety, it may be a good option for elderly patients with comorbidities, but it also carries an increased risk of subsequent myotomy, due to fibrosis at the injection sites.

A randomized controlled trial compared the efficacy and tolerability of two BoNT formulations in treating achalasia (ONA and ABO).⁵⁴ After BoNT injection was given, 90% of the ONA group and 83.5% of the ABO group reported a symptomatic response to the treatment. No differences were seen between the two formulations in any clinical variables and side effects were similar. At the end of the follow-up period, symptom relapse was documented in 12% of ONA patients and 24% of ABO patients. This was reported as non-significant although p values were not provided.

Strabismus:

Strabismus is the misalignment of 2 eyes so that both cannot be directed toward an object. Comitant strabismus occurs in children <6 years old and noncomitant has an onset later in life. A 2012 Cochrane Collaboration systematic review evaluated the efficacy of any BoNT in the treatment of strabismus compared with alternative treatment options.⁵⁵ A literature search was done to identify RCTs and a total of 4 met inclusion criteria (3 with ONA and 1 with ABO). Two trials found that there was no difference between BoNT and surgery for infantile esotropia. There was no evidence for a prophylactic effect of BoNT in a treatment trial of acute onset sixth nerve palsy. BoNT had a poorer response than surgery in a trial of patients with horizontal strabismus. Trials included both ONA and ABO and there was insufficient evidence to establish a dose effect. The American Academy of Ophthalmology concludes that there is insufficient evidence to make treatment recommendations for BoNT treatment for exotropia.⁵⁶

Sialorrhea

Sialorrhea is excessive drooling commonly seen in patients with neurological disorders, such as cerebral palsy, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).⁵⁷ Treatment approaches include anticholinergics, antireflux medications, radiation and surgery. More recently, BoNT has become a potential treatment option in these patients. Vashishta, et al conducted a meta-analysis on the available evidence for the use of BoNT A and BoNT B in the treatment of sialorrhea. There were eight studies (three utilizing ONA or ABO and five using RIM) with 181 patients that were included in the analysis. Four studies were in children with cerebral palsy, 2 with adults with Parkinson's disease, and 1 in ALS. The use of BoNT was found to significantly decrease the severity of drooling when compared to placebo using an outcome measure of drooling severity and frequency scales. Both BoNT A and BoNT B preparations were effective in productin similarly significant reductions in drooling severity.⁵⁷ Advantages over alternate treatments include a more acceptable safety profile than transdermal scopolamine, fewer drug interactions than scopolamine and glycopyrrolate and a safer alternative to systemic anticholinergic therapy.

An international consensus statement was released for the care of patients with drooling as a result of a neurological problem or anatomical abnormality of the jaw.⁵⁸ Literature was searched and appraised to make recommendations. Based on expert opinion only, it is recommended that injection of BoNT A into the salivary glands is given under ultrasound guidance. Due to acquired resistance to BoNT therapy, it is recommend that BoNT B be tried after treatment failure with BoNT A.

Tremor

According to a systematic review of the evidence for BTP for essential tremor (Ferreira and Sampaio, 2003), there is evidence of short-term reduction of tremor but no consistent improvement in disability and function. The review noted that BTP injections cause hand weakness, resulting in a "trade off" between benefits and harms. The review concluded that BTP versus placebo found short term improvement of clinical rating scales, but no consistent improvement of motor task performance or functional disability. The AAN concluded that "the effect of BTA on limb tremor in ET [essential tremor] is modest and is associated with dose-dependent hand weakness and may reduce head tremor and voice tremor associated with ET, but data are limited. When used to treat voice tremor, botulinum toxin A may cause breathiness, hoarseness, and swallowing difficulties."

The AAN's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson et al, 2008) stated that botulinum neurotoxin should be considered a treatment option for essential hand tremor in those patients who fail treatment with oral agents. On the other hand, there is insufficient evidence to draw a conclusion on the use of BTP in the treatment of head and voice tremor.

Other Indications:

BoNT has been studied in a number of other disorders where this is insufficient evidence to recommend its use. Several open-label studies have evaluated BoNT in gastroparesis and observed mild improvements in gastric emptying and modest improvement in symptoms.⁵⁹⁻⁶¹ Two double-blind placebo-controlled trials have showed no difference in improvement in symptoms compared with placebo.⁶² BoNT injection into the pylorus is not recommended as a treatment for gastroparesis. BoNT A has also been evaluated for use in restless legs syndrome; however, there is insufficient evidence to support the use, with one double-blind, RCT showing no significant benefit with BoNT A compared to placebo.^{63,64} A recent systematic review from the Cochrane Collaboration were unable to identify any controlled clinical trials assessing the efficacy and safety of BoNT for masseter hypertrophy.⁶⁵

Other areas in which larger, well-designed studies are needed to demonstrate effectiveness include cricopharyngeal dysphagia, gustatory epiphora (crocodile tears), Sphincter of Oddi dysfunction, pancreas divisum, anismus, , pelvic floor spasticity, chronic prostatic pain, severe paradoxical vocal cord movement, postparotidectomy sialoceles, severe bruxism, temporomandibular disorders, myofascial pain syndrome, brachial plexus palsy, thyroid associated ophthalmopathy, esophageal spasm, post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia, trismus and stridor in amyotrophic lateral sclerosis, proctalgia fugax, nasal hypersecretion, gastroparesis (including diabetic gastroparesis), Lichen simplex, lateral epicondylitis, Stiff-person syndrome, benign prostatic hyperplasia, traumatic sixth nerve palsy, Tourette's syndrome, and pain and/or wound healing after hemorrhoidectomy. Only small and uncontrolled open-label studies have been performed for these conditions.

References:

1. Simpson DM, Blitzer A, Brashear A, et al. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(19):1699-1706. doi:10.1212/01.wnl.0000311389.26145.95.
2. Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol*. 2011;18(1):5-18. doi:10.1111/j.1468-1331.2010.03042.x.
3. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. *JAMA*. 2012;307(16):1736-1745. doi:10.1001/jama.2012.505.
4. Little A, Vandegriff S, King V. Botulinum toxin A treatment for chronic headache and chronic migraine. Hayes Systematic Reviews (Subscription required). 2011. Available at: www.hayesinc.com. Accessed March 21, 2014.
5. National Institute for Health and Clinical Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. NICE technology appraisal guidance 260. 2012. Available at: <http://www.nice.org.uk/nicemedia/live/13776/59836/59836.pdf>. Accessed March 25, 2014.
6. Pringsheim T, Davenport WJ, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2012;39(2 Suppl 2):S1-59.
7. Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(19):1707-1714. doi:10.1212/01.wnl.0000311390.87642.d8.
8. Langevin P, Peloso PMJ, Lowcock J, et al. Botulinum toxin for subacute/chronic neck pain. *Cochrane Database Syst Rev*. 2011;(7):CD008626. doi:10.1002/14651858.CD008626.pub2.
9. Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, Furlan AD. Botulinum toxin injections for low-back pain and sciatica. *Cochrane Database Syst Rev*. 2011;(1):CD008257. doi:10.1002/14651858.CD008257.pub2.
10. VHA Pharmacy Benefits Management Services. Drug Class Review: Botulinum Toxins. 2013. Available at: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CDwQFjAA&url=http%3A%2F%2Fwww.pbm.va.gov%2FPPBM%2Fclinicalguidance%2Fdrugclassreviews%2FBotulinum_Toxins_Class_Review.docx&ei=mXwjU_yMLa2yygHgpoHwCA&usg=AFQjCNF2x54IHgXSzSHrm0ri6Yud8a40w&sig2=uHPwZVH2rWN5d0ANjavhtA&bvm=bv.62922401,d.aWc. Accessed March 14, 2014.
11. Nigam PK, Nigam A. BOTULINUM TOXIN. *Indian J Dermatol*. 2010;55(1):8-14. doi:10.4103/0019-5154.60343.

