Health Evidence Review Commission's Value-based Benefits Subcommittee

January 16, 2020

8:00 AM - 1:00 PM

Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
1/16/2020
8:00am - 1:00pm
Clackamas Community College
29373 SW Town Center Loop E,
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
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 **8:00 AM**

II. Staff report – Ariel Smits, Cat Livingston **8:05 AM**

III. Straightforward/Consent agenda – Ariel Smits **8:15 AM**
- **A.** Consent table
- **B.** Cytochrome P450 correction
- **C.** INR monitoring

IV. New Discussion Topics **8:30 AM**
- **A.** Bone marrow transplant for sickle cell disease

V. Previous Discussed Topics **9:15 AM**
- **A.** Neuropsychological testing guideline
- **B.** Chronic lower extremity venous disease/Compression stockings

VI. New Discussion Topics **10:00 AM**
- **A.** Delete pharmacist prescribing guideline
- **B.** Intracardiac echocardiogram
- **C.** Frequency specific microcurrent therapy and similar TENS-like therapies
- **D.** Yttrium 90 embolization mapping
- **E.** Vitamin D screening
- **F.** Fetal myelomeningocele repair
- **G.** iStent Inject
- **H.** Spinal cord stimulators
- **I.** Yoga and acupuncture for PSTD and anxiety

VII. Public comment **12:55 PM**

VIII. Adjournment – Kevin Olson **1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on November 14, 2019

For specific coding recommendations and guideline wording, please see the text of the 11/14/2019 VbBS minutes.

RECOMMENDED CODE MOVEMENT (changes to 1/1/2020 Prioritized List)

- Add the 2020 CDT, CPT, and HCPCS codes on various lines and lists
- Add wraparound services to the covered autism line
- Add neuropsychological status exams and neuropsychological testing services to the Diagnostic Procedures File with a new guideline
- Add coverage for intestinal transplants for patients with short gut syndrome failing total parenteral nutrition (TPN) to include all ages
- Add two codes for umbilical hernias to the uncovered hernia line
- Add a vestibular rehabilitation procedure to a dysfunction line
- Add a code for fall risk to the dysfunction line to enable coverage according to USPSTF recommendations
- Add new codes for patient-provider online interaction codes to lines with evaluation and management codes. Interprofessional consultation codes are recommended for addition to the OHP fee schedule.
- Make other various straightforward coding and guideline note changes as described in the meeting materials

RECOMMENDED GUIDELINE CHANGES (changes to 1/1/2020 Prioritized List)

- Add a new guideline regarding neuropsychological status exams and neuropsychological testing services
- Add a new guideline regarding counseling for prevention of peripartum mood disorders
- Edit the non-prenatal, non-hereditary cancer guideline to include indications for pharmacogenetic (P450) testing, modify the microarray analysis entries and include additional cystic fibrosis testing codes
- Edit the prenatal genetic testing guideline to remove restrictions on one non-prenatal test
- Edit the hereditary cancer genetic testing guideline to update NCCN references and clarify when breast cancer panel testing is covered
- Add new Ancillary guideline on non-face-to-face visits and telephonic and electronic consultation
- Delete the prior Guideline Note on telephone consultations
- Modify the preventive services guideline to clarify intended coverage of falls prevention
- Add a new guideline to the intestinal transplant line outlining when a patient was eligible for consideration for transplant
- Edit the breast reconstruction guideline and create a new guideline outlining coverage for revisions to breast surgeries
- Edit the hernia guideline to further define ventral hernia to include umbilical hernia and distinguish between incarcerated and obstructed hernias
- Edit the guidelines regarding cervical cancer screening and other preventive services to reflect US Preventive Services Task Force recommendation updates

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
November 14, 2019
8:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Holly Jo Hodges, MD, Vice Chair; Mark Gibson; Vern Saboe, DC; Adriane Irwin, PharmD; Gary Allen, DMD (via phone).

Members Absent: None.

Staff Present: Darren Coffman; Jason Gingerich; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Daphne Peck; Jaime Taylor.

Also Attending: Nat Jacobs, Diane Quiring, and Kellie Skenandore (Oregon Health Authority); Mark Rivas, Mary Hlady, and Jamie Caulkey (Providence Rehab); Edward Boyle, MD (via phone).

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

  The meeting was called to order at 8:05 am and roll was called. A quorum of members was present at the meeting. Minutes from the 8/8/19 VbBS meeting were reviewed and approved.

  Smits reviewed the errata; there were no questions or comments. Coffman announced his retirement at the end of November and Jason Gingerich's new role as the director of the HERC. This is also Mark Gibson's last meeting. Both Darren and Mark were thanked for their many years of outstanding service to the state.

- **Topic: Straightforward/Consent Agenda**

  Discussion: There was no discussion about the consent agenda items.

  Recommended Actions:
  1) Add F17.210 (Nicotine dependence, cigarettes, uncomplicated) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
  2) Remove 81507 (Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy) and 81420 (Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21) from line 1 PREGNANCY and add to Diagnostic Procedures File.
  3) Change the line title of line 25 to ABNORMAL PAP SMEARS; DYSPLASIA OF CERVIX AND CERVICAL CARCINOMA IN SITU, CERVICAL CONDYLOMA
     a. Remove the following codes from line 25 and advise HSD to add to the Diagnostic Workup File
        i. ICD10 R87.615 Unsatisfactory cytologic smear of cervix
        ii. ICD10 R87.616 Satisfactory cervical smear but lacking transformation zone

b. Add the following codes to line 25 and advise HSD to remove them from the Diagnostic Workup File
    i. ICD10 R87.618 Other abnormal cytological findings on specimens from cervix uteri
    ii. ICD10 R87.619 Unspecified abnormal cytological findings in specimens from cervix uteri

4) Remove ICD10 R87.625 (Unsatisfactory cytologic smear of vagina) from line 286 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS and advise HSD to add to the Diagnostic Workup File
5) Add ICD10 R87.811 (Vaginal high risk human papillomavirus (HPV) DNA test positive) to line 286 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS and advise HSD to remove from the Diagnostic Workup File
6) Remove ICD10 R87.820 (Cervical low risk human papillomavirus (HPV) DNA test positive) from line 25 ABNORMAL PAP SMEARS; DYSPLASIA OF CERVIX AND CERVICAL CARCINOMA IN SITU, CERVICAL and advise HSD to add to the Informational File
7) Advise HSD to remove ICD10 R87.821 (Vaginal low risk human papillomavirus (HPV) DNA test positive) from the Diagnostic Workup File and add to the Informational File
8) Modify GN173 as shown in Appendix A regarding 3D image rendering

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 6-0.

- **Topic: Oral Health Advisory Panel (OHAP)**

Discussion: There was no discussion about the staff recommendations regarding the 2020 CDT codes, which reflected input from the All Dental Plans Workgroup and OHAP members.

Recommended Action:
1) Place the 2020 CDT codes as shown in Appendix B

MOTION: To recommend the code placements as presented. CARRIES 6-0.

- **Topic: Behavioral Health Advisory Panel (BHAP)**

Discussion: Smits introduced the wraparound services for autism topic. There was discussion about the possible increase in cost to OHA and the CCOs. Nat Jacobs from OHA testified that these services are reserved for the top 5% of children with high needs to youth state programs. These services can reduce ER and other downstream costs. Adding wraparound service codes to the autism line creates consistency among mental health diagnoses. Hodges requested that HERC staff consult with actuarial services regarding the possible costs of this addition. Coffman noted that if VbBS approves this change today, OHA can still put a hold on implementation if the cost is found to be too high.

Recommended Action:
1) Add wraparound services to line 193 AUTISM SPECTRUM DISORDERS
    a. HCPCS H2021 (Community-based wrap-around services, per 15 minutes)
    b. HCPCS H2022 (Community-based wrap-around services, per diem)

MOTION: To recommend the code changes as presented. CARRIES 6-0.

Smits then introduced the neuropsychological status and testing topic. Hodges expressed concern that the suggested changes would greatly increase testing coverage volume, noting that there are many non-appropriate requests. Irwin expressed concern that these tests would be used for monitoring a condition rather than diagnosis, but Hodges felt that the CCOs could refuse coverage if the test had been done previously. The decision was to approve as suggested by staff and readdress the topic if CCOs find issues once they operationalize the change.

Recommended Actions:

1) Remove the following codes from all current lines on the Prioritized List and advise HSD to add these codes to the Diagnostic Procedures File
    a. CPT 96116 Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, [eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities]), by physician or other qualified health care professional, both face-to-face time with the patient and time interpreting test results and preparing the report; first hour
    b. CPT 96121 each additional hour
    c. CPT 96132 Neuropsychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed; first hour
    d. CPT 96133 each additional hour
2) Modify GN173 as shown in Appendix A, removing the entry for neurobehavioral status exams (CPT Codes 96116 and 96121)
3) Add a new diagnostic guideline **NEUROBEHAVIORAL STATUS EXAMS AND NEUROPSYCHOLOGICAL TESTING** as shown in Appendix C

MOTION: To recommend the code and guideline changes as presented. CARRIES 5-0. *(Absent: Saboe)*

Livingston introduced the summary on counseling for peripartum mood disorders. Irwin requested the addition of coverage for women with spontaneous or therapeutic pregnancy loss. The proposed guideline was modified to reflect this. The health and behavior assessment codes were already on the lines for spontaneous and therapeutic abortions. Staff was charged with determining if any ICD-10 codes should be added to the proposed new guideline to account for these populations. *[Note: at the 11/14/19 HERC meeting, the second paragraph of the new guideline, containing these codes, was removed from the guideline as the Commission decided it was unnecessary.]*

Recommended Actions:

1) Add a new guideline **COUNSELING FOR PREGNANT AND POSTPARTUM WOMEN** to various lines regarding counseling for prevention of peripartum mood disorders as shown in Appendix C
2) Add HCPCS H0004 (Behavioral health counseling and therapy, per 15 minutes) to Line 1 PREGNANCY *[Note: this addition was not approved by HERC at the 11/14/19 HERC meeting]*

MOTION: To recommend the code and guideline note changes as modified. CARRIES 6-0.

- **Topic: Genetics Advisory Panel**

Discussion:

Non-prenatal, non-hereditary cancer genetic guideline

Smits first reviewed issues with the Guideline Note D1 NON-PRENATAL GENETIC TESTING GUIDELINE. First, coverage of P450 testing was reviewed. The subcommittee modified the guideline wording to include additional classes of medications that do not have covered P450 testing in addition to psychiatric medications.

Smits then reviewed CALR testing. There was discussion about what panel test CPT code should be used; Smits indicated that it would be a generic molecular testing code. Hodges expressed concern about possible confusion with results that are part of the panel, but not requested by the provider. Olson felt that it is still cheaper to do the panel testing. The staff recommendation was approved.

There was no discussion about the changes to the entry for CPT 81229 or the CPT changes for cystic fibrosis carrier screening.

Guideline note D17 PRENATAL GENETIC TESTING

The one minor change recommended had no discussion.

GUIDELINE NOTE D25 HEREDITARY CANCER GENETIC TESTING

NCCN references were updated and the breast cancer panel testing section was clarified as in the summary document; there was no discussion.

Recommended Actions:

1) Remove the following codes from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS and advise HSD to add to the Diagnostic Procedure File:
    a. CPT 81226 (CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN))
    b. CPT 81230 (CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22))
    c. CPT 81231 (CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7))
2) Remove CPT 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)) from line 251 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM
3) Remove P450 codes CPT 81225, 81226, 81230 and 81231 (CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)) from GN173 as shown in appendix A.
4) Guideline Note D1 NON-PRENATAL GENETIC TESTING GUIDELINE as shown in Appendix A
5) Add CPT 81219 (CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9) to line 502/GN172
6) Modify Guideline note D17 PRENATAL GENETIC TESTING as shown in Appendix A
7) Modify *GUIDELINE NOTE D25 HEREDITARY CANCER GENETIC TESTING* as shown in Appendix A

MOTION: To recommend the code and guideline note changes as modified. CARRIES 5-0. *(Absent: Saboe)*

- **Topic: 2020 CPT Code Review**

Discussion: There was no discussion regarding the recommended placement of new codes with the following exceptions:

1) Orthopedic drug delivery devices: the option to place on various orthopedic lines was selected
2) Preperitoneal packing: Hodges suggested adding codes to the pregnancy line as well, for use in cases where a pre-eclamptic patient with severe bleeding needs preperitoneal packing after cesarean section. This was accepted.
3) Computerized dynamic posturography: the subcommittee removed the original code from current lines and place on line 662/GN173
4) Remote physiologic monitoring: HSD should also be advised to remove CPT codes 99453 and 99457 in addition to 99458 from the Ancillary File. Staff was charged to review that remote home INR monitoring is covered.

Recommended Actions:

1) 2020 CPT code placement as shown in Appendix B
2) Add entries for certain 2020 CPT codes to GN173 as shown in Appendix A
3) Modify GN161 SACROILIAC ANESTHETIC INJECTIONS AND SACROILIAC JOINT FUSION as shown in Appendix A
4) Advise HSD to add CPT 64640 (Destruction by neurolytic agent; other peripheral nerve or branch) to the Ancillary File and remove it from Line 662/GN173.
5) Modify GN148 BIOMARKER TESTS OF CANCER TISSUE as shown in Appendix A
6) Remove CPT 92548 (computerized dynamic posturography) from current lines and add to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS/GN173
7) Place the following codes on cardiac and pulmonary lines and advise HSD to remove CPT 99453 and 99457 from the Ancillary File:
    a. 99453 Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow rate), initial; set-up and patient education on use of equipment
    b. 99457 Remote physiologic monitoring treatment management services, 20 minutes or more of clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month
    c. 99458 Remote physiologic monitoring treatment management services, clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month; each additional 20 minutes (List separately in addition to code for primary procedure)
    d. <u>CARDIAC AND PULMONARY LINES</u>
        9 ASTHMA
        20 CYSTIC FIBROSIS
        48 CHRONIC RESPIRATORY DISEASE ARISING IN THE NEONATAL PERIOD

58 BRONCHIECTASIS
69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION
75 HYPERTENSION AND HYPERTENSIVE DISEASE
81 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS
97 HEART FAILURE
98 CARDIOMYOPATHY
110 CONGENITAL HEART BLOCK, OTHER OBSTRUCTIVE ANOMALIES OF HEART
172 HYPERTENSIVE HEART AND RENAL DISEASE
189 CHRONIC ISCHEMIC HEART DISEASE
202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
213 ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI
219 PULMONARY FIBROSIS
222 OCCUPATIONAL LUNG DISEASES
223 DISEASES AND DISORDERS OF AORTIC VALVE
225 ACUTE INFLAMMATION OF THE HEART DUE TO RHEUMATIC FEVER
233 ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS
257 DISEASES OF MITRAL, TRICUSPID, AND PULMONARY VALVES
264 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE
281 LIFE-THREATENING CARDIAC ARRHYTHMIAS
283 CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE
304 VIRAL PNEUMONIA
341 RHEUMATIC FEVER
347 CARDIAC ARRHYTHMIAS
366 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS
464 ATELECTASIS (COLLAPSE OF LUNG)
566 PLEURISY
635 CHRONIC BRONCHITIS
647 AGENESIS OF LUNG
653 CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
657 RESPIRATORY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

8) Add 99091 (Collection and interpretation of physiologic data (eg, ECG, blood pressure, glucose monitoring) digitally stored and/or transmitted by the patient and/or caregiver to the physician or other qualified health care professional, qualified by education, training, licensure/regulation (when applicable) requiring a minimum of 30 minutes of time, each 30 days) to the cardiac and pulmonary lines above, and additionally the following lines:
    1 PREGNANCY
    8 TYPE 1 DIABETES MELLITUS
    27 TYPE 2 DIABETES MELLITUS
9) Place 99454 (Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow rate), initial; device(s) supply with daily recording(s) or programmed alert(s) transmission, each 30) on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS and modify GN172 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as modified. CARRIES 6-0.

- **Topic: Telephone and email consult guideline**

Discussion: Livingston reviewed the issue summary. Hodges raised the question as to whether it should actually be an ancillary guideline. Coffman explained the proposal to make it a diagnostic guideline due to the issue of having an ancillary guideline with some appropriate codes not being on Prioritized List. Hodges said there are ongoing issues with regular access to HSD's Ancillary File. Subcommittee members clarified that having a guideline as ancillary would mean that electronic consultations for unfunded conditions such as fibromyalgia would not be covered. If the procedures are diagnostic, diagnostic workup of signs and symptoms as well as unfunded condition will continue to be covered, just like face-to-face consultations.

Gingerich raised the question about use of signs and symptoms codes and Hodges shared in her experience these get paid. The difficulty with making this a diagnostic guideline is that many of these consults would not be for diagnostic purposes, they would be to help with ongoing management of a chronic diagnosed condition. After this discussion, the decision was made to make this an ancillary guideline but clarify that it includes services related to the diagnostic workup. This would enable 1-2 consults to establish a diagnosis as is typically allowed.