12. Costa J, Borges A, Espírito-Santo C, et al. Botulinum toxin type A versus botulinum toxin type B for cervical dystonia. *Cochrane Database Syst Rev*. 2005;(1):CD004314. doi:10.1002/14651858.CD004314.pub2.
13. Dutton JJ, White JJ, Richard MJ. Myobloc for the treatment of benign essential blepharospasm in patients refractory to botox. *Ophthalm Plast Reconstr Surg*. 2006;22(3):173-177. doi:10.1097/01.iop.0000217382.33972.c4.
14. Chen JJ, Dashtipour K. Abo-, inco-, ona-, and rima-botulinum toxins in clinical therapy: a primer. *Pharmacotherapy*. 2013;33(3):304-318. doi:10.1002/phar.1196.
15. Novak I, Campbell L, Boyce M, Fung VSC, Cerebral Palsy Institute. Botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck: international consensus statement. *Eur J Neurol*. 2010;17 Suppl 2:94-108. doi:10.1111/j.1468-1331.2010.03130.x.
16. DynaMed. Botulinum Toxin Type A. Available at: <http://web.a.ebscohost.com/dynamed/detail?vid=5&sid=a892f1f9-99c4-4b53-8229-65aea99b71b1%40sessionmgr4004&hid=4209&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BIPXNpdGU%3d#db=dme&AN=232969>. Accessed March 14, 2014.
17. Costa J, Espírito-Santo C, Borges A, et al. Botulinum toxin type A therapy for blepharospasm. *Cochrane Database Syst Rev*. 2005;(1):CD004900. doi:10.1002/14651858.CD004900.pub2.
18. Costa J, Espírito-Santo C, Borges A, et al. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev*. 2005;(1):CD003633. doi:10.1002/14651858.CD003633.pub2.
19. Pappert EJ, Germanson T, Myobloc/Neurobloc European Cervical Dystonia Study Group. Botulinum toxin type B vs. type A in toxin-naïve patients with cervical dystonia: Randomized, double-blind, noninferiority trial. *Mov Disord*. 2008;23(4):510-517. doi:10.1002/mds.21724.
20. Comella CL, Jankovic J, Shannon KM, et al. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology*. 2005;65(9):1423-1429. doi:10.1212/01.wnl.0000183055.81056.5c.
21. Balash Y, Giladi N. Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. *Eur J Neurol*. 2004;11(6):361-370. doi:10.1111/j.1468-1331.2004.00845.x.
22. Baker JA, Pereira G. The efficacy of Botulinum Toxin A for spasticity and pain in adults: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. *Clin Rehabil*. 2013;27(12):1084-1096. doi:10.1177/0269215513491274.

23. Simpson DM, Gracies J-M, Graham HK, et al. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review) Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of. *Neurology*. 2008;70(19):1691-1698. doi:10.1212/01.wnl.0000311391.00944.c4.
24. Royal College of Physicians. , British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using botulinum toxin. National guidelines. London: RCP, 2009.
25. Love SC, Novak I, Kentish M, et al. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. *Eur J Neurol*. 2010;17 Suppl 2:9-37. doi:10.1111/j.1468-1331.2010.03126.x.
26. DynaMed. Migraine Prophylaxis in Adults. Available at: <http://web.b.ebscohost.com/dynamed/detail?vid=9&sid=59e6b65c-ba9a-47ec-b22d-25f272635553%40sessionmgr114&hid=113&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=253050>. Accessed March 14, 2014.
27. Benson RA, Palin R, Holt PJE, Loftus IM. Diagnosis and management of hyperhidrosis. *BMJ*. 2013;347:f6800.
28. Talarico-Filho S, Mendonça DO Nascimento M, Sperandeo DE Macedo F, DE Sanctis Pecora C. A double-blind, randomized, comparative study of two type A botulinum toxins in the treatment of primary axillary hyperhidrosis. *Dermatol Surg*. 2007;33(1 Spec No.):S44-50. doi:10.1111/j.1524-4725.2006.32331.x.
29. Dressler D. Comparing Botox and Xeomin for axillar hyperhidrosis. *J Neural Transm*. 2010;117(3):317-319. doi:10.1007/s00702-010-0372-0.
30. DynaMed. Botulinum toxin for hyperhidrosis. Available at: <http://web.a.ebscohost.com/dynamed/detail?vid=3&sid=0db58913-b7da-4edd-8409-d7d6197f67a4%40sessionmgr4002&hid=4107&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=361034>. Accessed April 15, 2014.
31. Solish N, Bertucci V, Dansereau A, et al. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg*. 2007;33(8):908-923. doi:10.1111/j.1524-4725.2007.33192.x.
32. National Institute for Health and Clinical Excellence. Urinary incontinence in neurological disease. Management of lower urinary tract dysfunction in nuerological disease. NICE clinical guideline 148. 2012. Available at: guidance.nice.org.uk/cg148.
33. Soljanik I. Efficacy and safety of botulinum toxin A intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review. *Drugs*. 2013;73(10):1055-1066. doi:10.1007/s40265-013-0068-5.

34. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2011;60(4):742-750. doi:10.1016/j.eururo.2011.07.002.
35. Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. *J Urol*. 2011;185(6):2229-2235. doi:10.1016/j.juro.2011.02.004.
36. Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Database Syst Rev*. 2011;(12):CD005493. doi:10.1002/14651858.CD005493.pub3.
37. Mangera A, Andersson K-E, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). *Eur Urol*. 2011;60(4):784-795. doi:10.1016/j.eururo.2011.07.001.
38. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188(6 Suppl):2455-2463. doi:10.1016/j.juro.2012.09.079.
39. Hartmann K, McPheeters M, Biller D, et al. Treatment of Overactive Bladder in Women. Evidence Report/Technology Assessment No. 187 (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). AHRQ Publication No. 09-E017. Rockville, MD: Agency for Healthcare Research and Quality. August 2009.
40. Geoffrion R, Urogynecology Committee. Treatments for Overactive Bladder: Focus on Pharmacotherapy. *J Obstet Gynaecol Can*. 2012;34(11):1092-1101.
41. Stohrer M, Block B, Castro-Diaz G, Del Popolo G, Kramer G. European Association of Urology: Guidelines on Neurogenic Lower Urinary Tract Dysfunction. *European Association of Urology*. 2011. Available at: <http://www.uroweb.org/gls/pdf/17%5FNeurogenic%20LUTS.pdf>.
42. Consortium for Spinal Cord Medicine. Bladder management for adults with spinal cord injury: a clinical practice guideline for health-care providers. *J Spinal Cord Med*. 2006;29(5):527-573.
43. NICE. Urinary incontinence in women. *NICE*. Available at: <http://www.nice.org.uk/>. Accessed April 11, 2014.
44. DynaMed. Anal Fissure: DynaMed Review. Available at: <http://web.a.ebscohost.com/dynamed/detail?vid=8&sid=0db58913-b7da-4edd-8409-d7d6197f67a4%40sessionmgr4002&hid=4107&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BIPXNpdGU%3d#db=dme&AN=113851>. Accessed March 30, 2014.
45. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. *Cochrane Database Syst Rev*. 2012;2:CD003431. doi:10.1002/14651858.CD003431.pub3.

46. Perry WB, Dykes SL, Buie WD, Rafferty JF, Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for the management of anal fissures (3rd revision). *Dis Colon Rectum*. 2010;53(8):1110-1115. doi:10.1007/DCR.0b013e3181e23dfe.
47. DynaMed. Achalasia: DynaMed Review. Available at: <http://web.a.ebscohost.com/dynamed/detail?vid=10&sid=0db58913-b7da-4edd-8409-d7d6197f67a4%40sessionmgr4002&hid=4107&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=114877>. Accessed April 15, 2014.
48. Ramzan Z, Nassri A. The role of Botulinum toxin injection in the management of achalasia. *Current Opinion in Gastroenterology*. 2013;29(4):468-73. doi:<http://dx.doi.org/10.1097/MOG.0b013e328362292a>.
49. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev*. 2006;(4):CD005046. doi:10.1002/14651858.CD005046.pub2.
50. Wang L, Li Y-M, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. *Dig Dis Sci*. 2009;54(11):2303-2311. doi:10.1007/s10620-008-0637-8.
51. Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol*. 2013;108(8):1238-1249; quiz 1250. doi:10.1038/ajg.2013.196.
52. Stefanidis D, Richardson W, Farrell TM, et al. SAGES guidelines for the surgical treatment of esophageal achalasia. *Surg Endosc*. 2012;26(2):296-311. doi:10.1007/s00464-011-2017-2.
53. Triadafilopoulos G, Boeckxstaens GE, Gullo R, et al. The Kagoshima consensus on esophageal achalasia. *Dis Esophagus*. 2012;25(4):337-348. doi:10.1111/j.1442-2050.2011.01207.x.
54. Annese V, Bassotti G, Coccia G, et al. Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia. The Gismad Achalasia Study Group. *Aliment Pharmacol Ther*. 1999;13(10):1347-1350.
55. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. *Cochrane Database Syst Rev*. 2012;2:CD006499. doi:10.1002/14651858.CD006499.pub3.
56. American Academy of Ophthalmology Pediatric Strabismus Panel. Preferred Practice Pattern Guidelines for Esotropia and Exotropia. San Francisco, CA: American Academy of Ophthalmology; 2012. Available at: www.aao.org/ppp.
57. Vashishta R, Nguyen SA, White DR, Gillespie MB. Botulinum toxin for the treatment of sialorrhea: a meta-analysis. *Otolaryngol Head Neck Surg*. 2013;148(2):191-196. doi:10.1177/0194599812465059.

58. Reddihough D, Erasmus CE, Johnson H, McKellar GMW, Jongerius PH, Cerebral Palsy Institute. Botulinum toxin assessment, intervention and aftercare for paediatric and adult drooling: international consensus statement. *Eur J Neurol*. 2010;17 Suppl 2:109-121. doi:10.1111/j.1468-1331.2010.03131.x.
59. Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointestinal Endoscopy*. 2002;55(7):920-923. doi:10.1067/mge.2002.124739.
60. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol*. 2002;97(7):1653-1660. doi:10.1111/j.1572-0241.2002.05823.x.
61. Lacy BE, Crowell MD, Schettler-Duncan A, Mathis C, Pasricha PJ. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes Care*. 2004;27(10):2341-2347.
62. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther*. 2007;26(9):1251-1258. doi:10.1111/j.1365-2036.2007.03467.x.
63. Nahab FB, Peckham EL, Hallett M. Double-blind, placebo-controlled, pilot trial of botulinum toxin A in restless legs syndrome. *Neurology*. 2008;71(12):950-951. doi:10.1212/01.wnl.0000325994.93782.a1.
64. Agarwal P, Sia C, Vaish N, Roy-Faderman I. Pilot trial of onabotulinumtoxin A (Botox) in moderate to severe restless legs syndrome. *Int J Neurosci*. 2011;121(11):622-625. doi:10.3109/00207454.2011.602774.
65. Fedorowicz Z, van Zuuren EJ, Schoones J. Botulinum toxin for masseter hypertrophy. *Cochrane Database Syst Rev*. 2013;9:CD007510. doi:10.1002/14651858.CD007510.pub3.

Appendix A: Dosing for BoNT Preparations

Indication	Abobotulinumtoxin A	Incobotulinumtoxin A	Onabotulinumtoxin A	Rimabotulinumtoxin B
Cervical dystonia	500 units IM divided among affected muscles	120 units IM divided among affected muscles	198 units – 300 units IM divided among affected muscles, max 50 units per site	2,500 units – 5,000 units IM divided among affected muscles
Upper limb spasticity	500 units – 1,500 units IM divided among affected muscles	80 units – 435 units IM divided among affected muscles	75 units – 360 units IM divided among affected muscles, max 50 units per site	1,000 units – 5,000 units IM divided among affected muscles
Blepharospasm	40 units – 120 units as divided injections	1.25 units – 2.5 units injected into medial and lateral pretarsal orbicularis oculi of the upper lid and lateral pretarsal orbicularis oculi of the lower lid	1.25 units – 2.5 units injected into medial and lateral pretarsal orbicularis oculi of the upper lid and lateral pretarsal orbicularis oculi of the lower lid	
Axillary hyperhidrosis	200 units intradermally per axilla		50 units intradermally per axilla	
Overactive Bladder/Urinary			100 units divided into 20 intradetrusor injections	5,000 units divided into 10 intradetrusor injections sparing

Incontinence			sparing the trigone	the trigone
Neurogenic detrusor overactivity	500 units divided into 20 intradetrusor injections sparing the trigone		200 units divided into 30 intradetrusor injections sparing the trigone	
Chronic migraine prophylaxis			155 units IM divided in 31 sites	
PES	200 units injected into the PES musculature		100 units injected into the PES musculature	

Treatment for Gender Dysphoria 2014

Question: What therapies should be included for treatment of gender dysphoria on the Prioritized List?

Question Source: HERC staff, OHA

Issue:

The October 1, 2014 Prioritized List includes Gender Dysphoria as a new, covered line (413). Currently, the only treatments on this line are office visits, psychotherapy and puberty suppression medication for transgender and gender-questioning youth. Other treatments for gender dysphoria include cross-sex hormone therapy and sex reassignment (gender reassignment) surgery.

Cross-sex hormone therapy and sex reassignment surgery were reviewed at the May and June, 2014 VBBS meetings. Evidence was reviewed about the efficacy of treatment, particularly in reducing suicide attempts, IV drug abuse, and other high risk behavior. Treatment was also found to significantly reduce depression and anxiety in patients. The cost of adding coverage for gender dysphoria treatments was found to be small. The subcommittee felt that the evidence supported adding cross-sex hormone therapy and sex reassignment surgery to the gender dysphoria line.