The discussion turned to a series of examples to see how the new proposed guideline would impact coverage. Members discussed getting rid of the requirement that the consulting provider needs to be a specialist. Examples given included:

- PCP in a remote location consults another PCP in a more urban location for a second opinion (therefore the consulting provider does not need to be a specialist)
- Provider consults another provider for advice regarding medication assisted treatment

Recommended Actions:

1. Add the following codes to all lines with E&M codes
    1) 98970-98972
    2) 99421-99423
2. Recommend HSD add the following codes to the fee schedule
    a. 99446-99449
    b. 98970-98972
    c. 99421-99423
    d. G2012
3. Delete 99444 and 98969 from all lines on the Prioritized List. The codes are now obsolete.
4. Delete Guideline Note 65 TELEPHONE AND EMAIL CONSULTATIONS from 638 lines of the Prioritized List.
5. Add a new ancillary guideline note named TELECONSULTATIONS AND NON-FACE-TO -FACE TELEHEALTH SERVICES as shown in Appendix C.
6. Recommend HSD update OARs (still refers to Health Services Commission and new language is indicated)

MOTION: To recommend the code and guideline note changes as amended. CARRIES 6-0.

- **Topic: 2020 HCPCS Code Review**

  Discussion: Smits reviewed the documents related to the 2020 HCPCS code placements. There was no discussion except for C1839 (Iris prosthesis). There was discussion that the iris prosthesis might be beneficial for children for reading, but the general thought was that the rare cases with aniridia in children could be dealt with through the exceptions process. The decision was to add C1839 to line 662/GN173.

  Recommended Actions:
  1) 2020 HCPCS code placement as shown in Appendix B
  2) Add entries for certain 2020 HCPCS codes to line 662 and GN173 as shown in Appendix A

  MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

- **Topic: Chronic lower extremity venous disease (CLEVD)**

  Discussion: Smits reviewed the summary document. Dr. Ed Boyle testified regarding the benefits of treatment on patients' quality of life. He noted that NICE coverage is much more expansive than the coverage contemplated by the HERC. He noted that treatment of CLEVD affects pain and quality of life. He felt that severe swelling should be included as an indication and would like to see severe pain as an indication as well. Olson commented that the HERC generally leans toward having objective findings around coverage, and that pain is subjective. Subjective indications are much more difficult for CCOs to manage. Boyle noted that private insurers manage benefits with pain as an indication, and that physicians are familiar with the documentation necessary to indicate the patient's pain. Boyle also was interested in expanding coverage to include stasis dermatitis. Olson asked whether there was a grading system for stasis dermatitis and Boyle indicated that there was not. Hodges agreed with the need to have objective findings to determine coverage. Boyle stated that the diagnosis of severe venous reflux is made by ultrasound findings. CMS and private insurers require the ultrasound findings when determining coverage. Hodges noted that it was hard to define stasis dermatitis—what level of skin change would be considered stasis dermatitis? Boyle argued that the proposed guideline as written only covers severe end stage CLEVD. He again reiterated that CMS covers severe refractory edema and stasis dermatitis and advocated for inclusion of these indications, which would match the major private insurers. There was discussion that treating less severe disease may not result in any improvements. There was general consensus that the proposed guideline should include objective measures only.

  Based on the discussion above, the VbBS members suggested modifying the proposed guideline to include ultrasound findings of severe reflux, defined as "severe axial venous reflux (>1 second in the greater or small saphenous vein or accessory saphenous vein)."

  There was further discussion about the proposed guideline requirement for 3 months of conservative therapy. Livingston raised the issue that this would include compression stockings, which are currently not covered by OHP. There was discussion about when compression stockings should be covered. There was suggested wording that the guideline include compression stockings only if the patient meets all the other guideline criteria. Mary Hlady from Providence Rehab noted that the physical therapy community could assist the HERC in determining which patients should qualify for compression stockings.

The decision was to table this topic and have HERC staff look at the evidence for the effectiveness of compression stockings, as well as which patients should have compression stockings covered by OHP.

Recommended Action:

1) HERC staff will look at the literature and work with community experts to determine the effectiveness of compression stockings for CLEVD, and what coverage for these stockings, if any, should be included in the proposed new guideline. This topic will be brought back to a future meeting for further discussion.

- **Topic: Vestibular rehabilitation**

Discussion: Livingston presented the issue summary. Saboe asked about the differential effectiveness of canalith repositioning versus other types of vestibular testing and interventions. Livingston pointed to the evidence in the issue summary which addressed a variety of types of vestibular rehabilitation, but that there is specific evidence for canalith repositioning. Members discussed the prioritization of vertiginous conditions below the funding line.

Public commenters, Mary Hlady and Jamie Caulkey , both physical therapists from Providence, expressed happiness that canalith repositioning would be moved to the funded region of the Prioritized List. They raised concern about the proposed limitation to those 65 years and older. Livingston clarified that while others may be at risk of falls, older adults were at higher risk based on the USPSTF review. Public comment discussed the importance of a variety of comorbidities, particularly neuromuscular conditions, that may increase morbidity of fall risk. Subcommittee members addressed that pairing on the neurologic dysfunction line would allow canalith repositioning to pair with a variety of neuromuscular conditions. There was a proposal to remove the proposed coding specification and allow pairing without age limitations. Subcommittee members adopted this proposal, as there is a high risk of bad outcomes for a variety of comorbid neuromuscular conditions which may affect younger patients.

Recommended Actions:

1) Add the following codes to Line 512 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM

97112	**Therapeutic procedure, 1 or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities**
S9476	Vestibular rehabilitation program, non-physician provider, per diem

2) Add Z91.81 *History of falling (and including those at risk of falling)* to Line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
    - Delete Z91.81 from Line 3
    - Add CPT code 95992 (Canalith repositioning) to Line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT
3) Modify Guideline Note 106 as shown in Appendix A.

MOTION: To recommend the code and guideline note changes as amended. CARRIES 6-0.

- **Topic: Indications for intestinal transplantation**

  Discussion: Smits reviewed the summary document. There was minimal discussion. There was general agreement that coverage should be expanded to all ages. The guideline was slightly modified to include "OR" at the end of each indication to clarify that only one indication was required.

  Recommended Actions:
  1) Change the line title for line 239 to Line 239 SHORT BOWEL SYNDROME ~~- AGE 5 OR UNDER~~ Treatment: INTESTINE AND INTESTINE/LIVER TRANSPLANT
  2) Adopt the new guideline for line 239 as shown in Appendix C
  3) Add 44133 (Donor enterectomy from living donor) and 44136 (Intestinal allotransplantation, from living donor) to line 662/GN173 as shown in Appendix A

  MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

- **Topic: Breast reconstruction revisions for previous cosmetic procedures**

  Discussion: Smits reviewed the summary document; there was minimal discussion.

  Recommended Actions:
  1) Revise GN79 BREAST RECONSTRUCTION as shown in Appendix A
  2) Add a new guideline BREAST SURGERY REVISION to multiple lines addressing revision of breast surgeries

  MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Topic: Umbilical hernias with non-intestinal obstruction**

  Discussion: Smits reviewed the summary document. The proposed guideline revisions were amended slightly to clarify the wording. There was some discussion about adding ICD10 codes K42.0 and K45.0 to line 524, as the descriptions include the word "obstruction." Staff clarified that these codes are used for incarceration, and the guideline defines their use as for this indication. True intestinal obstruction would remain on the covered upper hernia line.

  Recommended Actions:
  1) Add ICD-10 codes K42.0 (Umbilical hernia with obstruction, without gangrene) and K45.0 (Other specified abdominal hernia with obstruction, without gangrene) to line 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA) and keep on line 168
  2) Modify GN24 COMPLICATED HERNIAS as shown in Appendix A

  MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

- **Topic: USPSTF Recommendation Update for GN106**

  Discussion: Livingston reviewed the summary document; there was minimal discussion.

  Recommended Actions:
  1) Modify Guideline Note 1 ROUTINE CERVICAL CANCER SCREENING as shown in Appendix A
  2) Modify Guideline Note 106 PREVENTIVE SERVICES as shown in Appendix A

  MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Public comment on topics not on the agenda**

  No additional public comment was received.

- **Issues for next meeting:**
  - Chronic lower extremity venous disease and compression stockings
  - Intracardiac echocardiogram
  - Yttrium 90 embolization mapping
  - Vitamin D screening
  - Frequency specific microcurrent therapy and similar TENS-like therapies
  - Low level laser therapy
  - Fetal myelomeningocele repair

- **Next meeting:**

  January 16, 2020 at Clackamas Community College, Wilsonville Training Center, Wilsonville Oregon, Rooms 111-112.

- **Adjournment:**

  The meeting adjourned at 1:17 PM.

Appendix A
Revised Guideline Notes

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section E1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
   1) Change treatment,
   2) Change health monitoring,
   3) Provide prognosis, or
   4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children

B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
   1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context

D) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
   1) CPT 81228 and 81229, Cytogenomic constitutional microarray analysis ~~for copy number variants for chromosomal abnormalities~~: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
   ~~2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.~~ (combine with 81228 entry)

3) CPT 81243, 81244, 81171,81172 Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

E) Related to other tests with specific CPT codes:
1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
b) Diagnostic testing for cystic fibrosis (CF)
i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81221, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
c) Carrier testing for cystic fibrosis
i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220-81224) is covered once in a lifetime.
d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; introm 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.
e) CPT 81226-81231 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).
f) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin

20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

g) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

h) CPT 81247. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
   i) After G6PD enzyme activity testing is done and found to be normal; AND either
      (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
      (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.

i) CPT 81248. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.

j) CPT 81249. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
   i) after G6PD enzyme activity has been tested, and
   ii) the requirements under CPT 81247 above have been met, and
   iii) common variants (CPT 81247) have been tested for and not found.

k) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.

l) CPT 81332, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

m) CPT 81329, Screening for spinal muscular atrophy: is covered once in a lifetime for preconception testing or testing of the male partner of a pregnant female carrier

n) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test

o) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.

p) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.

q) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 7/2018 and found at http://www.acmg.net/PDFLibrary/Cystic-Fibrosis-Population-Based-Carrier-Screening-Standards.pdf.

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

A) Genetic counseling (CPT 96040, HPCPS S0265) for high-risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
B) Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
C) Validated questionnaire to assess genetic risk in all pregnant women
D) Screening high-risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
E) Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511,81512,82105,82677)
F) Cell free fetal DNA testing (CPT 81420, 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
G) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
H) CVS or amniocentesis (CPT 59000, 59015, 76945,76946, 82106, 88235, 88261-88264, 88267, 88269, 88280, 88283, 88285, 88289,88291) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
I) Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in (H) above.
J) FISH testing (CPT 88271, 88272, 88274, 88275, 81171, 81172) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
K) Screening for Tay-Sachs carrier status (CPT 81255) in high-risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
M) Screening for fragile X status (CPT 81243, 81244, 81171. 81172) in patients with a personal or family history of
    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure

c. unexplained early onset intellectual disability
d. fragile X intellectual disability
e. unexplained autism through the pregnant woman's maternal line

N) Screening for spinal muscular atrophy (CPT 81329) once in a lifetime
O) Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
P) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

A) Serum triple screen
B) ~~Screening for thrombophilia in the general population or for recurrent pregnancy loss~~
C) Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 1, ROUTINE CERVICAL CANCER SCREENING

Line 3

Cervical cancer screening is covered on Line 3 for women:

Age group in years	Type of screening covered	Frequency
<21	None	Never
21-29	Cytology alone Mandatory HPV testing (87620-87621) is not covered for women age 21-29	Every 3 years
30-65	~~Co-testing* or cytology alone~~ High-risk human papillomavirus (hrHPV) testing alone, co-testing (hrHPV and cytology) or cytology alone	Co-testing every 5 years hrHPV testing alone every 5 years Cytology alone every 3 years
>65	None Unless adequate screening* has not been achieved or it is <20 years after regression or appropriate management of a high-grade precancerous lesion	Never
Women who have had a hysterectomy with removal of cervix for non cervical cancer	None	Never

Age group in years	Type of screening covered	Frequency
related reasons (i.e. other than high grade precancerous lesion, CIN 2 or 3, or cervical cancer)		
Women who have abnormal testing	Per ASCCP** Guideline, until indicated to resume routine screening	Per ASCCP Guideline, until indicated to resume routine screening

~~*Co-testing is defined as simultaneous cytology and mandatory HPV testing.~~
* Adequate screening is defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years of the cessation of screening, with the most recent test occurring within 5 years.
** American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Saslow 2012)

Women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive) are intended to have screening more frequently than delineated in this guideline.

~~The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.~~

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,524

Complicated hernias are included on Line 168 if they cause symptoms of intestinal obstruction and/or strangulation. Incarcerated hernias (defined as non-reducible by physical manipulation) are also included on Line 168, excluding incarcerated ventral hernias. Incarcerated ventral hernias (including incarcerated abdominal incisional and umbilical hernias ~~and umbilical hernias~~) are included on Line 524, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation. Ventral hernias are defined as anterior abdominal wall hernias and include primary ventral hernias (epigastric, umbilical, Spigelian), parastomal hernias, and most incisional hernias (ventral incisional hernias). ICD-10-CM K42.0, K43.0, K43.3, K43.6, K45.0 and K46.0 are included on Line 524 when used to designate incarcerated abdominal incisional and umbilical hernias without intestinal obstruction or gangrene.

GUIDELINE NOTE 79, BREAST RECONSTRUCTION

Line 191

Breast reconstruction is only covered after mastectomy as a treatment for breast cancer or as prophylactic treatment for the prevention of breast cancer in a woman who qualifies under Guideline Note 3, and must be completed within 5 years of initial mastectomy. ~~Revision of previous reconstruction~~

~~is only covered in cases where the revision is required to address complications of the surgery (wound dehiscence, fistula, chronic pain directly related to the surgery, etc.). Revisions are not covered solely for cosmetic issues.~~

Breast reconstruction may include contralateral reduction mammoplasty (CPT 19318) or contralateral mastopexy (CPT 19316). Mastopexy is only to be covered when contralateral reduction mammaplasty is inappropriate for breast reconstruction and mastopexy will accomplish the desired reconstruction result

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,622

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2019 ~~January 1, 2018~~.
   1) http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
      a) Treatment of falls prevention with exercise interventions is included on Line 292.
   2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   1) http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity Schedule_FINAL.pdf.
   2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines as as updated by HRSA on December 20, 2016. Available at https://www.hrsa.gov/womens-guidelines-2016/index.html as of ~~3~~11/~~19~~5/2019.

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf

Colorectal cancer screening is included on Line 3 for average-risk adults aged 50 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year
D) Guaiac-based fecal occult blood test (gFOBT) every year

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered only for those who

A) Are healthy enough to undergo treatment if colorectal cancer is detected, and
B) Do not have comorbid conditions that would significantly limit their life expectancy.

Appendix A
Revised Guideline Notes

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 157,184,191,230,263,271,329

The use of tissue of origin testing (e.g. CPT 81504) is included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For early stage breast cancer, the following breast cancer genome profile tests are included on Line 191 when the listed criteria are met. One test per primary breast cancer is covered when the patient is willing to use the test results in a shared decision-making process regarding adjuvant chemotherapy. Lymph nodes with micrometastases less than 2 mm in size are considered node negative.

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (~~using~~ CPT ~~81599~~ 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

EndoPredict, Prosigna, and MammaPrint are not included on Line 191 for early stage breast cancer with involved axillary lymph nodes. Oncotype DX Breast Recurrence Score is not included on Line 191 for breast cancer involving four or more axillary lymph nodes or more extensive metastatic disease.

Oncotype DX Breast DCIS Score (CPT 81479) and Breast Cancer Index (CPT 81518) are included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 230.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 263 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Line 662.
For bladder cancer, Urovysion testing is included on Line 662.

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay, and Decipher Prostate RP (CPT 81542) are included on Line 662.

Appendix A
Revised Guideline Notes

The development of this guideline note was informed by a HERC coverage guidance on Biomarkers Tests of Cancer Tissue for Prognosis and Potential Response to Treatment; the prostate-related portion of that coverage guidance was superseded by a Coverage Guidance on Gene Expression Profiling for Prostate Cancer. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 161, SACROILIAC ~~ANESTHETIC~~ JOINT INJECTIONS AND SACROILIAC JOINT FUSION

Line 527

Sacroiliac joint (SIJ) injection (CPT 20610 and 27096, and HCPCS G0260) is included on this line for diagnostic sacroiliac injections with anesthetic only, but not for therapeutic injections or corticosteroid injections. Injections are only covered for patients for whom SIJ fusion surgery is being considered.