HERC staff was charged with refining wording of the guideline for gender dysphoria, with particular attention to the requirements for sex reassignment surgery. Proposed new scoring for the gender dysphoria line was briefly discussed, but needs further in-depth discussion. The specific surgical codes for addition to the gender dysphoria line also need approval.

Treatment for Gender Dysphoria 2014

CPT codes for sex reassignment surgery

CPT code	Code description	Current placement
19301-19304	Mastectomy	195 CANCER OF BREAST
53430	Urethroplasty, reconstruction of female urethra	91 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
54125	Amputation of penis; complete	262 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
54400-54417	Insertion/repair/removal of penile prosthesis	529 SEXUAL DYSFUNCTION Some on 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
54520	Orchiectomy, simple (including subcapsular), with or without testicular prosthesis, scrotal or inguinal approach	98,116,211,249,262,331,333,474
54660	Insertion of testicular prosthesis (separate procedure)	98 UNDESCENDED TESTICLE 249 TORSION OF TESTIS
54690	Laparoscopy, surgical; orchiectomy	98,116,428,474
55175-55180	Scrotoplasty	91, 262, 438 HYPOSPADIAS AND EPISPADIAS
55970	Intersex surgery; male to female	Excluded
55980	Intersex surgery; female to male	Excluded
56625	Vulvectomy simple; complete	291 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS
56800	Plastic repair of introitus	125,211,356,428
56805	Clitoroplasty for intersex state	428 ADRENOGENITAL DISORDERS,638 BENIGN CERVICAL CONDITIONS
56810	Perineoplasty, repair of perineum, nonobstetrical	125 ABUSE AND NEGLECT,428, 471 UTERINE PROLAPSE; CYSTOCELE
57106-57107	Vaginectomy, partial removal of vaginal wall;	291,471
57110-57111	Vaginectomy, complete removal of vaginal wall	291
57291-57292	Construction of artificial vagina	356 STRUCTURAL CAUSES OF AMENORRHEA
57335	Vaginoplasty for intersex state	428
58150, 58180, 58260-58262, 58275-58291, 58541-58544, 58550-58554, 58570-58573	Hysterectomy	Multiple lines, with several guidelines
58661	Laparoscopy, surgical; with removal of adnexal structures	Multiple lines
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral	Multiple lines

Treatment for Gender Dysphoria 2014

Note: Rhinoplasty, face-lifting, lip enhancement, facial bone reduction, blepharoplasty, breast augmentation, liposuction of the waist (body contouring), reduction thyroid chondroplasty, hair removal, voice modification surgery (laryngoplasty or shortening of the vocal cords), and skin resurfacing, which have been used in feminization, are considered cosmetic. Similarly, chin implants, nose implants, and lip reduction, which have been used to assist masculinization, are considered cosmetic.

Treatment for Gender Dysphoria 2014

HSC Staff Recommendations:

- 1) Add cross-sex hormone therapy and sex-reassignment surgery to line 413
GENDER DYSPHORIA for the January 1, 2015 PL
 - 1) Good evidence found for reduction in psychiatric symptoms and suicide attempts with treatment
 - 2) Overall cost for full spectrum of treatment expected to be minimal, with some cost savings with reduced suicide attempts, psychiatric care, etc.
 - 3) Add surgical codes as shown below (see table above for specifics)
 - i. Advise DMAP to remove CPT 55970 and 55980 from the Excluded List.
 - 4) Reprioritize line 413 as shown below
 - i. Change category from 7 to 6 given high rate of suicide in this group
 - ii. Change HL from 3 to 6 due to fatality from this condition
 - 5) Change the guideline for line 413 as shown below

Line 413

Condition: GENDER DYSPHORIA

Treatment: ~~MEDICAL/PSYCHOTHERAPY~~ MEDICAL AND SURGICAL TREATMENT: PSYCHOTHERAPY

ICD-9: 302.85 (Gender identity disorder in adolescents or adults)

ICD10: F64.1-F64.9 (Gender identity disorder)

CPT: 19301-19304, 53430, 54125, 54400-54417, 54520, 54660, 54690, 55175-55180, 55970, 55980, 56625, 56800, 56805, 56810, 57106-57107, 57110-57111, 57291-57292, 57335, 58150, 58180, 58260-58262, 58275-58291, 58541-58544, 58550-58554, 58570-58573, 58661, 58720, 90785, 90832-90840, 90846-90853, 90882, 90887, 96101, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99355, 99358-99378, 99381-99404, 99408-99412, 99429-99449, 99487-99496, 99605-99607

HCPCS: G0176, G0177, G0396, G0397, G0459, G0463, H0004, H0023, H0032, H0034, H0035, H2010, H2011, H2014, H2027, H2032, H2033, S9484, T1016

Scoring proposal (current scoring for line 413 in parentheses)

Category: 6 (7)

HL: 6 (3)

Suffering: 4 (4)

Population effects: 0 (0)

Vulnerable population: 0 (0)

Tertiary prevention: 3 (3)

Effectiveness: 2 (2)

Need for service: 1 (1)

Net cost: 2 (2)

Score: 1040

Approximate line placement: 312

Treatment for Gender Dysphoria 2014

GUIDELINE XXX GENDER DYSPHORIA

Line 413

Hormone treatment is included on this line for use in delaying the onset of puberty and/or continued pubertal development with GnRH analogues for gender questioning children and adolescents. This therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria, and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

- 1) have persistent, well-documented gender dysphoria
- 2) have the capacity to make a fully informed decision and to give consent for treatment
- 3) have any significant medical or mental health concerns reasonably well controlled
- 4) have a thorough psychosocial assessment by a qualified mental health professional with experience in working with patients with gender dysphoria

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

- 1) have persistent, well documented gender dysphoria
- 2) have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
- 3) have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
- 4) have the capacity to make a fully informed decision and to give consent for treatment
- 5) have any significant medical or mental health concerns reasonably well controlled
- 6) have two referrals from qualified mental health professionals with experience in working with patients with gender dysphoria who have independently assessed the patient. Such an assessment should include the clinical rationale supporting the patient's request for surgery, as well as the of the procedure(s)

Self-injurious problem behavior guideline

Question: Should applied behavioral analysis be added to the self-injurious behavior line with a guideline?

Question source: Value-based Benefits Subcommittee

Issue:

In June 2014 VbBS approved a new guideline on treatment of autistic spectrum disorder with applied behavioral analysis. Many of the studies and discussion centered around self-injurious behavior. There was a concern that the guideline adopted only impacted patients diagnosed with autism and did not affect non-autistic patients with self-injurious behaviors. The following language was approved for autistic spectrum individuals ages 13 and older:

GUIDELINE NOTE 75 APPLIED BEHAVIORAL ANALYSIS FOR AUTISM SPECTRUM DISORDER

Line 217

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI) (CPT 0359T-0363T), is included on line 313 for the treatment of autism spectrum disorders.

Individuals ages 1-12

Intensive interventions

Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365 other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration of less than one year and up to 3 years.

Less intensive ABA-based interventions

Self-injurious problem behavior guideline

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with proof of medical appropriateness and/or emergence of new problem behaviors. Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. There is insufficient quality evidence to support these interventions in this population, however, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with proof of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.