SIJ fusion (CPT 27279) is included on this line for patients who have all of the following:

A) Baseline score of at least 30% on the Oswestry Disability Index (ODI)
B) Undergone and failed a minimum six months of intensive non-operative treatment that must include non-opioid medication optimization and active therapy. Active therapy is defined as activity modification, chiropractic/osteopathic manipulative therapy, bracing, and/or active therapeutic exercise targeted at the lumbar spine, pelvis, SIJ and hip including a home exercise program. Failure of conservative therapy is defined as less than a 50% improvement on the ODI.
C) Typically unilateral pain that is caudal to the lumbar spine (L5 vertebrae), localized over the posterior SIJ, and consistent with SIJ pain.
D) Thorough physical examination demonstrating localized tenderness with palpation over the sacral sulcus (Fortin's point, i.e. at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine or PSIS) in the absence of tenderness of similar severity elsewhere (e.g. greater trochanter, lumbar spine, coccyx) and that other obvious sources for their pain do not exist.
E) Positive response to at least three of six provocative tests (e.g. thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test).
F) Absence of generalized pain behavior (e.g. somatoform disorder) and generalized pain disorders (e.g. fibromyalgia).
G) Diagnostic imaging studies that include ALL of the following:
    1) Imaging (plain radiographs and a CT or MRI) of the SIJ that excludes the presence of destructive lesions (e.g. tumor, infection), fracture, traumatic sacroiliac joint instability, or inflammatory arthropathy that would not be properly addressed by percutaneous SIJ fusion
    2) Imaging of the pelvis (AP plain radiograph) to rule out concomitant hip pathology
    3) Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that can be causing low back or buttock pain
    4) Imaging of the SIJ that indicates evidence of injury and/or degeneration
H) At least 75 percent reduction of pain for the expected duration of two anesthetics (on separate visits each with a different duration of action), and the ability to perform previously painful maneuvers, following an image-guided, contrast-enhanced intra-articular SIJ injection.

Appendix A
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GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 502

The following interventions are prioritized on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9	Individual test not cost-effective; should only be done as part of a gene panel	November 2019
99454	Remote monitoring of physiologic parameters, 30 days	This code does not require medical decision making nor communication with a patient	November, 2019

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
C1824	Cardiac contractility modulation	Insufficient evidence of effectiveness	November, 2019
C1839	Iris prosthesis	Insufficient evidence of effectiveness	November, 2019
C9756	Intraoperative near-infrared fluorescence lymphatic mapping of lymph node(s)	Insufficient evidence of effectiveness	November, 2019
C9757	Laminotomy with repair of annular defect with implantation of bone anchored annular closure device	Insufficient evidence of effectiveness	November, 2019
15773, 15774	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet	Insufficient evidence of effectiveness; utilization mainly for cosmetic purposes	November 2019
20560, 20561	Dry needling	Insufficient evidence of effectiveness	November 2019

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Procedure Code	Intervention Description	Rationale	Last Review
44133, 44136	Donor enterectomy and intestinal allotransplantation from living donor	Insufficient evidence of effectiveness	November 2019
64451, 64625	Anesthetic or steroid injection and/or radiofrequency ablation, nerves innervating the sacroiliac joint, with image guidance	Insufficient evidence of effectiveness	November 2019
~~64640~~	~~Destruction by neurolytic agent; other peripheral nerve or branch~~	~~Insufficient evidence of effectiveness~~	~~May, 2019 (knee osteoarthritis)~~
64454, 64624	Nerve blocks and/or destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed	Insufficient evidence of effectiveness	May, 2019
76376-76377	3D rendering of imaging studies	No additional proven benefit beyond the standard study, therefore not reimbursed separately	November 2019
78429-78434, 78459, 78491-78492	Myocardial imaging, positron emission tomography (PET), metabolic evaluation and/or perfusion	Insufficient evidence of benefit, unclear harms of radiation exposure	January, 2015 Updated November 2019 Coverage Guidance Blog
~~78491-78492~~	~~Myocardial imaging, positron emission tomography (PET), perfusion~~	~~Insufficient evidence of benefit, unclear harms of radiation exposure~~	~~January, 2015~~ ~~Coverage Guidance Blog~~
~~81225,81226, 81230-81231~~	~~Cytochrome P450 gene analysis~~	~~Insufficient evidence of effectiveness~~	~~December, 2011~~ ~~November, 2017~~
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities	Insufficient evidence of effectiveness	November 2019
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	Insufficient evidence of effectiveness	January 2018

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Procedure Code	Intervention Description	Rationale	Last Review
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis	Insufficient evidence of effectiveness	November 2019
92548, 92549	Computerized dynamic posturography	Insufficient evidence of effectiveness	November 2019
93356	Myocardial strain imaging using speckle tracking-derived assessment of myocardial mechanics	Insufficient evidence of effectiveness	November 2019
~~96116~~ ~~96121~~	~~Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities)~~		~~November, 2018~~

Appendix B
2020 CPT Codes

Code	Code Description	Placement Recommendation
15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)	Ancillary Procedure File
15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate	191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)	191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
15773	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
15774	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; each additional 25 cc injectate, or part thereof (List separately in addition to code for primary procedure)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
20560	Needle insertion(s) without injection(s); 1 or 2 muscle(s)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
20561	Needle insertion(s) without injection(s); 3 or more muscles	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
20700	Manual preparation and insertion of drug-delivery device(s), deep (eg, subfascial) (List separately in addition to code for primary procedure)	47, 80,82,98,107,131,132,150,153,160,183, 184,199,200,205,207,235,254,272,285,292, 309,346,355,356,359,372,376,379,401,418, 424,431,442,505,527,529,558,578,598,643
20701	Removal of drug-delivery device(s), deep (eg, subfascial) (List separately in addition to code for primary procedure)	47, 80,82,98,107,131,132,150,153,160,183, 184,199,200,205,207,235,254,272,285,292, 309,346,355,356,359,372,376,379,401,418, 424,431,442,505,527,529,558,578,598,643
20702	Manual preparation and insertion of drug-delivery device(s), intramedullary (List separately in addition to code for primary procedure)	47, 80,82,98,107,131,132,150,153,160,183, 184,199,200,205,207,235,254,272,285,292, 309,346,355,356,359,372,376,379,401,418, 424,431,442,505,527,529,558,578,598,643

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Code	Code Description	Placement Recommendation
20703	Removal of drug-delivery device(s), intramedullary (List separately in addition to code for primary procedure)	47, 80,82,98,107,131,132,150,153,160,183, 184,199,200,205,207,235,254,272,285,292, 309,346,355,356,359,372,376,379,401,418, 424,431,442,505,527,529,558,578,598,643
20704	Manual preparation and insertion of drug-delivery device(s), intra-articular (List separately in addition to code for primary procedure)	47, 80,82,98,107,131,132,150,153,160,183, 184,199,200,205,207,235,254,272,285,292, 309,346,355,356,359,372,376,379,401,418, 424,431,442,505,527,529,558,578,598,643
20705	Removal of drug-delivery device(s), intra-articular (List separately in addition to code for primary procedure)	47, 80,82,98,107,131,132,150,153,160,183, 184,199,200,205,207,235,254,272,285,292, 309,346,355,356,359,372,376,379,401,418, 424,431,442,505,527,529,558,578,598,643
21601	Excision of chest wall tumor including rib(s)	200 CANCER OF BONES 262 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS 372 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS
21602	Excision of chest wall tumor involving rib(s), with plastic reconstruction; without mediastinal lymphadenectomy	200, 262, 372
21603	Excision of chest wall tumor involving rib(s), with plastic reconstruction; with mediastinal lymphadenectomy	200, 262, 372
33016	Pericardiocentesis, including imaging guidance, when performed	81 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS
33017	Pericardial drainage with insertion of indwelling catheter, percutaneous, including fluoroscopy and/or ultrasound guidance, when performed; 6 years and older without congenital cardiac anomaly	81 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS
33018	Pericardial drainage with insertion of indwelling catheter, percutaneous, including fluoroscopy and/or ultrasound guidance, when performed; birth through 5 years of age or any age with congenital cardiac anomaly	81 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS
33019	Pericardial drainage with insertion of indwelling catheter, percutaneous, including CT guidance	81 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS

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Code	Code Description	Placement Recommendation
33858	Ascending aorta graft, with cardiopulmonary bypass, includes valve suspension, when performed; for aortic dissection	284 DISSECTING OR RUPTURED AORTIC ANEURYSM
33859	Ascending aorta graft, with cardiopulmonary bypass, includes valve suspension, when performed; for aortic disease other than dissection (eg, aneurysm)	325 NON-DISSECTING ANEURYSM WITHOUT RUPTURE
33871	Transverse aortic arch graft, with cardiopulmonary bypass, with profound hypothermia, total circulatory arrest and isolated cerebral perfusion with reimplantation of arch vessel(s) (eg, island pedicle or individual arch vessel reimplantation)	134 INTERRUPTED AORTIC ARCH 284 DISSECTING OR RUPTURED AORTIC ANEURYSM 325 NON-DISSECTING ANEURYSM WITHOUT RUPTURE
34717	Endovascular repair of iliac artery at the time of aorto-iliac artery endograft placement by deployment of an iliac branched endograft including pre-procedure sizing and device selection, all ipsilateral selective iliac artery catheterization(s), all associated radiological supervision and interpretation, and all endograft extension(s) proximally to the aortic bifurcation and distally in the internal iliac, external iliac, and common femoral artery(ies), and treatment zone angioplasty/stenting, when performed, for rupture or other than rupture (eg, for aneurysm, pseudoaneurysm, dissection, arteriovenous malformation, penetrating ulcer, traumatic disruption), unilateral (List separately in addition to code for primary procedure)	284 DISSECTING OR RUPTURED AORTIC ANEURYSM 325 NON-DISSECTING ANEURYSM WITHOUT RUPTURE
34718	Endovascular repair of iliac artery, not associated with placement of an aorto-iliac artery endograft at the same session, by deployment of an iliac branched endograft, including pre-procedure sizing and device selection, all ipsilateral selective iliac artery catheterization(s), all associated radiological supervision and interpretation, and all endograft extension(s) proximally to the aortic bifurcation and distally in the internal iliac, external iliac, and common femoral artery(ies), and treatment zone angioplasty/stenting, when performed, for other than rupture (eg, for aneurysm, pseudoaneurysm, dissection, arteriovenous malformation, penetrating ulcer), unilateral	284 DISSECTING OR RUPTURED AORTIC ANEURYSM 325 NON-DISSECTING ANEURYSM WITHOUT RUPTURE

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Code	Code Description	Placement Recommendation
35702	Exploration not followed by surgical repair, artery; upper extremity (eg, axillary, brachial, radial, ulnar)	236 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS 349 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE
35703	Exploration not followed by surgical repair, artery; lower extremity (eg, common femoral, deep femoral, superficial femoral, popliteal, tibial, peroneal)	236 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS 349 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE
46948	Hemorrhoidectomy, internal, by transanal hemorrhoidal dearterialization, 2 or more hemorrhoid columns/groups, including ultrasound guidance, with mucopexy, when performed	472 THROMBOSED AND COMPLICATED HEMORRHOIDS 618 UNCOMPLICATED HEMORRHOIDS
49013	Preperitoneal pelvic packing for hemorrhage associated with pelvic trauma, including local exploration	1 PREGNANCY 183 FRACTURE OF PELVIS, OPEN AND CLOSED
49014	Re-exploration of pelvic wound with removal of preperitoneal pelvic packing, including repacking, when performed	1 PREGNANCY 183 FRACTURE OF PELVIS, OPEN AND CLOSED
62328	Spinal puncture, lumbar, diagnostic; with fluoroscopic or CT guidance	Diagnostic Procedures File
62329	Spinal puncture, therapeutic, for drainage of cerebrospinal fluid (by needle or catheter); with fluoroscopic or CT guidance	19 HYDROCEPHALUS AND BENIGN INTRACRANIAL HYPERTENSION 125 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD 196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN 285COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 294 CANCER OF BRAIN AND NERVOUS SYSTEM 371 ENCEPHALOCELE
64451	Injection(s), anesthetic agent(s) and/or steroid; nerves innervating the sacroiliac joint, with image guidance (ie, fluoroscopy or computed tomography)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
64454	Injection(s), anesthetic agent(s) and/or steroid; genicular nerve branches, including imaging guidance, when performed	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

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Code	Code Description	Placement Recommendation
64624	Destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
64625	Radiofrequency ablation, nerves innervating the sacroiliac joint, with image guidance (ie, fluoroscopy or computed tomography)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
66987	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification), complex, requiring devices or techniques not generally used in routine cataract surgery (eg, iris expansion device, suture support for intraocular lens, or primary posterior capsulorrhexis) or performed on patients in the amblyogenic developmental stage; with endoscopic cyclophotocoagulation	139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE 296 CATARACT 370 AMBLYOPIA 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
66988	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1 stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification); with endoscopic cyclophotocoagulation	139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE 296 CATARACT 370 AMBLYOPIA 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
74221	Radiologic examination, esophagus, including scout chest radiograph(s) and delayed image(s), when performed; double-contrast (eg, high-density barium and effervescent agent) study	Diagnostic Procedures File
74248	Radiologic small intestine follow-through study, including multiple serial images (List separately in addition to code for primary procedure for upper GI radiologic examination)	Diagnostic Procedures File
78429	Myocardial imaging, positron emission tomography (PET), metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), single study; with concurrently acquired computed tomography transmission scan	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

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Code	Code Description	Placement Recommendation
78430	Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); single study, at rest or stress (exercise or pharmacologic), with concurrently acquired computed tomography transmission scan	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
78431	Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); multiple studies at rest and stress (exercise or pharmacologic), with concurrently acquired computed tomography transmission scan	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
78432	Myocardial imaging, positron emission tomography (PET), combined perfusion with metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), dual radiotracer (eg, myocardial viability);	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
78433	Myocardial imaging, positron emission tomography (PET), combined perfusion with metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), dual radiotracer (eg, myocardial viability); with concurrently acquired computed tomography transmission scan	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
78434	Absolute quantitation of myocardial blood flow (AQMBF), positron emission tomography (PET), rest and pharmacologic stress (List separately in addition to code for primary procedure)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
78830	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT) with concurrently acquired computed tomography (CT) transmission scan for anatomical review, localization and determination/detection of pathology, single area (eg, head, neck, chest, pelvis), single day imaging	Diagnostic Procedures File

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Code	Code Description	Placement Recommendation
78831	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), minimum 2 areas (eg, pelvis and knees, abdomen and pelvis), single day imaging, or single area imaging over 2 or more days	Diagnostic Procedures File
78832	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT) with concurrently acquired computed tomography (CT) transmission scan for anatomical review, localization and determination/detection of pathology, minimum 2 areas (eg, pelvis and knees, abdomen and pelvis), single day imaging, or single area imaging over 2 or more days	Diagnostic Procedures File
78835	Radiopharmaceutical quantification measurement(s) single area (List separately in addition to code for primary procedure)	Diagnostic Procedures File
80145	Adalimumab	Diagnostic Procedures File
80187	Posaconazole	Diagnostic Procedures File
80230	Infliximab	Diagnostic Procedures File
80235	Lacosamide	Diagnostic Procedures File
80280	Vedolizumab	Diagnostic Procedures File
80285	Voriconazole	Diagnostic Procedures File
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence	Diagnostic Procedures File
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant	Diagnostic Procedures File
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)	191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score	191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER

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Code	Code Description	Placement Recommendation
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
87563	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma genitalium, amplified probe technique	Diagnostic Procedures File
90619	Meningococcal conjugate vaccine, serogroups A, C, W, Y, quadrivalent, tetanus toxoid carrier (MenACWY-TT), for intramuscular use	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90694	Influenza virus vaccine, quadrivalent (aIIV4), inactivated, adjuvanted, preservative free, 0.5 mL dosage, for intramuscular use	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90912	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health care professional contact with the patient	455 URINARY INCONTINENCE
90913	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; each additional 15 minutes of one-on-one physician or other qualified health care professional contact with the patient (List separately in addition to code for primary procedure)	455 URINARY INCONTINENCE
92201	Ophthalmoscopy, extended; with retinal drawing and scleral depression of peripheral retinal disease (eg, for retinal tear, retinal detachment, retinal tumor) with interpretation and report, unilateral or bilateral	Any line with 92226
92202	Ophthalmoscopy, extended; with drawing of optic nerve or macula (eg, for glaucoma, macular pathology, tumor) with interpretation and report, unilateral or bilateral	Any line with 92226