Self-injurious problem behavior guideline

Line: 462
 Condition: STEREOTYPY/HABIT DISORDER AND SELF-ABUSIVE BEHAVIOR DUE TO NEUROLOGICAL DYSFUNCTION
 (See Guideline Notes 64,65)
 Treatment: CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION
 ICD-9: 307.3
 CPT: 90785,90832-90840,90846-90853,90882,90887,96101,98966-98969,99051,99060,99201-99215,99224,99324-99350,99366,99441-99449,99487-99496,99605-99607
 HCPCS: G0176,G0177,G0410,G0411,G0425-G0427,G0459,G0463,H0004,H0023,H0032,H0034-H0039,H2010-H2014,H2021-H2023,H2027,H2032,S9125,S9480,S9484,T1016

Code	Code Description
90785	Interactive complexity (List separately in addition to the code for primary procedure)
90832	Psychotherapy, 30 minutes with patient and/or family member
90833	Psychotherapy, 30 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90834	Psychotherapy, 45 minutes with patient and/or family member
90836	Psychotherapy, 45 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90837	Psychotherapy, 60 minutes with patient and/or family member
90838	Psychotherapy, 60 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90839	Psychotherapy for crisis; first 60 minutes
90840	Psychotherapy for crisis; each additional 30 minutes (List separately in addition to code for primary service)
90846	Family psychotherapy (without the patient present)
90847	Family psychotherapy (conjoint psychotherapy) (with patient present)
90849	Multiple-family group psychotherapy
90853	Group psychotherapy (other than of a multiple-family group)
90882	Environmental intervention for medical management purposes on a psychiatric patient's behalf with agencies, employers, or institutions
90887	Interpretation or explanation of results of psychiatric, other medical examinations and procedures, or other accumulated data to family or other responsible persons, or advising them how to assist patient
96101	Psychological testing (includes psychodiagnostic assessment of emotionality, intellectual abilities, personality and psychopathology, eg, MMPI, Rorschach, WAIS), per hour of the psychologist's or physician's time, both face-to-face time administering tests to the patient and time interpreting these test results and preparing the report

Recommendations:

- 1) Add a guideline

GUIDELINE NOTE XXX Applied Behavioral Analysis (ABA) Interventions for Self-Injurious Behavior *Line 462*

Targeted ABA-based interventions towards self-injurious problem behaviors are included on this line when meeting criteria as defined in

Self-injurious problem behavior guideline

guideline note 75 APPLIED BEHAVIORAL ANALYSIS FOR AUTISM SPECTRUM DISORDER.

2) Add the following codes to Line 462

Code	Description	Recommendation
0359T	Behavior identification assessment	Add to 462
Follows 0359T 0360T 16-45 min 0361T each additional 30 min	Observational behavioral follow-up assessment	Add to 462
Follows 0359T 0362T 16-45 min 0363T each additional 30 min	Exposure behavioral follow-up assessment	Add to 462
0364T first 30 min 0365T each additional 30 min	Adaptive behavior treatment by protocol	Add to 462
0366T first 30 min 0367T each additional 30 min	Group adaptive behavior treatment by protocol	Add to 462
0368T first 30 min 0369T each additional 30 min	Adaptive behavior treatment with protocol modification	Add to 462
0370T	Family adaptive behavior treatment guidance	Add to 462
0371T	Multiple-family group adaptive behavior treatment guidance	Do not add
0372T	Adaptive behavior treatment social skills group	Do not add
0373T first 60 minutes of technicians' time, 0374T each additional 30 minutes of technicians' time	Exposure adaptive behavior treatment with protocol modification	Add to 462



CPT® Category III Codes

The following CPT codes are an excerpt of the CPT Category III code set, a temporary set of codes for emerging technologies, services, and procedures.

For more information on the criteria for CPT Category I, II and III codes, see [Applying for Codes](#).

To assist users in reporting the most recently approved Category III codes, the AMA's CPT Web site features updates of the CPT Editorial Panel actions and early release of the Category III codes in July and January in a given CPT cycle. This was approved by the CPT Editorial Panel as a part of the 1998-2000 CPT-5 projects. These dates for early release correspond with the three annual CPT Editorial Panel meetings for each CPT cycle (June, October, and February). Although publication of Category III codes through early release to the CPT web site allows for expedient dispersal of the code and descriptor, early availability does not imply that these codes are immediately reportable before the posted implementation date.

Publication of the Category III codes to this Web site takes place on a semiannual basis when the codes have been approved by the CPT Editorial Panel. The full set of temporary Category III codes for emerging technology, procedures and services are published annually in the code set for each CPT publication cycle.

As with CPT Category I codes, inclusion of a descriptor and its associated code number does not represent endorsement by the AMA of any particular diagnostic or therapeutic procedure or service. Inclusion or exclusion of a procedure or service does not imply any health insurance coverage or reimbursement policy.

Background information for Category III codes

CPT Category III codes are a set of temporary codes that allow data collection for emerging technology, services, and procedures. These codes are intended to be used for data collection to substantiate widespread usage or to provide documentation for the Food and Drug Administration (FDA) approval process. The CPT Category III codes may not conform to the following CPT Category I code requirements:

- All devices and drugs necessary for performance of the procedure or service have received FDA clearance or approval when such is required for performance of the procedure or service.
- The procedure or service is performed by many physicians or other qualified health care professionals across the United States.
- The procedure or service is performed with frequency consistent with the intended clinical use (ie, a service for a common condition should have high volume, whereas a service commonly performed for a rare condition may have low volume).
- The procedure or service is consistent with current medical practice.
- The clinical efficacy of the procedure or service is documented in literature that meets the requirements set forth in the CPT code change application.

These codes have an alpha character as the 5th character in the string preceded by four digits (e.g. 1234T) and are located in a separate section of the CPT codebook following the Medicine section. The introductory language for this code section explains the purpose of these codes.

CPT Category III codes are intended to be used for data collection purposes to substantiate widespread usage or to provide documentation for the FDA approval process. Category III codes are not developed as a result of Panel review of an incomplete proposal, the need for more information, or a lack of CPT



Advisory Committee support of a code change application.

CPT Category III codes are not referred to the AMA-Specialty RVS Update Committee (RUC) for valuation because no relative value units (RVUs) are assigned to these codes. Payment for these services or procedures is based on the policies of payers and not on a yearly fee schedule.

In general, a given Category III code will be archived five years from the date of initial publication or extension unless a modification of the archival date is specifically noted at the time of a revision or change to a code (eg, addition of parenthetical instructions, reinstatement).

Category III codes for CPT 2015

It is important to note that, because future CPT Editorial Panel or Executive Committee actions may affect these items, codes and descriptor language may differ at the time of publication. Also, future Panel actions may result in gaps in code number sequencing. A cross-reference will appear in the Category III section of the CPT codebook to direct users to the newly established CPT Category I code.

Unless otherwise indicated, the symbol ● indicates new procedure codes that will be added to the CPT codebook in 2015.

Category III codes

The following section contains a set of temporary codes for emerging technology, services, and procedures. Category III codes allow data collection for these services or procedures. Use of unlisted codes does not offer the opportunity for the collection of specific data. If a Category III code is available, this code must be reported instead of a Category I unlisted code. This is an activity that is critically important in the evaluation of health care delivery and the formation of public and private policy. The use of the codes in this section allows physicians and other qualified health care professionals, insurers, health services researchers, and health policy experts to identify emerging technology, services and procedures for clinical efficacy, utilization, and outcomes.

The inclusion of a service or procedure in this section neither implies nor endorses clinical efficacy, safety, or the applicability to clinical practice. The codes in this section may not conform to the usual requirements for CPT Category I codes established by the Editorial Panel. The nature of emerging technology, services, and procedures is such that the requirements for the Category I criteria may not be met. For these reasons, temporary codes for emerging technology, services, and procedures have been placed in a separate section of the CPT codebook, and the codes are differentiated from CPT Category I codes by the use of the alphanumeric characters.

Services/procedures described in this section make use of alphanumeric characters. These codes have an alpha character as the 5th character in the string (ie, four digits followed by the letter T). The digits are not intended to reflect the placement of the code in the Category I section of CPT nomenclature. Codes in this section may or may not eventually receive a Category I CPT code. In either case, in general, a given Category III code will be archived five years from the date of initial publication or extension unless a modification of the archival date is specifically noted at the time of a revision or change to a code (eg, addition of parenthetical instructions, reinstatement). Services/procedures described by Category III codes which have been archived after five years, without conversion, must be reported using the Category I unlisted code unless another specific cross reference is established at the time of archiving.

New codes or revised codes are released semi-annually via the AMA/CPT internet site, to expedite dissemination for reporting. The full set of temporary codes for emerging technology, services, and procedures are published annually in the CPT codebook. Go to www.ama-assn.org/go/cpt for the most current listing.

Category III codes 0340T- 0346T were accepted at the May 2013 CPT Editorial Panel meeting for the 2015 CPT production cycle. Therefore, these codes do not appear in the 2014 CPT codebook. However, due to the Category III code early release policy, these codes are effective on January 1, 2014, following the six - month implementation period which began on July 1, 2013. Shaded text refers to additional refinements accepted at the October 2013 CPT Editorial Panel meeting for the 2015 CPT production cycle.

●0340T Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance	Released July 1, 2013 Implemented January 1, 2014 Moderate Sedation symbol ☉ added October 2013	CPT 2015
(Do not report code 0340T in conjunction with 76940, 77013, 77022)		
●0341T Quantitative pupillometry with interpretation and report, unilateral or bilateral	Released July 1, 2013 Implemented January 1, 2014	CPT 2015
●0342T Therapeutic apheresis with selective HDL delipidation and plasma reinfusion	Released July 1, 2013 Implemented January 1, 2014	CPT 2015
●0343T Transcatheter mitral valve repair percutaneous approach including transseptal puncture when performed; initial prosthesis	Released July 1, 2013 Implemented January 1, 2014	CPT 2015
●0344T additional prosthesis (es) during same session (List separately in addition to code for primary procedure)	Released July 1, 2013 Implemented January 1, 2014	CPT 2015
(Use 0343T in conjunction with 0344T)		
●0345T Transcatheter mitral valve repair percutaneous approach via the coronary sinus	Released July 1, 2013 Implemented January 1, 2014	CPT 2015
(0343T is applicable for initial prosthesis placed during a session even when patient has an existing mitral valve prosthesis in place)		

	(Do not report 0343T, 0344T, 0345T in conjunction with 93451, 93452, 93453, 93456, 93457, 93458, 93459, 93460, 93461 for diagnostic left and right heart catheterization procedures intrinsic to the valve repair procedure)		
	(Do not report 0345T in conjunction with 93453, 93454 for coronary angiography intrinsic to the valve repair procedure)		
●0346T	Ultrasound, elastography (List separately in addition to code for primary procedure)	Released July 1, 2013 Implemented January 1, 2014	CPT 2015
	(Use 0346T in conjunction with 76536, 76604, 76645, 76700, 76705, 76770, 76775, 76830, 76856, 76857, 76870, 76872, 76881, 76882)		
	(For elastography without ultrasound imaging, use an unlisted code)	Refinement approved October 2013	
Category III codes were accepted at the October 2013 CPT Editorial Panel meeting for the 2015 CPT production cycle. However, due to the Category III code early release policy, these codes are effective on July 1, 2014, following the six-month implementation period which begins January 1, 2014.			
●0347T	Placement of interstitial device(s) in bone for radiostereometric analysis (RSA)	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
●0348T	Radiologic examination, radiostereometric analysis (RSA); spine, (includes, cervical, thoracic and lumbosacral, when performed)	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
●0349T	upper extremity(ies), (includes shoulder, elbow and wrist, when performed)	Released January 1, 2014 Implemented July 1, 2014	CPT 2015

●0350T	lower extremity(ies), (includes hip, proximal femur, knee and ankle, when performed)	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
●0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real time intraoperative	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
●0352T	interpretation and report, real time or referred	Released January 1, 2014 Implemented July 1, 2014	
(Do not report 0352T in conjunction with 0351T when performed by the same physician)			
●0353T	Optical coherence tomography of breast, surgical cavity; real time intraoperative	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
(Report 0353T once per session)			
●0354T	interpretation and report, real time or referred	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
(Do not report 0354T in conjunction with 0353T when performed by the same physician)			
●0355T	Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), colon, with interpretation and report	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
(Use 0355T for imaging of distal ileum, when performed)			
(Do not report 0355T in conjunction with 91110, 91111)			
●0356T	Insertion of drug-eluting implant (including punctual dilation and implant removal when performed) into lacrimal canaliculus, each	Released January 1, 2014 Implemented July 1, 2014	CPT 2015

●0358T Bioelectrical impedance analysis whole body composition assessment, supine position, with interpretation and report	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
Adaptive Behavior Assessments <i>Behavior identification assessment (0359T)</i> conducted by the physician or other qualified health care professional, includes a detailed behavioral history, patient observation, administration of standardized and non-standardized tests and structured guardian/caregiver interview to identify and describe deficient adaptive or maladaptive behaviors (eg, impaired social skills and communication deficits, destructive behaviors, and additional functional limitations secondary to maladaptive behaviors). 0359T also includes the physician's or other qualified health care professional's interpretation of results and development of plan of care, which may include further observational or exposure behavioral follow-up assessment(s) (0360T, 0361T, 0362T, 0363T), discussion of findings and recommendations with the primary guardian(s)/caregiver(s), and preparation of report. <i>Observational behavioral follow-up assessment (0360T, 0361T)</i> is administered by a technician under the direction of a physician or other qualified health care professional. The physician or other qualified health care professional may or may not be on-site during the face-to-face assessment process. Codes 0360T, 0361T include the physician's or other qualified health care professional's interpretation of results, discussion of findings and recommendations with the primary caregiver(s), and preparation of report. Codes 0360T, 0361T describe services provided to patients who present with specific destructive behavior(s) (eg, self- injurious behavior, aggression, property destruction) or behavioral problems secondary to repetitive behaviors or deficits in communication or social relatedness. These assessments include use of structured observation and/or standardized and non-standardized tests to determine levels of adaptive behavior. Areas assessed may include cooperation, motivation, visual understanding, receptive and expressive language, imitation, requests, labeling, play and leisure and social interactions. Specific destructive behavior(s) assessments include structured observational testing to examine events, cues, responses, and consequences associated with the behavior(s).		CPT 2015