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Code	Code Description	Placement Recommendation
92549	Computerized dynamic posturography sensory organization test (CDP-SOT), 6 conditions (ie, eyes open, eyes closed, visual sway, platform sway, eyes closed platform sway, platform and visual sway), including interpretation and report; with motor control test (MCT) and adaptation test (ADT)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
93356	Myocardial strain imaging using speckle tracking-derived assessment of myocardial mechanics (List separately in addition to codes for echocardiography imaging)	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
93985	Duplex scan of arterial inflow and venous outflow for preoperative vessel assessment prior to creation of hemodialysis access; complete bilateral study	Diagnostic Procedures File
93986	Duplex scan of arterial inflow and venous outflow for preoperative vessel assessment prior to creation of hemodialysis access; complete unilateral study	Diagnostic Procedures File
95700	Electroencephalogram (EEG) continuous recording, with video when performed, setup, patient education, and takedown when performed, administered in person by EEG technologist, minimum of 8 channels	Diagnostic Procedures File
95705	Electroencephalogram (EEG), without video, review of data, technical description by EEG technologist, 2-12 hours; unmonitored	Diagnostic Procedures File
95706	Electroencephalogram (EEG), without video, review of data, technical description by EEG technologist, 2-12 hours; with intermittent monitoring and maintenance	Diagnostic Procedures File
95707	Electroencephalogram (EEG), without video, review of data, technical description by EEG technologist, 2-12 hours; with continuous, real-time monitoring and maintenance	Diagnostic Procedures File
95708	Electroencephalogram (EEG), without video, review of data, technical description by EEG technologist, each increment of 12-26 hours; unmonitored	Diagnostic Procedures File
95709	Electroencephalogram (EEG), without video, review of data, technical description by EEG technologist, each increment of 12-26 hours; with intermittent monitoring and maintenance	Diagnostic Procedures File

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Code	Code Description	Placement Recommendation
95710	Electroencephalogram (EEG), without video, review of data, technical description by EEG technologist, each increment of 12-26 hours; with continuous, real-time monitoring and maintenance	Diagnostic Procedures File
95711	Electroencephalogram with video (VEEG), review of data, technical description by EEG technologist, 2-12 hours; unmonitored	Diagnostic Procedures File
95712	Electroencephalogram with video (VEEG), review of data, technical description by EEG technologist, 2-12 hours; with intermittent monitoring and maintenance	Diagnostic Procedures File
95713	Electroencephalogram with video (VEEG), review of data, technical description by EEG technologist, 2-12 hours; with continuous, real-time monitoring and maintenance	Diagnostic Procedures File
95714	Electroencephalogram with video (VEEG), review of data, technical description by EEG technologist, each increment of 12-26 hours; unmonitored	Diagnostic Procedures File
95715	Electroencephalogram with video (VEEG), review of data, technical description by EEG technologist, each increment of 12-26 hours; with intermittent monitoring and maintenance	Diagnostic Procedures File
95716	Electroencephalogram with video (VEEG), review of data, technical description by EEG technologist, each increment of 12-26 hours; with continuous, real-time monitoring and maintenance	Diagnostic Procedures File
95717	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation and report, 2-12 hours of EEG recording; without video	Diagnostic Procedures File
95718	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation and report, 2-12 hours of EEG recording; with video (VEEG)	Diagnostic Procedures File
95719	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, each increment of greater than 12 hours, up to 26 hours of EEG recording, interpretation and report after each 24-hour period; without video	Diagnostic Procedures File

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Code	Code Description	Placement Recommendation
95720	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, each increment of greater than 12 hours, up to 26 hours of EEG recording, interpretation and report after each 24-hour period; with video (VEEG)	Diagnostic Procedures File
95721	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation, and summary report, complete study; greater than 36 hours, up to 60 hours of EEG recording, without video	Diagnostic Procedures File
95722	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation, and summary report, complete study; greater than 36 hours, up to 60 hours of EEG recording, with video (VEEG)	Diagnostic Procedures File
95723	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation, and summary report, complete study; greater than 60 hours, up to 84 hours of EEG recording, without video	Diagnostic Procedures File
95724	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation, and summary report, complete study; greater than 60 hours, up to 84 hours of EEG recording, with video (VEEG)	Diagnostic Procedures File
95725	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation, and summary report, complete study; greater than 84 hours of EEG recording, without video	Diagnostic Procedures File

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Code	Code Description	Placement Recommendation
95726	Electroencephalogram (EEG), continuous recording, physician or other qualified health care professional review of recorded events, analysis of spike and seizure detection, interpretation, and summary report, complete study; greater than 84 hours of EEG recording, with video (VEEG)	Diagnostic Procedures File
96156	Health behavior assessment, or re-assessment (ie, health-focused clinical interview, behavioral observations, clinical decision making)	All lines with 96150
96158	Health behavior intervention, individual, face-to-face; initial 30 minutes	All lines with 96152
96159	Health behavior intervention, individual, face-to-face; each additional 15 minutes (List separately in addition to code for primary service)	All lines with 96152
96164	Health behavior intervention, group (2 or more patients), face-to-face; initial 30 minutes	All lines with 96153
96165	Health behavior intervention, group (2 or more patients), face-to-face; each additional 15 minutes (List separately in addition to code for primary service)	All lines with 96153
96167	Health behavior intervention, family (with the patient present), face-to-face; initial 30 minutes	All lines with 96154
96168	Health behavior intervention, family (with the patient present), face-to-face; each additional 15 minutes (List separately in addition to code for primary service)	All lines with 96154
96170	Health behavior intervention, family (without the patient present), face-to-face; initial 30 minutes	All lines with 96155
96171	Health behavior intervention, family (without the patient present), face-to-face; each additional 15 minutes (List separately in addition to code for primary service)	All lines with 96155

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Code	Code Description	Placement Recommendation
97129	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (eg, managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; initial 15 minutes	91 SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH PERSISTENT SYMPTOMS 178 INTRACEREBRAL HEMORRHAGE 196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN 201 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 317 STROKE 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION
97130	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (eg, managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; each additional 15 minutes (List separately in addition to code for primary procedure)	91, 178, 196, 201, 285, 317, 345, 377
98970	Qualified nonphysician health care professional online digital evaluation and management service, for an established patient, for up to 7 days, cumulative time during the 7 days; 5-10 minutes	Add to all lines with E&M codes
98971	Qualified nonphysician health care professional online digital evaluation and management service, for an established patient, for up to 7 days, cumulative time during the 7 days; 11-20 minutes	Add to all lines with E&M codes
98972	Qualified nonphysician health care professional online digital evaluation and management service, for an established patient, for up to 7 days, cumulative time during the 7 days; 21 or more minutes	Add to all lines with E&M codes

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Code	Code Description	Placement Recommendation
99421	Online digital evaluation and management service, for an established patient, for up to 7 days, cumulative time during the 7 days; 5-10 minutes	Add to all lines with E&M codes
99422	Online digital evaluation and management service, for an established patient, for up to 7 days, cumulative time during the 7 days; 11-20 minutes	Add to all lines with E&M codes
99423	Online digital evaluation and management service, for an established patient, for up to 7 days, cumulative time during the 7 days; 21 or more minutes	Add to all lines with E&M codes
99458	Remote physiologic monitoring treatment management services, clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month; each additional 20 minutes (List separately in addition to code for primary procedure)	9, 20, 48, 58, 69, 75 81, 97, 98, 110, 172, 189, 202, 213, 219, 222, 223, 225, 233, 257, 281, 283, 304, 341, 347, 366, 464, 566, 635, 647, 653, 657
99473	Self-measured blood pressure using a device validated for clinical accuracy; patient education/training and device calibration	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS 75 HYPERTENSION AND HYPERTENSIVE DISEASE 97 HEART FAILURE 172 HYPERTENSIVE HEART AND RENAL DISEASE 264 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE 534 HYPOTENSION
99474	Self-measured blood pressure using a device validated for clinical accuracy; separate self-measurements of two readings one minute apart, twice daily over a 30-day period (minimum of 12 readings), collection of data reported by the patient and/or caregiver to the physician or other qualified health care professional, with report of average systolic and diastolic pressures and subsequent communication of a treatment plan to the patient	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS 75 HYPERTENSION AND HYPERTENSIVE DISEASE 97 HEART FAILURE 172 HYPERTENSIVE HEART AND RENAL DISEASE 264 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE 534 HYPOTENSION

Appendix B
2020 HCPCS

HCPCS	LONG DESCRIPTION	Recommended Placement
C1824	Generator, cardiac contractility modulation (implantable)	**662** CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
C1839	Iris prosthesis	**662** CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
C9756	Intraoperative near-infrared fluorescence lymphatic mapping of lymph node(s) (sentinel or tumor draining) with administration of indocyanine green (icg) (list separately in addition to code for primary procedure)	**662** CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
C9757	Laminotomy (hemilaminectomy), with decompression of nerve root(s), including partial facetectomy, foraminotomy and excision of herniated intervertebral disc, and repair of annular defect with implantation of bone anchored annular closure device, including annular defect measurement, alignment and sizing assessment, and image guidance; 1 interspace, lumbar	**662** CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing	**8** TYPE 1 DIABETES MELLITUS
G2058	Chronic care management services, each additional 20 minutes of clinical staff time directed by a physician or other qualified health care professional, per calendar month (list separately in addition to code for primary procedure). (do not report g2058 for care management services of less than 20 minutes additional to the first 20 minutes of chronic care management services during a calendar month). (use g2058 in conjunction with 99490). (do not report 99490, g2058 in the same calendar month as 99487, 99489, 99491)).	Any line with CPT 99490
G2061	Qualified nonphysician healthcare professional online assessment, for an established patient, for up to seven days, cumulative time during the 7 days; 5-10 minutes	Add to all lines with E&M codes

HCPCS	LONG DESCRIPTION	Recommended Placement
G2062	Qualified nonphysician healthcare professional online assessment service, for an established patient, for up to seven days, cumulative time during the 7 days; 11-20 minutes	Add to all lines with E&M codes
G2063	Qualified nonphysician qualified healthcare professional assessment service, for an established patient, for up to seven days, cumulative time during the 7 days; 21 or more minutes	Add to all lines with E&M codes
G2064	Comprehensive care management services for a single high-risk disease, e.g., principal care management, at least 30 minutes of physician or other qualified health care professional time per calendar month with the following elements: one complex chronic condition lasting at least 3 months, which is the focus of the care plan, the condition is of sufficient severity to place patient at risk of hospitalization or have been the cause of a recent hospitalization, the condition requires development or revision of disease-specific care plan, the condition requires frequent adjustments in the medication regimen, and/or the management of the condition is unusually complex due to comorbidities	Any line with CPT 99487
G2065	Comprehensive care management for a single high-risk disease services, e.g. principal care management, at least 30 minutes of clinical staff time directed by a physician or other qualified health care professional, per calendar month with the following elements: one complex chronic condition lasting at least 3 months, which is the focus of the care plan, the condition is of sufficient severity to place patient at risk of hospitalization or have been cause of a recent hospitalization, the condition requires development or revision of disease-specific care plan, the condition requires frequent adjustments in the medication regimen, and/or the management of the condition is unusually complex due to comorbidities	Any line with CPT 99487

HCPCS	LONG DESCRIPTION	Recommended Placement
G2066	Interrogation device evaluation(s), (remote) up to 30 days; implantable cardiovascular physiologic monitor system, implantable loop recorder system, or subcutaneous cardiac rhythm monitor system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results	Diagnostic Procedures File
G2067	Medication assisted treatment, methadone; weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing, if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2068	Medication assisted treatment, buprenorphine (oral); weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2069	Medication assisted treatment, buprenorphine (injectable); weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2070	Medication assisted treatment, buprenorphine (implant insertion); weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2071	Medication assisted treatment, buprenorphine (implant removal); weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER

Appendix B
2020 HCPCS

HCPCS	LONG DESCRIPTION	Recommended Placement
G2072	Medication assisted treatment, buprenorphine (implant insertion and removal); weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2073	Medication assisted treatment, naltrexone; weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2074	Medication assisted treatment, weekly bundle not including the drug, including substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER
G2075	Medication assisted treatment, medication not otherwise specified; weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing, if performed (provision of the services by a medicare-enrolled opioid treatment program)	4 SUBSTANCE USE DISORDER

HCPCS	LONG DESCRIPTION	Recommended Placement
G2076	Intake activities, including initial medical examination that is a complete, fully documented physical evaluation and initial assessment by a program physician or a primary care physician, or an authorized healthcare professional under the supervision of a program physician qualified personnel that includes preparation of a treatment plan that includes the patient's short-term goals and the tasks the patient must perform to complete the short-term goals; the patient's requirements for education, vocational rehabilitation, and employment; and the medical, psycho- social, economic, legal, or other supportive services that a patient needs, conducted by qualified personnel (provision of the services by a medicare-enrolled opioid treatment program); list separately in addition to code for primary procedure	4 SUBSTANCE USE DISORDER
G2077	Periodic assessment; assessing periodically by qualified personnel to determine the most appropriate combination of services and treatment (provision of the services by a medicare-enrolled opioid treatment program); list separately in addition to code for primary procedure	4 SUBSTANCE USE DISORDER
G2080	Each additional 30 minutes of counseling in a week of medication assisted treatment, (provision of the services by a medicare-enrolled opioid treatment program); list separately in addition to code for primary procedure	4 SUBSTANCE USE DISORDER
G2082	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation	7 MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE
G2083	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post-administration observation	7 MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE

Appendix B
2020 HCPCS

HCPCS	LONG DESCRIPTION	Recommended Placement
G2086	Office-based treatment for opioid use disorder, including development of the treatment plan, care coordination, individual therapy and group therapy and counseling; at least 70 minutes in the first calendar month	4 SUBSTANCE USE DISORDER
G2087	Office-based treatment for opioid use disorder, including care coordination, individual therapy and group therapy and counseling; at least 60 minutes in a subsequent calendar month	4 SUBSTANCE USE DISORDER
G2088	Office-based treatment for opioid use disorder, including care coordination, individual therapy and group therapy and counseling; each additional 30 minutes beyond the first 120 minutes (list separately in addition to code for primary procedure)	4 SUBSTANCE USE DISORDER

Appendix B
New CDT 2020 Codes

Procedure	Nomenclature	Recommended placement
D0419	Assessment of salivary flow by measurement	EXCLUDED FILE
D1551	Re-cement or re-bond bilateral space maintainer – maxillary	53 PREVENTIVE DENTAL SERVICES
D1552	Re-cement or re-bond bilateral space maintainer – mandibular	53 PREVENTIVE DENTAL SERVICES
D1553	Re-cement or re-bond unilateral space maintainer – per quadrant	53 PREVENTIVE DENTAL SERVICES
D1556	Removal of fixed unilateral space maintainer – per quadrant	53 PREVENTIVE DENTAL SERVICES
D1557	Removal of fixed bilateral space maintainer – maxillary	53 PREVENTIVE DENTAL SERVICES
D1558	Removal of fixed bilateral space maintainer – mandibular	53 PREVENTIVE DENTAL SERVICES
D2753	Crown - porcelain fused to titanium or titanium alloy	591 ADVANCED RESTORATIVE-ELECTIVE
D5284	Removable unilateral partial denture – one piece flexible base (including clasps and teeth)- per quadrant	591 ADVANCED RESTORATIVE-ELECTIVE
D5286	Removable unilateral partial denture – one piece resin (including clasps and teeth) - per quadrant	591 ADVANCED RESTORATIVE-ELECTIVE
D6082	Implant supported crown - porcelain fused to predominantly base alloys	619 IMPLANTS
D6083	Implant supported crown - porcelain fused to noble alloys	619 IMPLANTS
D6084	Implant supported crown - porcelain fused to titanium or titanium alloy	619 IMPLANTS
D6086	Implant supported crown - predominantly base alloys	619 IMPLANTS
D6087	Implant supported crown - noble alloys	619 IMPLANTS

Appendix B
New CDT 2020 Codes

Procedure	Nomenclature	Recommended placement
D6088	Implant supported crown - titanium/titanium alloys	619 IMPLANTS
D6097	Abutment supported crown - porcelain fused to titanium or titanium alloys	619 IMPLANTS
D6098	Implant supported retainer for metal FPD - porcelain fused to predominantly base alloys	619 IMPLANTS
D6099	Implant supported retainer for metal FPD - porcelain fused to noble alloys	619 IMPLANTS
D6120	Implant supported retainer - porcelain fused to titanium or titanium alloy	619 IMPLANTS
D6121	Implant supported retainer for metal FPD - predominantly base alloys	619 IMPLANTS
D6122	Implant supported retainer for metal FPD - noble alloys	616 IMPLANTS
D6123	Implant supported retainer for metal FPD- titanium or titanium alloy	619 IMPLANTS
D6195	Abutment supported retainer - porcelain fused to titanium or titanium alloy	619 IMPLANTS
D6243	Pontic - porcelain fused to titanium or titanium alloys	619 IMPLANTS
D6753	Retainer crown - porcelain fused to titanium or titanium alloys	619 IMPLANTS
D6784	Retainer crown ¾ - titanium and titanium alloys	591 ADVANCED RESORATIVE-ELECTIVE
D7922	Placement of intra-socket biological dressing to aid in hemostasis or clot stabilization, per site	EXCLUDED FILE
D8696	Repair of orthodontic appliance – maxillary	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 257 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 615 ORTHODONTIA

Appendix B
New CDT 2020 Codes

Procedure	Nomenclature	Recommended placement
D8697	Repair of orthodontic appliance – mandibular	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 256 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 618 ORTHODONTIA
D8698	Re-cement or re-bond fixed retainer – maxillary	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 256 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 618 ORTHODONTIA
D8699	Re-cement or re-bond fixed retainer – mandibular	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 256 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 618 ORTHODONTIA
D8701	Repair of fixed retainer, includes reattachment – maxillary	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 257 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 615 ORTHODONTIA
D8702	Repair of fixed retainer, includes reattachment – mandibular	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 256 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 618 ORTHODONTIA
D8703	Replacement of lost or broken retainer – maxillary	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 256 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 618 ORTHODONTIA
D8704	Replacement of lost or broken retainer – mandibular	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 256 DEFORMATIES OF HEAD 300 CLEFT PALATE AND/OR CLEFT LIP 618 ORTHODONTIA
D9997	Dental case management – patients with special health care needs	ANCILLARY

Appendix C
New Guideline Notes

DIAGNOSTIC GUIDELINE D26, NEUROBEHAVIORAL STATUS EXAMS AND NEUROPSYCHOLOGICAL TESTING

Neurobehavioral status exams (CPT 96116 and 96121) and neuropsychological testing services (CPT 96132 and 96133) are only covered when all of the following are met:

1) Symptoms are not explained by an existing diagnosis; AND
2) When the results of such testing will be used to develop a care plan.

GUIDELINE NOTE 197, COUNSELING FOR PREGNANT AND POSTPARTUM WOMEN

Lines 1, 3, 35, 63

Counseling for the prevention of peripartum mood disorders for pregnant and postpartum women (including up to 1 year after birth or pregnancy loss) are included on these lines according to USPSTF recommendations https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/perinatal-depression-preventive-interventions and should be coded with health behavior assessment and intervention procedure codes.

Supervision of pregnancy codes (ICD-10 O09.X, Z34.X), encounter for screening for maternal depression (ICD-10 Z13.32), and encounter for routine postpartum follow-up (ICD-10 Z39.2) are appropriate to pair with health behavior assessment and interventions for these purposes.

[Note: purple wording above was removed from the guideline by the HERC at the 11/14/19 HERC meeting]

ANCILLARY GUIDELINE NOTE A5, TELECONSULTATIONS AND NON-FACE-TO -FACE TELEHEALTH SERVICES

Patient to Clinician Services (via telephone or electronic)

Telephonic and electronic services, including services related to diagnostic workup (CPT 98966-98968, 99441-99443, 99421-99423, 98970-98972, G2012, G2061-G2063) between a patient and clinician must meet the following criteria:

1) Ensure pre-existing relationship as demonstrated by at least one prior office visit within the past 36 months.
2) Documentation must:
    a. model SOAP charting, or be as described in program's OAR;
    b. include patient history, provider assessment, treatment plan and follow-up instructions;
    c. support the assessment and plan;
    d. be retained in the patient's medical record and be retrievable.
3) Medical decision making (or behavioral health intervention/ psychotherapy) is necessary.
4) Ensure permanent storage (electronic or hard copy) of the encounter.
5) Meet HIPAA standards for privacy.

6) Include a patient-clinician agreement of informed consent, which is discussed with and signed by the patient and documented in the medical record.
7) Not be billed when the same services are billed as care plan oversight or anticoagulation management (CPT codes 99339-99340, 99374-99380 or 99363-99364).
8) When a telephone or electronic service refers to an E/M service performed and billed by the physician within the previous seven days, it is not separately billable, regardless of whether it is the result of patient-initiated or physician-requested follow-up.
9) This service is not billed if the service results in the patient being seen within 24 hours or the next available appointment.
10) If the service relates to and takes place within the postoperative period of a procedure provided by the physician, the service is considered part of the procedure and is not be billed separately.

Examples of reimbursable telephone or electronic services include but are not limited to:
1) Extended counseling when person-to-person contact would involve an unwise delay.
2) Treatment of relapses that require significant investment of provider time and judgment.
3) Counseling and education for patients with complex chronic conditions.

Examples of non-reimbursable telephone consultations include but are not limited to:
1) Prescription renewal.
2) Scheduling a test.
3) Reporting normal test results.
4) Requesting a referral.
5) Follow up of medical procedure to confirm stable condition, without indication of complication or new condition.
6) Brief discussion to confirm stability of chronic problem and continuity of present management.

Clinician-to-Clinician Telehealth Consultations (telephonic and electronic)

Telehealth consultations are defined as the use, including use related to diagnostic workup, of telehealth to facilitate collaboration between two or more clinicians. Requirements for coverage of electronic consultation or telephonic interprofessional consultation are as follows:

Appendix C
New Guideline Notes

Consulting Providers (99451, 99446-9)

- Consult must be requested by another provider
- Can be for a new or exacerbated condition
- Cannot be reported more than 1 time per 7 days for the same patient
- Cumulative time spent reported, even if time occurs over multiple days
- Cannot be reported if a transfer of care or request for face-to-face visit occurs as a result of the consultation within the next 14 days
- Cannot be reported if the patient was seen by the consultant within the past 14 days
- Request and reason for consultation request must be documented in the patient's medical record
- Requires a minimum of 5 minutes

Requesting Providers (99452)

- eConsult must be reported by requesting provider (not for the transfer of a patient or request for face-to-face consult)
- Reported only when the patient is not on-site and with the provider at the time of consultation
- Cannot be reported more than 1 time per 14 days per patient
- Requires a minimum of 16 minutes. Includes time for referral prep and/or communicating with the consultant.
- Can be reported with prolonged services, non-direct

Limited information provided by one clinician to another that does not contribute to collaboration (e.g., interpretation of an electroencephalogram, report on an x-ray or scan, or reporting the results of a diagnostic test) is not considered a consultation.

GUIDELINE NOTE 199, INTESTINE TRANSPLANT

Line 239

Intestine transplant is included on this line only for patients with failure of total parenteral nutrition (TPN) as indicated by one of the following, and no contraindications to transplant:

1) Impending or overt liver failure due to TPN, indicated by elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastro-esophageal varices, coagulopathy, peristomal bleeding, or hepatic fibrosis/cirrhosis; OR
2) Thrombosis of ≥ 2 central veins, including jugular, subclavian, and femoral veins; OR
3) Two or more episodes of systemic sepsis due to line infection, per year, or one episode of septic shock, acute respiratory distress syndrome, and/or line related fungemia; OR
4) Frequent episodes of dehydration despite IV fluid supplementation; OR
5) Other complications leading to loss of vascular access

Appendix C
New Guideline Notes

GUIDELINE NOTE 196, BREAST SURGERY REVISION

Lines 191,285,312,424,560,636,642

Revision of previous breast reconstruction, augmentation, or other breast surgery is only covered in cases where the revision is required to address complications of the surgery (wound dehiscence, fistula, chronic pain directly related to the surgery, etc.). For capsular contracture, only stage 4 contractures with chronic pain are covered for revision surgery/capsulotomy. Revisions of breast reconstruction, augmentation or other breast surgery are not covered solely for cosmetic issues.

Section 2.0

Staff Report

January 2020
Errata

1) Changes approved by VbBS/HERC in October 2018 regarding medical indications for circumcision were left out of the minutes and not put into the Prioritized List in error.
    a. Add CPT 54150 (Circumcision, using clamp or other device with regional dorsal penile or ring block), 54160 (Circumcision, surgical excision other than clamp, device, or dorsal slit; neonate (28 days of age or less)) and 54161 (Circumcision, surgical excision other than clamp, device, or dorsal slit; older than 28 days of age) to lines 21 VESICOURETERAL REFLUX and 413 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS
    b. Add CPT 54150 (Circumcision, using clamp or other device with regional dorsal penile or ring block) and 54160 (Circumcision, surgical excision other than clamp, device, or dorsal slit; neonate (28 days of age or less)) to line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    c. Remove ICD-10 N48.0 (Leukoplakia of penis) from line 242 DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU and add to line 413 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS
    d. Add ICD-10 Z87.440 (Personal history of urinary (tract) infections) to line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
        i. HSD was advised to remove ICD-10 Z87.440 from the Informational File
2) Additional corrections:
    a. The title to guideline note 172 was missing from the PDF list for a few days in December but has been restored.
    b. Obsolete CPT code 97127 was replaced with new CPT codes 97129 and 97130 (Therapeutic interventions that focus on cognitive function) in GUIDELINE NOTE 90 COGNITIVE REHABILITATION.
    c. In GUIDELINE NOTE 173 INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS, the entry for HCPCS code C9746 (Transperineal implantation of permanent adjustable balloon continence device) was deleted as this code is obsolete. Obsolete CPT C9741 was also removed from the entry for CardioMEMs.
    d. CPT code 46948 (Hemorrhoidectomy, internal, by transanal hemorrhoidal dearterialization, 2 or more hemorrhoid columns/groups, including ultrasound guidance, with mucopexy, when performed) was moved from line 472 to line 474 THROMBOSED AND COMPLICATED HEMORRHOIDS. It remains on line 621.
    e. The entry for CPT code 78459 (Myocardial imaging, positron emission tomography (PET), metabolic evaluation) was deleted from Guideline Note 173. This code is now listed in a separate entry along with other related codes 78429-78434 and 78491-78492.
    f. Codes 97110 (Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility) and 97530 (Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes) were removed from line 512 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM.
    g. HCPCS code G2012 Brief communication technology-based service, e.g. virtual check-in, by a physician or other qualified health care professional who can report evaluation and management services, provided to an established patient, not originating from a related

e/m service provided within the previous 7 days nor leading to an e/m service or procedure within the next 24 hours or soonest available appointment; 5-10 minutes of medical discussion was added back to all lines with evaluation and management codes.

h. CPT code 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)) was removed from line 252 (it is now recommended for the Diagnostic Procedure File).

i. Guideline note D26 had incorrect codes when approved at the November 2019 meeting. The codes were corrected.

DIAGNOSTIC GUIDELINE D26, NEUROBEHAVIORAL STATUS EXAMS AND NEUROPSYCHOLOGICAL TESTING

Neurobehavioral status exams (CPT 96116 and 96121) and neuropsychological testing services (CPT 96132 and 96133 ~~96116 and 96121~~) are only covered when all of the following are met:

1) Symptoms are not explained by an existing diagnosis; AND
2) When the results of such testing will be used to develop a care plan.

Section 3.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—January 2020

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
99490	Chronic care management services, at least 20 minutes of clinical staff time directed by a physician or other qualified health care professional, per calendar month, with the following required elements: multiple (two or more) chronic conditions expected to last at least 12 months, or until the death of the patient; chronic conditions place the patient at significant risk of death, acute exacerbation/decompensation, or functional decline; comprehensive care plan established, implemented, revised, or monitored.	346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS 361 SCOLIOSIS 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS 661 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	99490 is on all other lines with E&M codes	Add 99490 to lines 346, 361, 529, and 661
G2058	Chronic care management services, each additional 20 minutes of clinical staff time directed by a physician or other qualified health care professional, per calendar month (list separately in addition to code for primary procedure)	346, 361, 529, and 661	G2058 was added to all lines with 99490 with the 2020 HCPCS review in November, 2019	Add G2058 to lines 346, 361, 529, and 661

Consent Agenda Issues—January 2020

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
M40.0 M40.4 M40.5	Postural kyphosis Postural lordosis Lordosis, unspecified	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS 659 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	Postural kyphosis and lordosis need no treatment but education on better posture. Lordosis is the normal curvature of the spine and also does not require treatment. These codes are being overused by PT according to one CCO who requested movement to an uncovered line. They were added to the covered back line as part of a code series.	Remove M40.0, M40.4 and M40.5 from lines 402 and 529 Add M40.0, M40.4 and M40.5 to line 659

Cytochrome P450 Correction

Issue: CPT 81225 (CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)) was missed at the November, 2019 discussion regarding P450 testing. The other P450 codes were removed from line 662 and added to the Diagnostic Procedures File. CPT 81225 was struck from GN173 INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS, but no other action was approved for it.

On review, HERC staff identified that the code series added to Diagnostic Guideline D1, in addition to not including CPT 81225, including two non-P450 codes in error.

HERC staff recommendations:

1) Remove CPT 81225 (CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)) from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS and recommend that HSD add the code to the Diagnostic Procedure File.
2) Modify the entry regarding P450 testing in section D of DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE as shown below.
    a. CPT 8122556 81227, 81230-81231 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding psychiatric medications and are not covered for testing prior to psychiatric medication therapy, except when required in the FDA labelling for the medication.

INR Monitoring

Issue: the CPT codes for INR monitoring are on nearly all lines, including many that stakeholders feel are not appropriate. HERC staff feels that it would be less confusing to have these codes be on the Diagnostic Procedures File. One related ICD-10 code would also need to be moved from lines on the Prioritized List to The Diagnostic Workup File.

CPT Code	**Code Description**	**Current Placement**
93792	Patient/caregiver training for initiation of home international normalized ratio (INR) monitoring under the direction of a physician or other qualified health care professional, face-to-face, including use and care of the INR monitor, obtaining blood sample, instructions for reporting home INR test results, and documentation of patient's/caregiver's ability to perform testing and report results	640 lines
93793	Anticoagulant management for a patient taking warfarin, must include review and interpretation of a new home, office, or lab international normalized ratio (INR) test result, patient instructions, dosage adjustment (as needed), and scheduling of additional test(s), when performed	640 lines
ICD-10 Codes		
Z51.81	Encounter for therapeutic drug level monitoring	Diagnostic Workup File
Z79.01	Long term (current) use of anticoagulants	14 cardiac lines

HERC staff recommendations:

1) Remove CPT 93792-93793 from all current lines on the Prioritized List and advise HSD to add to the Diagnostic Procedures File
2) Remove ICD-10 Z79.01 from all current lines on the Prioritized List and advise HSD to add to the Diagnostic Workup File

Section 4.0

New Discussion Items

Bone Marrow Transplant for Severe Sickle Cell Disease

Question: Should bone marrow transplant (BMT) be covered for qualifying patients with severe sickle cell disease (SSD)?

Question source: OHSU BMT transplant program, CCO, OHSU sickle cell program

Issue: Sickle cell disease is an inherited disorder of the red blood cells, with higher incidence among persons of African ancestry. Symptoms include severe anemia, jaundice, infection, delayed growth, pain crises, chronic pain, strokes, and damage to various organs. Treatments are generally supportive and include blood transfusions and pain medication. Bone marrow transplant has been used to treat severe sickle cell disease in certain patients, generally those with repeated episodes of acute chest syndrome, stroke, or other severe disease symptoms, and who have an unaffected HLA matched sibling to serve as the donor.

OHSU recently contacted the HERC to request a review of BMT for SSD. In 2016, Medicare approved coverage for the procedure, as long as it is conducted as part of an approved, prospective clinical trial to allow for evidence development. BMT is currently the only curative therapy for SSD, though genetic therapies are being tested in humans.

HSC/HERC history:

1) Sickle cell disease ICD-9 diagnosis was deleted from the bone transplant line in June 2000, with the note that "sickle cell disease is not an indication for transplant."
2) In December 2003, HSC discussed bone marrow transplant for sickle cell disease, and noted that "between 5-20% of patients with sickle cell have severe morbidity from vaso-occlusive crisis resulting in pulmonary, renal, and central nervous system damage. Indications for bone marrow transplant include a history of strokes, recurrent chest syndrome or recurrent vaso-occlusive crises; however, it is not clear whether or not it [BMT] significantly prolongs survival."
3) In March 2004, a cost-effectiveness analysis of bone marrow transplant for sickle cell disease was reviewed, and there was "no difference in QALY based on intention to treat analysis." Based on this, "It was elected to remove sickle cell disease from the current bone marrow transplant line."