Exposure behavioral follow-up assessment (0362T, 0363T) is administered by the physician or other qualified health care professional with the assistance of one or more technicians. Codes 0362T, 0363T include the physician's or other qualified health care professional's interpretation of results, discussion of findings and recommendations with the primary caregiver(s), and preparation of report. The typical patients for 0362T, 0363T include patients with one or more specific severe destructive behavior(s) (eg, self-injurious behavior, aggression, property destruction). Specific severe destructive behavior(s) are assessed using structured testing to examine events, cues, responses, and consequences associated with the behavior(s).		
Codes 0362T, 0363T include exposing the patient to a series of social and environmental conditions associated with the destructive behavior(s). Assessment methods include using testing methods designed to examine triggers, events, cues, responses, and consequences, associated with the before mentioned maladaptive behavior(s). This assessment is completed in a structured, safe environment. Codes 0360T, 0361T, 0362T, 0363T are reported following 0359T based on the time that the patient is face-to-face with one or more technician(s). Only count the time of one technician when two or more are present. Codes 0360T, 0361T, 0362T, 0363T are reported per the CPT Time Rule (eg, a unit of time is attained when the mid-point is passed). See Table 1. The time reported with 0360T, 0361T, 0362T, 0363T is over a single day and is not cumulative over a longer period. Do not report 0359T, 0360T, 0361T, 0362T, 0363T in conjunction with 90785-90899, 96101-96125, 96150, 96151, 96152, 96153, 96154, 96155 on the same date. (For psychiatric diagnostic evaluation, see 90791, 90792) (For speech evaluations, see 92521, 92522, 92523, 92524) (For occupational therapy evaluation, see 97003, 97004) (For medical team conference, see 99366, 99367, 99368) (For health and behavior assessment/intervention, see 96150, 96151, 96152, 96153, 96154, 96155) (For neurobehavioral status exam, use 96116) (For neuropsychological testing, use 96118)		

Table1

**Reporting of 0360T, 0361T, 0362T, 0363T per CPT Time Rule
Utilizing Face-to-Face Technician Time**

Less than 16 min	Not reportable
16 – 45 min	0360T or 0362T
46 – 75 min	0360T and 0361T, or 0362T and 0363T
Each additional increment up to 30 min	Additional 0361T or 0363T

●0359T	Behavior identification assessment, by the physician or other qualified health care professional, face-to-face with patient and caregiver(s), includes administration of standardized and non-standardized tests, detailed behavioral history, patient observation and caregiver interview, interpretation of test results, discussion of findings and recommendations with the primary guardian(s)/caregiver(s), and preparation of report	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
●0360T	Observational behavioral follow-up assessment, includes physician or other qualified health care professional direction with interpretation and report, administered by one technician; first 30 minutes of technician time, face-to-face with the patient	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
+●0361T	each additional 30 minutes of technician time, face-to-face with the patient (List separately in addition to code for primary service)	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
(Use 0361T in conjunction with 0360T)			
●0362T	Exposure behavioral follow-up assessment, includes physician or other qualified health care professional direction with interpretation and report, administered by physician or other qualified health care professional with the assistance of one or more technicians; first 30 minutes of technician(s) time, face-to-face with the patient	Released January 1, 2014 Implemented July 1, 2014	CPT 2015

+●0363T	each additional 30 minutes of technician(s) time, face-to-face with the patient (List separately in addition to code for primary procedure)	Released January 1, 2014 Implemented July 1, 2014	CPT 2015
(Use 0363T in conjunction with 0362T)			
(0362T, 0363T are reported based on a single technician's face-to-face time with the patient and not the combined time of multiple technicians)			
Do not report 0359T, 0360T, 0361T, 0362T, 0363T in conjunction with 90785-90899, 96101-96125, 96150, 96151, 96152, 96153, 96154, 96155)			
Coding Tip If the physician or other qualified health care professional personally performs the technician activities, his or her time engaged in these activities may be included as part of the required technician time to meet the elements of the code.			
Adaptive Behavior Treatment Adaptive behavior treatment codes 0364T-0374T describe services provided to patients, presenting with deficient adaptive or maladaptive behaviors (eg, impaired social skills and communication, destructive behaviors, or additional functional limitations secondary to maladaptive behaviors). Specific target problems and treatment goals are based on results of previous assessments (see 0359T-0363T).		Released March 2014 Implemented July 1, 2014	CPT 2015
Adaptive behavior treatment by protocol and group adaptive behavior treatment by protocol are administered by a technician face-to-face with one patient (0364T, 0365T), or two or more patients (0366T, 0367T) under the direction of a physician or other qualified health care professional, utilizing a behavior intervention protocol designed in advance by the physician or other qualified health care professional who may or may not provide direct supervision during the face-to-face therapy. Do not report 0366T, 0367T if the			

Adaptive behavior treatment with protocol modification (0368T, 0369T) is administered by a physician or other qualified health care professional face-to-face with a single patient. The physician or other qualified health care professional resolves one or more problems with the protocol and may simultaneously instruct a technician and/or guardian(s)/caregiver(s) in administering the modified protocol. Physician or other qualified health care professional instruction of the technician without the patient present is not reported separately.		
Family adaptive behavior treatment guidance and multiple-family group adaptive behavior treatment guidance are administered by a physician or other qualified health care professional face-to-face with guardian(s)/caregiver(s), without the presence of a patient, and involves identifying problem behaviors and deficits and teaching guardian(s)/caregiver(s) of one patient (0370T) or multiple patients (0371T) to utilize treatment protocols designed to reduce maladaptive behaviors and/or skill deficits. Do not report 0371T if the group is larger than 8 patients.		
Adaptive behavior treatment social skills group (0372T) is administered by a physician or other qualified health care professional face-to-face with multiple patients, focusing on social skills training and identifying and targeting individual patient social deficits and problem behaviors. The physician or other qualified health care professional monitors the needs of individual patients and adjusts the therapeutic techniques during the group, as needed. Services to increase target social skills may include modeling, rehearsing, corrective feedback, and homework assignments. In contrast to adaptive behavior treatment by protocol techniques (0364T-0367T), adjustments required in social skills group setting are made in real time rather than for a subsequent service. Do not report 0372T if the group is larger than 8 patients.		
Codes 0364T-0369T, 0372T may include services involving patient interaction with other individuals, including other patients. Report group services (0366T, 0367T, 0372T) only for patients who are participating in the interaction in order to meet their own individual treatment goals.		
Coding Tips If the physician or other qualified health care professional personally performs the technician activities, his or her time engaged in these activities may be reported as technician time. Each minute is only counted once whether 1 or more than one treating individual is present		

●0364T	Adaptive behavior treatment by protocol , administered by technician, face-to-face with one patient; first 30 minutes of technician time	Released March 2014 Implemented July 1, 2014	CPT 2015
+●0365T	each additional 30 minutes of technician time (List separately in addition to code for primary procedure)	Released March 2014 Implemented July 1, 2014	CPT 2015
(Use 0365T in conjunction with 0364T)			
(Do not report 0364T, 0365T in conjunction with 90785-90899, 92507, 96101-96155, 97532)			
●0366T	Group adaptive behavior treatment by protocol, administered by technician, face-to-face with two or more patients; first 30 minutes of technician time	Released March 2014 Implemented July 1, 2014	CPT 2015
+●0367T	each additional 30 minutes of technician time (List separately in addition to code for primary procedure)	Released March 2014 Implemented July 1, 2014	CPT 2015
(Use 0367T in conjunction with 0366T)			
(Do not report 0366T, 0367T if the group is larger than 8 patients)			
(Do not report 0366T, 0367T in conjunction with 90785-90899, 92508, 96101-96155, 97150)			
●0368T	Adaptive behavior treatment with protocol modification administered by physician or other qualified health care professional with one patient; first 30 minutes of patient face-to-face time	Released March 2014 Implemented July 1, 2014	CPT 2015
+●0369T	each additional 30 minutes of patient face-to-face time (List separately in addition to code for primary procedure)	Released March 2014 Implemented July 1, 2014	CPT 2015