Current Prioritized List status:

1) ICD-10 D57 series (sickle cell disease) is on the medical line 194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN
2) Bone marrow transplant is found on lines:
    a. 95 HEREDITARY IMMUNE DEFICIENCIES
    b. 114 APLASTIC ANEMIAS; AGRANULOCYTOSIS
    c. 116 HODGKIN'S DISEASE
    d. 163 NON-HODGKIN'S LYMPHOMAS
    e. 179 ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME
    f. 261 MULTIPLE MYELOMA
    g. 331 ACUTE PROMYELOCYTIC LEUKEMIA
    h. 396 ACUTE MYELOID LEUKEMIA
    i. 399 CHRONIC MYELOID LEUKEMIA

Evidence

1) **Oringanje 2017**, Cochrane review of BMT for SSD
    a. Ten trials were identified by the initial search and none for the update. None of these trials were suitable for inclusion in this review (not RCTs or quasi-RCTs)
    b. Reports on the use of hematopoietic stem cell transplantation improving survival and preventing symptoms and complications associated with sickle cell disease are currently limited to observational and other less robust studies. No randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations was found.
    c. Conclusion: Over 30 years after the discovery of the use of hematopoietic stem cells to cure sickle cell disease (SCD), it is surprising that there are no randomized controlled trials to provide concrete evidence for its use in people with SCD…this leaves observational studies to assess these interventions. These studies report that hematopoietic stem cell transplantations (HSCT) does improve survival and/or prevent symptoms and complications associated with SCD but there is the issue of risk which is still being investigated. In the absence of any relevant randomized controlled trial comparing HSCT to standard care or comparing the different methods of HSCT in SCD, this systematic review found no evidence for or against these interventions.
2) **Gluckman 2017**, registry study of outcomes of HLA identical sibling BMT for SCC
    a. N=1000 patients (846 children, 154 adults)
        i. The median age at transplantation was 9 years (range 4 months to 54 years), and the median follow-up was longer than 5 years.
        ii. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), and Eurocord databases
    b. The 5-year event-free survival and overall survival were 91.4% (95% confidence interval, 89.6%-93.3%) and 92.9% (95% confidence interval, 91.1%-94.6%), respectively [note: reported survival in SCD overall is 93.4% from birth to adulthood]. Event free survival was lower with increasing age at transplantation (hazard ratio [HR], 1.09; P<.001) and higher for transplantation performed after 2006 (HR, 0.95; P 5 .013). Twenty-three patients experienced graft failure
    c. 70 patients (7%) died, with the most common cause of death being infection. followed by GVHD (n = 9), toxicity (n = 9), hemorrhage (n=3), secondary malignancy (n=2; 1 CNS lymphoma and 1 cerebral tumor), and other or not specified causes (n = 33).
    a. Conclusion: The excellent outcome of a cohort transplanted over the course of 3 decades confirms the role of HLA-identical sibling transplantation for children and adults with SCD.
3) **Shenoy 2017**, trial of unrelated BMT for SSD
    a. N=29 children
    b. Blood and Marrow Transplant Clinical Trials Network (BMT CTN) phase 2 trial conducted from 2008 to 2014
    c. Transplant indications included stroke (n 5 12), transcranial Doppler velocity >200 cm/s (n = 2), ≥3 vaso-occlusive pain crises per year (n = 12), or ≥2 acute chest syndrome episodes (n = 4) in the 2 years preceding enrollment. Median follow-up was 26 months (range, 12-62 months)
    d. graft rejection rate was 10%.
    e. The 1- and 2-year event free survival rates were 76% and 69%, respectively. The corresponding rates for overall survival were 86% and 79%. The day 100 incidence rate of grade II-IV acute GVHD was 28%, and the 1-year incidence rate of chronic GVHD was

62%; 38% classified as extensive. There were 7 GVHD-related deaths. A 34% incidence of posterior reversible encephalopathy syndrome was noted in the first 6 months.

f. Although the 1-year EFS met the prespecified target of ≥75%, this regimen cannot be considered sufficiently safe for widespread adoption without modifications to achieve more effective GVHD prophylaxis.

4) **Arnold 2017,** retrospective cohort study of health care utilization after BMT for SSD
   a. Databases study, children transplanted for SSD in the US 2000-2013
      i. Center for International Blood and Marrow Transplant Research (CIBMTR) database
      ii. Healthcare utilization data from the Pediatric Health Information System, a confidential database of 43 member hospitals in the USA
      iii. The most commonly documented transplant indication was stroke (29%) followed by recurrent vaso-occlusive crises (22%). However, 39% had stroke as a documented SCD complication, 55% vaso-occlusive crises, and 53% acute chest syndrome.
      iv. The most common source of a graft for transplantation was a matched sibling donor (MSD) (42%)
   b. The 2-year overall survival was 90% [95% confidence interval (CI): 85-95%]: 96% (95% CI: 89-100%) for cord blood transplant (CBT), 94% (95% CI: 86-98%) for MSD transplants, and 74% (95% CI: 54-90%) for transplants from well-matched unrelated donors (MUD) (*P*=0.002)
   c. The cumulative incidence of acute GvHD at day 100 was 14% (95% CI: 9-20%), and chronic GvHD developed in 31% (95% CI: 23-38%) at 2 years.
   d. Among 161 patients with a 2-year overall survival rate of 90% (95% confidence interval [CI] 85-95%) mortality was significantly higher in those who underwent late transplantation versus early (hazard ratio (HR) 21, 95% CI 2.8-160.8, *P*=0.003) and unrelated compared to matched sibling donor transplantation (HR 5.9, 95% CI 1.7-20.2, *P*=0.005). Chronic graft versus host disease was significantly more frequent among those translanted late (HR 1.9, 95% CI 1.0-3.5, *P*=0.034) and those who received an unrelated graft (HR 2.5, 95% CI 1.2-5.4; *P*=0.017).
   e. Merged data for 176 patients showed that the median total adjusted transplant cost per patient was $467,747 (range: $344,029-$799,219). Healthcare utilization was lower among recipients of matched sibling donor grafts and those with low severity disease compared to those with other types of donor and disease severity types (*P*<0.001 and *P*=0.022, respectively); no association was demonstrated with late transplantation (*P*=0.775).
   f. Among patients with 2-year pre- and post-transplant data (n=41), early transplantation was associated with significant reductions in admissions (*P*<0.001), length of stay (*P*<0.001), and cost (*P*=0.008).
   g. Conclusion: Reduced post-transplant healthcare utilization inpatient care indicates that transplantation may provide a sustained decrease in healthcare costs over time

<u>Expert society guidelines</u>

1) **Majhail 2015**, The American Society for Blood and Marrow Transplantation (ASBMT) Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation
   a. Sickle cell disease is listed as an indication for allogenic HCT, noted to be standard of care with clinical evidence available

2) **Angelucci 2014**, European guidelines for BMT for SSD
    a. Young patients with symptomatic SCD who have an HLA matched sibling donor should be transplanted as early as possible, preferably at pre-school age.
    b. Unmanipulated BM or UCB (whenever available) from matched sibling donors are the recommended stem cell source.
    c. SCT from unrelated BM or CB donors should only be considered in the presence of at least one of the indications suggested by Walters et al (stroke, recurrent vaso-occlusive pain, etc.) and should be performed only in the context of controlled trials in experienced centers

Other payer policies:

1) Aetna 2019
    a. Aetna considers allogeneic hematopoietic cell transplantation medically necessary for the treatment of sickle cell anemia in children or young adults when the member meets transplanting institution's written eligibility criteria. In the absence of such criteria, Aetna considers allogeneic hematopoietic cell transplantation medically necessary for the treatment of sickle cell anemia in children or young adults when both of the following criteria are met:
        i. Members have a haploidentical to HLA-matched donor; *and*
        ii. Members with either a history of stroke or at increased risk of stroke or end-organ damage (recurrent chest syndrome, recurrent vaso-occlusive crises, and red blood cell alloimmunization on chronic transfusion therapy).
    b. Aetna considers autologous hematopoietic cell transplantation for thalassemia major or sickle cell anemia in children or young adults experimental and investigational due to insufficient evidence in the peer-reviewed literature.

2) Cigna 2019
    a. Myeloablative allogeneic HSCT is considered medically necessary for the treatment of a child or young adult at increased risk of complications of sickle cell disease (SCD) or thalassemia major.
    b. Non-myeloablative allogeneic HSCT for a child or young adult with SCD or thalassemia major is considered experimental, investigational or unproven.
    c. HSCT for an adult with SCD or thalassemia major is considered experimental, investigational or unproven.

Bone Marrow Transplant for Severe Sickle Cell Disease

HERC staff summary:
Bone marrow transplant for sickle cell disease from an HLA matched sibling is recommended by expert groups, and has retrospective cohort data to support its effectiveness. There are no RCT level data to support this intervention; however, transplants in the US are being performed as part of clinical trials to collect such data. Unrelated matched donor transplant has higher risks of graft-vs-host disease and lower survival rates compared to sibling transplants. Sickle cell disease affects a vulnerable population, which should be considered in decisions regarding therapy.

Insurance coverage is currently limited to patients 40 and younger, per experts.

HERC staff recommendations:

1) Add ICD-10 D57 series (sickle cell disease) to line 114 APLASTIC ANEMIAS; AGRANULOCYTOSIS Treatment: BONE MARROW TRANSPLANT
    a. Modify the line title of line 114 to APLASTIC ANEMIAS; AGRANULOCYTOSIS; SICKLE CELL DISEASE
    b. Keep D57 series on line 194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN for medical therapy
2) Add a guideline to line 114 as shown below
    a. Discuss whether to require sibling donor or any matched donor
    b. Discuss if any age limits should apply

GUIDELINE XXX BONE MARROW TRANSPLANT FOR SICKLE CELL DISEASE
Line 114
Allogeneic hematopoietic cell transplantation for sickle cell disease is included on this line only when all of the following are met:

1) Patient is age 40 or younger; *and*
2) Patient has a haploidentical to HLA-matched sibling donor; *and*
3) Patient has either a history of stroke or is at increased risk of stroke or end-organ damage (recurrent chest syndrome, recurrent vaso-occlusive crises, and red blood cell alloimmunization on chronic transfusion therapy).

Cochrane Library

Cochrane Database of Systematic Reviews

Hematopoietic stem cell transplantation for people with sickle cell disease (Review)

Oringanje C, Nemecek E, Oniyangi O

Oringanje C, Nemecek E, Oniyangi O.
Hematopoietic stem cell transplantation for people with sickle cell disease.
Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD007001.
DOI: 10.1002/14651858.CD007001.pub4.

www.cochranelibrary.com

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[Intervention Review]

Hematopoietic stem cell transplantation for people with sickle cell disease

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ABSTRACT

Background

Sickle cell disease is a genetic disorder involving a defect in the red blood cells due to its sickled hemoglobin. The main therapeutic interventions include preventive and supportive measures. Hematopoietic stem cell transplantations are carried out with the aim of replacing the defective cells and their progenitors (hematopoietic (i.e. blood forming) stem cells) in order to correct the disorder. This is an update of a previously published review.

Objectives

To determine whether stem cell transplantation can improve survival and prevent symptoms and complications associated with sickle cell disease. To examine the risks of stem cell transplantation against the potential long-term gain for people with sickle cell disease.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Group's Haemoglobinopathies Trials Register complied from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and quarterly searches of MEDLINE.

Unpublished work was identified by searching the abstract books of major conference proceedings and we conducted a search of the website: www.ClinicalTrials.gov.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 06 October 2015.

Selection criteria

Randomized controlled and quasi-randomized studies that compared any method of stem cell transplantation with either each other or with any of the preventive or supportive interventions (e.g. periodic blood transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen) in people with sickle cell disease irrespective of the type of sickle cell disease, gender and setting.

Data collection and analysis

No relevant trials were identified.

Main results

Ten trials were identified by the initial search and none for the update. None of these trials were suitable for inclusion in this review.

Authors' conclusions

Reports on the use of hematopoietic stem cell transplantation improving survival and preventing symptoms and complications associated with sickle cell disease are currently limited to observational and other less robust studies. No randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations was found. Thus, this systematic review identifies the need for a multicentre randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in people with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Transplantation of blood-forming stem cells for children with sickle cell disease

Review question

We reviewed the evidence about the cure rate and risks of hematopoietic stem cell transplantation for people with sickle cell disease.

Background

Sickle cell disease is a genetic disorder mainly characterized by the presence of deformed, sickle-shaped red blood cells in the blood stream. These cells deprive tissues of blood and oxygen resulting in periodic and recurrent painful attacks. Complications include acute chest syndrome and stroke. Although sickle cell disease is responsive to preventive and supportive measures such as the use of prophylactic antibodies and periodic blood transfusion, these do not provide a cure. The use of hematopoietic (blood forming) stem cell transplantation involves replacing the deformed red blood cells and its stem cells with stem cells from a healthy donor thereby producing normal red blood cells. These stem cells can be derived from either the bone marrow or blood (umbilical cord blood or peripheral blood) of a healthy individual. This is an update of a previously published review.

Search date

The evidence is current to: October 2015.

Key results

There are no randomized controlled trials assessing the benefits and risks; the most appropriate source of stem cells; or the most eligible participants (those who have experience severe complication or those who have not) of the procedure in people with sickle cell disease.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a genetic hemoglobin disorder that can cause severe pain crises and dysfunction of virtually every organ system in the body, ultimately causing premature death. SCD occurs when the haemoglobin variant Haemoglobin S gene is inherited from both parents; the homozygous state (HbSS) is the most prevalent form of the disease (Serjeant 2001). Other clinically significant types of SCD are compound heterozygous conditions in which the sickle haemoglobin interacts with other abnormal haemoglobins, such as haemoglobin C (HbSC) or ß-thalassaemia (HbSb+ and HbSb0) (Lane 2001). Annually, worldwide, there are approximately 275,000 SCD affected conceptions or births (Modell 2008). Significant morbidity and premature death may result from SS disease with average life expectancy estimated at between 42 years and 53 years for men; and between 48 years and 58 years for women (Platt 1994). The disease is characterized by the presence of distorted, sickle-shaped red blood cells in the blood stream. These distorted cells can get trapped in small blood vessels,

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TRANSPLANTATION

CME Article

Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation

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Key Points

- HLA-identical sibling transplantation for SCD offers excellent long-term survival.
- Mortality risk is higher for older patients; event-free survival has improved in patients transplanted after 2006.

Despite advances in supportive therapy to prevent complications of sickle cell disease (SCD), access to care is not universal. Hematopoietic cell transplantation is, to date, the only curative therapy for SCD, but its application is limited by availability of a suitable HLA-matched donor and lack of awareness of the benefits of transplant. Included in this study are 1000 recipients of HLA-identical sibling transplants performed between 1986 and 2013 and reported to the European Society for Blood and Marrow Transplantation, Eurocord, and the Center for International Blood and Marrow Transplant Research. The primary endpoint was event-free survival, defined as being alive without graft failure; risk factors were studied using a Cox regression models. The median age at transplantation was 9 years, and the median follow-up was longer than 5 years. Most patients received a myeloablative conditioning regimen (n = 873; 87%); the remainder received reduced-intensity conditioning regimens (n = 125; 13%). Bone marrow was the predominant stem cell source (n = 839; 84%); peripheral blood and cord blood progenitors were used in 73 (7%) and 88 (9%) patients, respectively. The 5-year event-free survival and overall survival were 91.4% (95% confidence interval, 89.6%-93.3%) and 92.9% (95% confidence interval, 91.1%-94.6%), respectively. Event-free survival was lower with increasing age at transplantation (hazard ratio [HR], 1.09; $P < .001$) and higher for transplantations performed after

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2006 (HR, 0.95; *P* = .013). Twenty-three patients experienced graft failure, and 70 patients (7%) died, with the most common cause of death being infection. The excellent outcome of a cohort transplanted over the course of 3 decades confirms the role of HLA-identical sibling transplantation for children and adults with SCD. (*Blood*. 2017;129(11):1548-1556)

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Disclosures

CME questions author Laurie Barclay, freelance writer and reviewer, Medscape, LLC, owns stock, stock options, or bonds from Pfizer. Author Mark C. Walters serves as Medical Director for ViaCord's Processing Laboratory. Associate Editor Robert Zeiser and the remaining authors declare no competing financial interests.

Learning objectives

1. Distinguish characteristics of HLA-identical sibling transplantation for sickle cell disease (SCD) and hematopoietic recovery, based on an international, retrospective, registry-based survey.
2. Describe graft-versus-host disease and event-free survival in HLA-identical sibling transplantation for SCD.
3. Determine overall survival and risk factors associated with survival in HLA-identical sibling transplantation for SCD.

Release date: March 16, 2017; Expiration date: March 16, 2018

Background

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide. SCD affects more than 100 000 Americans and occurs in about 1 in 500 African-American births and in 1 in every 1000 to 1400 Hispanic-American births.[1] Similar rates are reported in European and Caribbean countries; for example, it is estimated that there are approximately 12 000 cases in France. In Brazil, the mean incidence of SCD is 1 per 1000 births, with 3000 new cases per year.[2] However, the frequency of the disease worldwide is uncertain and is likely to be underestimated in Asia and Africa. The implementation of newborn screening, penicillin prophylaxis, vaccination, narcotics, transfusions, and hydroxyurea (HU) has improved survival, with more than 95% of children in developed countries surviving to adulthood.[3-5] Further, the completion of 4 major randomized clinical trials since the 1990s has provided evidenced-based guidelines for primary and secondary stroke prevention in SCD.[6] Survival in children has improved to an extent that the mortality rate is now 0.5 per 100 000 persons.[7] In contrast, survival is lower in adults, with a mortality rate exceeding 2.5 per 100 000 persons.[7] Despite these remarkable advances in supportive therapy of SCD, most patients suffer from considerable disabilities and early mortality.[1,2,8-10]

Allogeneic hematopoietic stem cell transplant (HSCT) is currently the only curative treatment of severe SCD, but access is limited for several reasons, including donor availability and sociocultural and economic barriers. SCD and transplant physicians alike debate the burden of morbidity from a chronic disease and mortality from the disease vs the curative option with transplantation and the risk for transplant-related complications and mortality. In this regard, a panel of experts published consensus recommendations reporting that young patients with symptomatic SCD with a HLA-identical sibling should be transplanted as early as possible, preferably at preschool age.[11] They also recommended that unrelated or alternative donor transplantation should only be considered in the presence of markers of disease severity, such as cerebral vasculopathy, recurrent acute chest syndrome, severe vaso-occlusive disease, sickle nephropathy, osteonecrosis, priapism, severe erythroid allo-immunization, and failure to benefit from or an unwillingness to continue supportive therapy, including HU.[11] Although several reports have demonstrated that HLA-identical sibling transplantation with bone marrow (BM) or umbilical cord blood (CB) establishes normal hematopoiesis and is associated with excellent survival, most studies were conducted at single institutions or in the context of clinical trials.[12-17] The current study sought to describe outcomes after HLA-identical sibling transplantation for SCD worldwide.

Methods

Study design

With the goal of analyzing the role of HSCT for patients affected by SCD, we designed an international, retrospective, registry-based survey. Data were collected from the Center for International Blood and Marrow Transplant Research (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), and Eurocord databases. Children and adults who underwent HSCT as first transplant before December 31, 2013, were included. All donors were HLA-identical siblings; stem cell source included BM, peripheral blood (PB), or CB. Recipients of HLA-mismatched related donor (including haploidentical donors) and HLA-matched or mismatched unrelated donor transplants were excluded.

All patients or legal guardians gave informed consent for research. The study was conducted in compliance with the Declaration of Helsinki. The internal review board of EBMT/Eurocord and the institutional review board for the National Marrow Donor Program approved the study.

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TRANSPLANTATION

A trial of unrelated donor marrow transplantation for children with severe sickle cell disease

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Key Points

- Children with sickle cell disease engrafted unrelated donor marrow after reduced intensity conditioning.
- A high incidence of GVHD and associated mortality compromised safety of the trial.

Children with sickle cell disease experience organ damage, impaired quality of life, and premature mortality. Allogeneic bone marrow transplant from an HLA-matched sibling can halt disease progression but is limited by donor availability. A Blood and Marrow Transplant Clinical Trials Network (BMT CTN) phase 2 trial conducted from 2008 to 2014 enrolled 30 children aged 4 to 19 years; 29 were eligible for evaluation. The primary objective was 1-year event-free survival (EFS) after HLA allele-matched (at HLA-A, -B, -C, and -DRB1 loci) unrelated donor transplant. The conditioning regimen included alemtuzumab, fludarabine, and melphalan. Graft-versus-host disease (GVHD) prophylaxis included calcineurin inhibitor, short-course methotrexate, and methylprednisolone. Transplant indications included stroke (n = 12), transcranial Doppler velocity >200 cm/s (n = 2), ≥3 vaso-occlusive pain crises per year (n = 12), or ≥2 acute chest syndrome episodes (n = 4) in the 2 years preceding enrollment. Median follow-up was 26 months (range, 12-62 months); graft rejection was 10%. The 1- and 2-year EFS rates were 76% and 69%, respectively. The corresponding rates for overall survival were 86% and 79%. The day 100 incidence rate of grade II-IV acute GVHD was 28%, and the 1-year incidence rate of chronic GVHD was 62%; 38% classified as extensive. There were 7 GVHD-related deaths. A 34% incidence of posterior reversible encephalopathy syndrome was noted in the first 6 months. Although the 1-year EFS met the prespecified target of ≥75%, this regimen cannot be considered sufficiently safe for widespread adoption without modifications to achieve more effective GVHD prophylaxis. The BMT CTN #0601 trial was registered at www.clinicaltrials.gov as #NCT00745420. (*Blood*. 2016;128(21):2561-2567)

Introduction

Sickle cell disease (SCD) is a monogenic hemoglobin disorder characterized by hemolytic anemia with variable clinical manifestations after endothelial damage and vasculopathy.[1] Hypoperfusion results in multiple organ damage. In patients with severe disease, symptoms manifest early and progress during childhood. Allogeneic hematopoietic cell transplantation can replace sickle erythropoiesis. The results of HLA-matched sibling donor transplants are excellent, with event-free survival (EFS) in excess of 90% and with acceptable rates of graft rejection (GR) and graft-versus-host disease (GVHD).[2-5] HLA-matched sibling donor transplants account for the majority of transplants performed worldwide for hemoglobinopathy.[6,7] However, only 18% of patients with SCD have an HLA-matched sibling donor in the United States.[8] HLA-matched adult unrelated donors (URDs) have been used to expand the donor pool for nonmalignant hematologic disorders, but their role in SCD transplants is unclear.[9-11] Although the likelihood of finding an HLA-matched

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ARTICLE

Clinical risks and healthcare utilization of hematopoietic cell transplantation for sickle cell disease in the USA using merged databases

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ABSTRACT

Advances in allogeneic hematopoietic cell transplantation for sickle cell disease have improved outcomes, but there is limited analysis of healthcare utilization in this setting. We hypothesized that, compared to late transplantation, early transplantation (at age <10 years)

improves outcomes *and* decreases healthcare utilization. We performed a retrospective study of children transplanted for sickle cell disease in the USA during 2000-2013 using two large databases. Univariate and Cox models were used to estimate associations of demographics, sickle cell disease severity, and transplant-related variables with mortality and chronic graft-*versus*-host disease, while Wilcoxon, Kruskal-Wallis, or linear trend tests were applied for the estimates of healthcare utilization. Among 161 patients with a 2-year overall survival rate of 90% (95% confidence interval [CI] 85-95%) mortality was significantly higher in those who underwent late transplantation versus early (hazard ratio (HR) 21, 95% CI 2.8-160.8, *P*=0.003) and unrelated compared to matched sibling donor transplantation (HR 5.9, 95% CI 1.7-20.2, *P*=0.005). Chronic graftversus host disease was significantly more frequent among those translanted late (HR 1.9, 95% CI 1.0-3.5, *P*=0.034) and those who received an unrelated graft (HR 2.5, 95% CI 1.2-5.4; *P*=0.017). Merged data for 176 patients showed that the median total adjusted transplant cost per patient was $467,747 (range: $344,029-$799,219). Healthcare utilization was lower among recipients of matched sibling donor grafts and those with low severity disease compared to those with other types of donor and disease severity types (*P*<0.001 and *P*=0.022, respectively); no association was demonstrated with late transplantation (*P*=0.775). Among patients with 2-year pre- and post-transplant data (n=41), early transplantation was associated with significant reductions in admissions (*P*<0.001), length of stay (*P*<0.001), and cost (*P*=0.008). Early transplant outcomes need to be studied prospectively in young children without severe disease and an available matched sibling to provide conclusive evidence for the superiority of this approach. Reduced post-transplant healthcare utilization inpatient care indicates that transplantation may provide a sustained decrease in healthcare costs over time.

Introduction

Sickle cell disease (SCD) affects approximately 100,000 people in the United States of America (USA) with 2,000 new cases detected via newborn screening annually. There is a lack of clinical predictors to estimate overall outcomes of SCD-associated morbidities, including painful crises and organ dysfunction, which respond variably to medical management, have a devastating impact on quality of life, and can lead to premature death.[1] As a result, many people with SCD are left with sequelae of the disease and its complications. Allogeneic hematopoietic cell transplantation (alloHCT) remains the only established curative option for these individuals.

Despite mounting evidence of rising alloHCT success rates over time, such that the 5-year disease-free survival in children with SCD is now 92%, many still regard alloHCT as an experimental therapy, only for patients with severe disease.[2,3] The indications for alloHCT remain unclear for non-transplant providers when compared to the benefits of medical management.[4] In addition, a recent retrospective study from Belgium suggested that patients with SCD managed medically with hydroxyurea may have a better survival than those treated with alloHCT.[5]

However, short-term improvements in outcome with medical therapy must be balanced against a disease with an unpredictable clinical course and substantial impact on healthcare utilization. USA individuals with SCD account for an estimated $1.6 billion per year in healthcare costs.[6] SCD ranked fifth among the top ten diagnoses of hospital stays among Medicaid super-utilizers.[7] The substantial healthcare utilization and cost of SCD-related morbidity suggests that a greater focus on curative approaches for this disease is needed.

AlloHCT, when successful, can be curative, but also carries the risks of death and substantial morbidity from chronic graft-*versus*-host disease (GvHD). In addition, the initial cost of alloHCT represents a significant financial burden of approximately $400,000 in the transplant year.[8] This research investigates alloHCT for pediatric SCD using a comprehensive, systematic database analysis exploring patient-, disease-, and transplant-related variables that may reduce healthcare utilization over time while sustaining excellent clinical outcomes. The findings may provide transplant and non-transplant physicians with additional information to help choose between recommending medical therapy and alloHCT.

Methods

Data sources

Outcomes analysis

The Center for International Blood and Marrow Transplant Research (CIBMTR) database contains alloHCT data for recipients and their donors. Data are collected prior to and at various intervals post-alloHCT. Upon CIBMTR registration, a weighted randomization scheme selects a subset of patients for more detailed data collection in comprehensive research forms (CRF) which provide more specific transplant-related data (SCD complications, pre-transplant therapy, etc.) (*Online Supplementary Figure A1*).

Healthcare utilization analysis

CIBMTR data on all alloHCT recipients are submitted as transplant essential data (TED) (*Online Supplementary Figure A2*). TED forms record donor and recipient demographic, clinical, and transplant data but lack specific CRF data.

The Pediatric Health Information System (PHIS; Children's Hospital Association, Overland Park, KS, USA) records the corresponding inpatient healthcare utilization data. PHIS, a confidential database of 43 member hospitals in the USA (*Online Supplementary Figure A3*), has participating hospitals submit de-identified data with an encrypted medical record number for identification of readmissions at the same hospital. Institutional and patient-specific information, including patient's age, date of service, visit codes, length of stay (LOS), adjusted costs, and daily billing data, are collected. The PHIS has been merged for similar research purposes including a number of recent scientific publications.[9]

Merging and validating datasets

Patients in the PHIS database who underwent alloHCT for SCD during the study period were identified utilizing International Classification of Diseases version 9 (ICD9) and alloHCT diagno-

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Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation

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Abstract

Approximately 20,000 hematopoietic cell transplantation (HCT) procedures are performed in the United States annually. With advances in transplantation technology and supportive care practices, HCT has become safer and patient survival continues to improve over time. Indications for HCT continue to evolve as research refines the role for HCT in established indications and identifies emerging indications where HCT may be beneficial. The American Society for Blood and Marrow Transplantation (ASBMT) established a multi-stakeholder task force consisting of transplant experts, payer representatives and a patient advocate to provide guidance on 'routine' indications for HCT. This white paper presents the recommendations from the Task Force. Indications for HCT were categorized as (1) Standard of care, where indication for HCT is well defined and supported by evidence, (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but HCT has been shown to be effective therapy, (3) Standard of care, rare indication, for rare diseases where HCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible, (4) Developmental, for diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option, and (5) Not generally recommended, where available evidence does not support the routine use of HCT. The ASBMT will periodically review these guidelines and will update them as new evidence becomes available.

Keywords

Hematopoietic cell transplantation; Autologous transplantation; Allogeneic transplantation; Indications; Clinical Trials; Standard of care; Routine care

Introduction

Hematopoietic stem cell transplantation (HCT) using hematopoietic progenitor cells from the patient (autologous HCT) or a donor (allogeneic HCT) is a potentially curative therapy for many life-threatening cancers and non-malignant disorders. Approximately 20,000 HCTs are performed in the United States (US) each year.[1] The number of annual procedures is projected to increase due to several advancements in the field of HCT,[2] such as routine use of reduced intensity conditioning regimens which allows HCT in older patients who have a high incidence of hematologic malignancies, emerging indications for HCT, and introduction of alternative graft sources such that nearly all patients who need a transplant now have a donor. At the same time, early and long-term HCT outcomes continue to improve with significant improvements in patient selection for HCT, transplantation technology and preventive and supportive care practices.[3-6]

The American Society for Blood and Marrow Transplantation (ASBMT), in response to a need identified by patients, providers, payers and policy makers, established a Task Force to provide guidance on indications for HCT, that is, which indications may be considered as routine care versus indications where evidence is emerging or insufficient. The Task Force consisted of clinical experts, payers, and patient advocates and was charged with providing consensus guidelines for clinically appropriate indications for HCT based on best prevailing evidence. This white paper presents the recommendations from the Task Force.

Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel

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ABSTRACT

Thalassemia major and sickle cell disease are the two most widely disseminated hereditary hemoglobinopathies in the world. The outlook for affected individuals has improved in recent years due to advances in medical management in the prevention and treatment of complications. However, hematopoietic stem cell transplantation is still the only available curative option. The use of hematopoietic stem cell transplantation has been increasing, and outcomes today have substantially improved compared with the past three decades. Current experience world-wide is that more than 90% of patients now survive hematopoietic stem cell transplantation and disease-free survival is around 80%. However, only a few controlled trials have been reported, and decisions on patient selection for hematopoietic stem cell transplantation and transplant management remain principally dependent on data from retrospective analyses and on the clinical experience of the transplant centers. This consensus document from the European Blood and Marrow Transplantation Inborn Error Working Party and the Paediatric Diseases Working Party aims to report new data and provide consensus-based recommendations on indications for hematopoietic stem cell transplantation and transplant management.

Introduction

Thalassemia major (TM) originated in Mediterranean, Middle Eastern, and Asian regions, and sickle cell disease (SCD) originated from throughout central Africa. However, because of migration, both diseases now occur globally and represent a growing health problem in many countries.[1] Despite the remarkable improvements in medical therapy for hemoglobinopathies,[2,3] hematopoietic stem cell transplantation (HSCT) still remains the only available curative approach. Although both TM and SCD are hemoglobinopathies, they are two distinct diseases requiring different approaches to HSCT, based on their different clinical features and course of disease. While transfusion dependency for TM is a priori an indication for HSCT, the indications for HSCT in SCD are less clearly defined because of the variability of the disease course. The literature shows there is a wide experience in transplantation for TM, whereas only a few hundred transplants have been performed for SCD.[4,5] There are a number of possible reasons for this difference, including a lack of consensus about the indications and time point for HSCT in SCD, and the low chance of identifying an unrelated donor for SCD patients.[6,7] Table 1 shows the principal differences between TM and SCD from the transplant perspective.

So far, only a few prospective clinical trials have been reported in these diseases, and the decision to perform HSCT and the details of transplant management remain principally dependent on data derived from predominantly retrospective investigations and on the clinical expertise of

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Section 5.0

Previously Discussed Items

Neuropsychological Status Exams and Neuropsychological Testing

Question: How should the newly adopted guideline regarding neuropsychological testing be modified for pre-epilepsy surgery indications?

Question source: OHSU epilepsy surgery department

Issue: At the November 2019 VbBS/HERC meetings, the neuropsychological testing CPT code (CPT 96132-96133) were made Diagnostic with a new guideline as suggested by the BHAP. However, the OHSU epilepsy surgery department requires this testing prior to epilepsy surgery. The guideline as adopted would not allow such testing as it requires "symptoms not explained by current diagnosis." The epilepsy surgery patients have an established diagnosis; rather, this testing is used to see if the epilepsy surgery will affect various areas of functioning. These codes had previously been added to the epilepsy surgery guideline to allow this specialized use.

HERC staff recommendations:

1) Modify the newly adopted Diagnostic Guideline as shown below

DIAGNOSTIC GUIDELINE DXX, NEUROBEHAVIORAL STATUS EXAMS AND NEUROPSYCHOLOGICAL TESTING

Neurobehavioral status exams (CPT 96116 and 96121) and neuropsychological testing services (CPT 96132 and 96133) are only covered when all of the following are met:

1) Symptoms are not explained by an existing diagnosis; AND
2) When the results of such testing will be used to develop a care plan.

OR when neuropsychological testing is done as part of the pre-operative evaluation prior to epilepsy surgery.

Lower Extremity Chronic Venous Disease
January 2020

Question: Should coverage of lower extremity chronic venous disease (e.g. varicose veins) on the Prioritized List be moved to a higher priority line?

Question source: HERC Staff, Dr. Ed Boyle

Issue: Coverage of lower extremity chronic venous disease (LECVD) was discussed at the August and November VbBS meetings. Currently, varicose veins that cause swelling or pain are including on line 639 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION, with various treatments pairing on that line. A similar condition to varicose veins, post-thrombotic syndrome, is included on line 519 POSTTHROMBOTIC SYNDROME. If a varicose vein is associated with an ulcer, treatment is paired on line 379 CHRONIC ULCER OF SKIN. If the varicose vein is causing inflammation (phlebitis), then the diagnosis is included on line 516 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL. Based on discussion in August and November it would appear VBBS intent would be to move superficial thrombophlebitis to the funded region, along with significant bleeding. At the November meeting there was an outstanding question about whether compression stockings should be included for these conditions, or just surgery. If compression stockings are covered, then there would need to be a determination of whether a trial of conservative therapy (including compression stockings) would be required prior to surgery.