(Use 0369T in conjunction with 0368T)			
(Do not report 0368T, 0369T in conjunction with 90791, 90792, 90846, 90847, 90887, 92507, 97532)			
●0370T	Family adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present)	Released March 2014 Implemented July 1, 2014	CPT 2015
●0371T	Multiple-family group adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present)	Released March 2014 Implemented July 1, 2014	CPT 2015
(Do not report 0371T when the families of more than 8 patients are participants)			
(Do not report 0370T, 0371T in conjunction with 90791, 90792, 90846, 90847, 90887)			
●0372T	Adaptive behavior treatment social skills group, administered by physician or other qualified health care professional face-to-face with multiple patients	Released March 2014 Implemented July 1, 2014	CPT 2015
(Do not report 0372T if the group is larger than 8)			
(Do not report 0372T in conjunction with 90853, 92508, 97150)			

Exposure Adaptive Behavior Treatment With Protocol Modification Codes 0373T, 0374T describe services provided to patients with one or more specific severe destructive behaviors (eg, self-injurious behavior, aggression, property destruction), with direct supervision by a physician or other qualified health care professional which requires two or more technicians face-to-face with the patient for safe treatment. Technicians elicit behavioral effects of exposing the patient to specific environmental conditions and treatments. Technicians record all occurrences of targeted behaviors. The physician or other qualified health care professional reviews and analyzes data and refines the therapy using single-case designs; ineffective components are modified or replaced until discharge goals are achieved (eg, reducing destructive behavior by at least 90%, generalizing the treatment effects across caregivers and settings, or maintaining the treatment effects over time). The therapy is conducted in a structured, safe environment. Precautions may include environmental modifications and/or protective equipment for the safety of the patient or the technicians.	Released March 2014 Implemented July 1, 2014	CPT 2015
●0373T Exposure adaptive behavior treatment with protocol modification requiring two or more technicians for severe maladaptive behavior(s); first 60 minutes of technicians' time, face-to-face with patient	Released March 2014 Implemented July 1, 2014	CPT 2015
+●0374T each additional 30 minutes of technicians' time face-to-face with patient (List separately in addition to code for primary procedure)	Released March 2014 Implemented July 1, 2014	CPT 2015
(Use 0374T in conjunction with 0373T)		
(0373T, 0374T are reported based on a single technician's face-to-face time with the patient and not the combined time of multiple technicians)		
(Do not report 0373T, 0374T in conjunction with 90785-90899, 96101-96155)		

Standardized Assessment Tools for Evaluation Progress of Applied Behavioral Analysis for Autism Spectrum Disorder

Question

What should be the appropriate standardized tools for health plans to measure progress in patients received applied behavioral analysis (ABA) for autism spectrum disorder?

Question source

Value-based Benefits Subcommittee (VbBS), Health Evidence Review Commission (HERC)

Background

On June 12, 2014 the VbBS and HERC approved a new guideline for the Prioritized List of Health Services about applied behavioral analysis for autism spectrum disorder. The autism line was also reranked from 313 to 199. The approved new guideline note is as follows, to go into effect on January 1, 2015.

GUIDELINE NOTE 75, APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER

Line 313

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 0359T-0374T, is included on line 313 for the treatment of autism spectrum disorders.

ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in guideline note 6, REHABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.

Individuals ages 1-12

Intensive interventions

Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. **Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI,**

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WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months.

Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. The quality of evidence is insufficient to support these interventions in this population. However, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards

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meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.

VbBS and HERC deliberations and conclusions

Ongoing coverage of ABA is based on demonstrated progress towards goals. The guideline language gives examples of assessments that may be used but does not further delineate appropriate ones and mentions pre-defined objectives but does not clarify what these may be.

Subcommittee members and CCO medical and behavioral health directors have expressed interest in a “community standard” for assessing progress towards goals with ABA.

Evidence

The Center for Evidence-based Policy scoped the question through their trusted sources and guideline search and found the following sources which either focused primarily on diagnosis or on specific interventions:

NICE

- Autism – Management and Support of Children and Young People on the Autism Spectrum (08/2013)
- Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum (9/2011)
- Autistic Spectrum Conditions in Adults (expected publication 6/2012)
- **In development:** Diagnostic tests for Autism Spectrum Disorders (ASD) in preschool children – Protocol only published online March 2011

SIGN

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SIGN. (2007). *Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorder*. Edinburgh: SIGN.

New Zealand Ministries of Health and Education. (2008). *New Zealand autism spectrum disorder guideline*. Wellington: Ministries of Health and Education.

Other guidelines:

Cincinnati Children's Hospital Medical Center. (2009). *Best evidence statement (BEST). Outcomes assessment tool for children with autism spectrum disorder (ASD)*. Cincinnati, OH: Cincinnati Children's Hospital Medical Center.

Cincinnati Children's Hospital Medical Center. (2009). *Best evidence statement (BEST). Use of motor and self-care assessment tools for children with autism spectrum disorder (ASD)*. Cincinnati, OH: Cincinnati Children's Hospital Medical Center.

Cincinnati Children's Hospital Medical Center. (2009). *Best evidence statement (BEST). Use of sensory assessment tools with children diagnosed with autism spectrum disorder (ASD)*. Cincinnati, OH: Cincinnati Children's Hospital Medical Center.

Filipek, P.A., Accardo, P.J., Ashwal, S., (2000). Practice parameter: Screening and diagnosis of autism: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. *Neurology*, 55, 468. [reaffirmed 2010].

Tomchek, S.D., & Case-Smith, J. (2009). *Occupational therapy practice guidelines for children and adolescents with autism*. Bethesda, MD: American Occupational Therapy Association (AOTA). [for purchase]

Johnson, C.P., Myers, S.M., & the Council on Children with Disabilities. (2007). Identification and evaluation of children with autism spectrum disorder. *Pediatrics*, 120(5), 1183-1215. [reaffirmed 12/1/2010]

Meyers, S.M., Johnson, & the Council on Children with Disabilities. (2007). Management of children with autism spectrum disorder. *Pediatrics*, 120(5), 1162-1182. [reaffirmed 12/1/2010]

CDC, AAP, DHS, & Medical Home Initiative. (2007). Autism A.L.A.R.M and screening algorithm. Retrieved May 9, 2011, from <http://www.medicalhomeinfo.org/downloads/pdfs/AutismAlarm.pdf>

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HERC Staff Assessment

A deeper dive into evidence sources is unlikely to be fruitful. They will not address specific tools to use, rather are mostly focused on diagnosis, or on specific therapies, rather than on the monitoring progress towards goals.

HERC Staff Recommendations

- 1) Do not attempt further evidence work through the usual HERC process as this is unlikely to yield needed answers
- 2) Refer issue to the Oregon Commission on Autism Spectrum Disorder, who can engage autism experts and CCO behavioral health management to develop a consensus “best practice” as to what types of assessments are appropriate and can be used across CCOs.