HERC staff reviewed the evidence of effectiveness of various treatments for varicose veins, including conservative care, minimally invasive surgery, and vein stripping. The majority of the literature on treatment of lower extremity chronic venous disease focuses on comparing various endovascular or surgical treatments against other such interventions. For the purposes of HERC coverage determination, the question of interest is comparing no or standard therapy (compression therapy) against invasive interventions. For this question, the literature is sparse, and studies are generally of low quality. NICE concluded that compression therapy vs no therapy reduced patient symptoms, but reductions were small and possibly not clinically significant. NICE concluded that, based on 5 studies, surgery resulted in better quality of life compared to compression therapy, but the effect was small and possibly not clinically significant (low quality evidence); surgery also resulted in significant clinical benefit at reducing patients' symptoms (aching, itching, and swelling). NICE concluded that surgery was cost effect compared to conservative care. There was no evidence review found comparing compression or other conservative therapy vs endovenous interventions. Based on systematic reviews and meta-analyses, there is no difference in outcomes between the various surgical and endovenous interventions.

Expert submitted literature included an RCT of conservative vs surgical therapy for varicose veins (Michaels 2006). In this study of 246 patients with severe reflex (significant skin changes, reflux >1 s in the groin, LVS or popliteal fossa, above-knee varicose veins >5 mm in diameter of any varicose veins in upper third of thigh, below-knee varicose veins >5 mm in more than one quadrant) and a BMI <32, there was a clinically significant improvement in quality of life, and a subsequent economic evaluation found a cost per QALY of £3500-£7175 depending on the type of surgery. Of note, no significant differences in any measured outcome were found in patients with mild or moderate vein reflux between conservative and surgical therapy groups.

Expert groups and NICE recommend treatment of lower extremity chronic venous disease for a much wider range of indications that is currently included on the Prioritized List.

Testimony was heard from Dr. Ed Boyle a vein surgeon, and from representatives of Medtronix, which manufactures devices used in minimally invasive vein surgery. Dr. Boyle testified that the HERC coverage only treats the end stage of CLEVD, and he recommended expanding coverage to include refractory lower extremity edema, pain, bleeding from a varicosity, and stasis dermatitis. Dr. Boyle testified that conservative therapy is significantly less effective than invasive therapy for non-ulcerated varicose veins. There is high quality evidence that interventions targeted to reduce venous reflux by eliminating the saphenous veins and its varicose branches are superior to conservative therapy. From a payer policy perspective, however, there is ample predicate to support a policy that defines the indication that a procedure should be for patients with moderate to severe venous symptoms who have tried and failed conservative measures. In a system with constrained financial resources, this is an approach where utilization can be best directed to those who need it most.

Dr. Boyle testified at the November meeting that severe swelling and/or severe pain affecting quality of life as well as stasis dermatitis should be covered indications for vein surgery. There was hesitation on the part of VbBS members to include subjective criteria such as pain or swelling for coverage. VbBS members agreed with the proposed guideline criteria to cover varicose veins in the presence of ulcers (current coverage), recurrent superficial thrombophlebitis (historic intention of coverage, but not current covered), and serious bleeding.

Dr. Boyle felt that ultrasound findings of severe venous reflux with the above symptoms would be adequate criteria for coverage. Based on this discussion, the VbBS members suggested modifying the HERC staff proposed guideline to include ultrasound findings of severe reflux, defined as “severe axial venous reflux (>1 second in the greater or small saphenous vein or accessory saphenous vein).”

There was further discussion about the proposed guideline requirement for 3 months of conservative therapy. Livingston raised the issue that this would include compression stockings, which are currently not covered by OHP. There was discussion about when compression stockings should be covered. There was suggested wording that the guideline include compression stockings only if the patient meets all the other guideline criteria. The decision was to table this topic and have HERC staff look at the evidence for the effectiveness of compression stockings, as well as which patients should have compression stockings covered by OHP.

Evidence for compression stockings

1) **Shingler 2013**, Cochrane review of compression stockings for chronic lower extremity venous disease
    a. N=7 studies (356 patients)
        i. Patients varicose veins without healed or active venous ulceration were included.
        ii. Different levels of pressure were exerted by the stockings in the studies, ranging from 10 to 50 mmHg.
        iii. One study assessed compression hosiery versus no compression hosiery, but no data was reported for the group randomized to no stockings. The other six compared different types or pressures of stockings.
        iv. The methodological quality of all included trials was unclear, mainly because of inadequate reporting.
    b. No studies assessed symptom change when wearing stockings compared to not wearing stockings
    c. The symptoms subjectively improved with the wearing of stockings across trials that assessed this outcome, but these assessments were not made by comparing one randomised arm of a trial with a control arm and are therefore subject to bias.
    d. **Authors' conclusions** There is insufficient, high quality evidence to determine whether or not compression stockings are effective as the sole and initial treatment of varicose veins in people without healed or active venous ulceration, or whether any type of stocking is superior to any other type. Future research should consist of a large RCT of participants with trunk varices either wearing or not wearing compression stockings to assess the efficacy of this intervention.
2) **Azirar 2019,** Cochrane review of compression stockings for treatment of post-thrombotic syndrome
    a. N=4 trials (116 patients)
    b. Two trials studied the effect of graduated elastic compression stockings (GECS) on improvement of PTS symptoms. One study reported beneficial haemodynamic effects, while the other found no benefits on PTS severity compared to placebo (very low-certainty evidence). There was very limited evidence available for adverse effects and quality of life (QoL). The two studies did not report on compliance rates during the study period.
    c. **Authors' conclusions** There is very low-certainty evidence regarding the use of GECS for treatment of PTS as assessed by two small studies of short duration. One study reported beneficial haemodynamic effects, while one found no benefits on PTS severity compared to control/placebo stockings. There is very limited evidence for adverse effects, patient satisfaction, QoL, and compliance rates. High certainty evidence to support the use of compression therapy in prevention of PTS is lacking and any conclusions drawn from current evidence should be interpreted with care. Further research is needed to assess whether compression can result in long-term reduction and relief of the symptoms caused by PTS, or prevent deterioration and leg ulceration

Evidence based expert guidelines

1) **Rabe 2017**, evidence based consensus statement on compression stockings
    a. N=51 articles

i. Symptoms: Reviewed studies finding that venous symptoms, quality of life (QoL) and edema formation in patients with lower clinical classes of chronic venous diseases (CVD) (C1s–C3) can be significantly improved by low-pressure compression stockings, compared with placebo stockings
    1. Recommendation 1: We recommend the use of MCS (medical compression stockings) to alleviate venous symptoms in patients with CVD (GRADE 1B)
    2. Recommendation 2: We recommend the use of MCS to improve QoL and venous severity scores in patients with CVD (GRADE 1B)
    3. Recommendation 3: We recommend the use of MCS to prevent leg swelling in patients with CVD (GRADE 1B)

ii. Venous stasis: The improvement of skin changes – including eczema, induration and lipodermatosclerosis, caused by chronic venous insufficiency (CVI) – by compression therapy is regularly observed in routine clinical practice. However, there is a paucity of evidence from RCTs. The recommendation to use MCS for the improvement of skin changes in general is therefore based on low-level evidence.
    1. Recommendation 5: We suggest MCS for the improvement of skin changes in patients with CVD (GRADE 1C)

iii. Recurrence of lower extremity ulceration: all evidence was comparing low vs high pressure stockings (no studies of compression stockings vs no stockings).
    1. Recommendation 7: We recommend the use of MCS to reduce recurrence of VLU (GRADE 1A)

iv. Prevention of clinical progression in chronic venous disease. There is insufficient information from RCTs on the prevention of CVD progression by MCS that would allow for an evidence-based recommendation.
    1. Recommendation 10: Insufficient data are available on the use of MCS for the prevention of CVD progression, so we recommend further studies are needed to be able to make evidence-based recommendations

HERC staff summary

There is minimal published data supporting the use of compression stockings for the treatment of chronic lower extremity venous disease or post-thrombotic syndrome, based on trusted sources. This technology is standard of care, and generally low risk. One possible reason for the lack of evidence to support use is that compliance with use is typically low.

Previous discussion of this topic at several meetings led to a consensus among VbBS members for coverage of varicose veins in the presence of ulceration, recurrent superficial thrombophlebitis or serious bleeding. The consensus was that swelling, pain, or stasis dermatitis were not sufficient criteria for coverage.

HERC staff recommendations:

1) Add coverage of chronic lower extremity venous disease for patients with recurrent thrombophlebitis, consistent with prior HSC/HERC intent to cover with "cellulitis;" add coverage for bleeding varicose veins
    a. Add varicose veins with other complications to line 379 CHRONIC ULCER OF SKIN and keep on line 519 POSTTHROMBOTIC SYNDROME/639 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
        i. ICD10 I83.89 (Varicose veins of lower extremities with other complications)
        ii. ICD10 I87.09 (Postthrombotic syndrome with other complications of lower extremity)
    b. Adopt a new guideline note to line 379 as shown below
        i. Discuss whether to include wording in purple given limited evidence of effectiveness of compression stockings
2) Clarify when ulceration is an indication for varicose vein treatment in the new guideline
3) Modify the line title of line 379 to CHRONIC ULCER OF SKIN; VARICOSE VEINS WITH MAJOR COMPLICATIONS

GUIDELINE NOTE XXX, TREATMENT OF CHRONIC LOWER EXTREMITY VENOUS DISEASE

Lines 379,519,639

Surgical treatment of chronic lower extremity venous disease is only included on line 379 when

1) The patient has had an adequate 3-month trial of conservative therapy and failed; AND
2) Ultrasound findings of severe axial venous reflux (>1 second in the greater or small saphenous vein or accessory saphenous vein; AND
3) The patient has one of the following:
    a. Non-healing skin ulceration in the area of the varicose vein(s), OR
    b. Recurrent episodes of superficial thrombophlebitis, OR
    c. Serious bleeding from varicose vein(s)

Compression stockings are included on line 379 as part of conservative therapy if the patient meets criteria #2 and #3 above.

Otherwise, these diagnoses are included on lines 519 or 639.

Compression stockings for the initial treatment of varicose veins in patients without venous ulceration (Review)

Shingler S, Robertson L, Boghossian S, Stewart M

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 12

http://www.thecochranelibrary.com

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[Intervention Review]

Compression stockings for the initial treatment of varicose veins in patients without venous ulceration

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ABSTRACT

Background

Compression hosiery or stockings are often the first line of treatment for varicose veins in people without either healed or active venous ulceration. Evidence is required to determine whether the use of compression stockings can effectively manage and treat varicose veins in the early stages. This is an update of a review first published in 2011.

Objectives

To assess the effectiveness of compression stockings for the only and initial treatment of varicose veins in patients without healed or active venous ulceration.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched August 2013) and CENTRAL (2013, Issue 5).

Selection criteria

Randomised controlled trials (RCTs) were included if they involved participants diagnosed with primary trunk varicose veins without healed or active venous ulceration (Clinical, Etiology, Anatomy, Pathophysiology (CEAP) classification C2 to C4). Included trials assessed compression stockings versus no treatment, compression versus placebo stockings, or compression stockings plus drug intervention versus drug intervention alone. Trials comparing different lengths and pressures of stockings were also included. Trials involving other types of treatment for varicose veins (either as a comparator to stockings or as an initial non-randomised treatment), including sclerotherapy and surgery, were excluded.

Data collection and analysis

Two authors assessed the trials for inclusion and quality (SS and LR). SS extracted the data, which were checked by LR. Attempts were made to contact trial authors where missing or unclear data were present.

Main results

Seven studies involving 356 participants with varicose veins without healed or active venous ulceration were included. Different levels of pressure were exerted by the stockings in the studies, ranging from 10 to 50 mmHg. One study assessed compression hosiery versus no compression hosiery. The other six compared different types or pressures of stockings. The methodological quality of all included trials was unclear, mainly because of inadequate reporting.

The symptoms subjectively improved with the wearing of stockings across trials that assessed this outcome, but these assessments were not made by comparing one randomised arm of a trial with a control arm and are therefore subject to bias.

Meta-analyses were not undertaken due to inadequate reporting and actual or suspected high levels of heterogeneity.

Authors' conclusions

There is insufficient, high quality evidence to determine whether or not compression stockings are effective as the sole and initial treatment of varicose veins in people without healed or active venous ulceration, or whether any type of stocking is superior to any other type. Future research should consist of a large RCT of participants with trunk varices either wearing or not wearing compression stockings to assess the efficacy of this intervention. If compression stockings are found to be beneficial, further studies assessing which length and pressure is the most efficacious could then take place.

PLAIN LANGUAGE SUMMARY

Wearing stockings to provide compression for the treatment of varicose veins

Evidence from randomised controlled trials is not sufficient to determine if compression stockings as the only and initial treatment are effective in managing and treating varicose veins in the early stages. Varicose veins are widened veins that twist and turn and are visible under the skin of the leg. They generally do not cause medical problems although many sufferers seek medical advice. Symptoms that may occur include pain, ankle swelling, tired legs, restless legs, night cramps, heaviness, itching and distress from their cosmetic appearance. Complications such as oedema, pigmentation, inflammation and ulceration can also develop. Compression stockings are often the first line of treatment and come in a variety of lengths, knee length to full tights, and apply different pressures to support the flow of blood in the veins.

Seven studies involving 356 participants with varicose veins and who had not experienced venous ulceration were included in this review. One study assessed compression hosiery versus no compression hosiery. The other six compared different types or pressures of stockings, ranging from 10 to 50 mmHg. The methodological quality of the included trials was unclear and not all studies assessed the same outcomes. One study included only pregnant women whilst other studies included participants who were on surgical waiting lists, that is, people who had sought medical intervention for their varicose veins.

The participants' subjective symptoms, and foot swelling and blood flow (physiological measures) improved in all of the studies that assessed these outcomes when stockings were worn, but these assessments were not made by comparing one randomised arm of the trial with a control arm in the same study. Conclusions from the individual studies regarding the optimum pressure provided by stockings were conflicting, although the results of one study suggested that lower pressured stockings (20 mmHg) may be as effective as higher pressured stockings (30 to 40 mmHg) for relieving symptoms. Conclusions regarding the optimum length of the stockings were inconclusive. No severe or long lasting side effects were noted.

BACKGROUND

Description of the condition

Varicose veins are tortuous, widened veins in the subcutaneous tissue of the lower limb (Campbell 2006). Varicose veins that

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Compression therapy for treating post-thrombotic syndrome (Review)

Azirar S, Appelen D, Prins MH, Neumann MHAM, de Feiter ANP, Kolbach DN

Azirar S, Appelen D, Prins MH, Neumann MHAM, de Feiter ANP, Kolbach DN.
Compression therapy for treating post-thrombotic syndrome.
Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD004177.
DOI: 10.1002/14651858.CD004177.pub2.

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[Intervention Review]

Compression therapy for treating post-thrombotic syndrome

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ABSTRACT

Background

Post-thrombotic syndrome (PTS) is a long-term complication of deep vein thrombosis (DVT) characterised by chronic complaints such as oedema and skin changes including; venous ectasia, varicose veins, redness, eczema, hyperpigmentation, and in severe cases fibrosis of the subcutaneous adipose in the affected limb. These chronic complaints are the effects of venous outflow restriction that can cause symptoms such as heaviness, itching, pain, cramps, and paraesthesia. Twenty to fifty percent of people with DVT develop post-thrombotic complications. Several non-pharmaceutical measures are used for prevention of PTS during the acute phase of DVT. These include elevation of the legs and compression therapy. There have been limited studies regarding the effectiveness of compression therapy for prevention or treatment of PTS. As a result, clinicians and guidelines differ in their assessment of compression therapy during treatment of DVT and in the treatment of PTS. This is an update of a review first published in 2003.

Objectives

To assess the effectiveness of compression therapy for treatment of post-thrombotic syndrome, including elastic compression stockings and mechanical devices compared with no intervention, placebo and with each other.

Search methods

For this update, the Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registries on 2 July 2018.

Selection criteria

We included trials that evaluated compression therapy for the treatment of PTS. The primary outcomes were severity of PTS and adverse effects. There were no restrictions on date or language. Two review authors (SA, DNK) independently assessed whether potentially relevant studies met the inclusion criteria.

Data collection and analysis

One review author extracted and summarised data and one review author (DNK) verified them. We resolved disagreements by discussion. We assessed methodological study quality with the Cochrane 'Risk of bias' tool. We used GRADE to assess the overall certainty of the evidence supporting the outcomes assessed in this review.

Main results

We identified four trials, with 116 participants, investigating the effectiveness of compression therapy for treatment of PTS. The methodology used by each trial was too heterogeneous to perform a meta-analysis, so we reported our findings narratively.

Two trials studied the effect of graduated elastic compression stockings (GECS) on improvement of PTS symptoms. One study reported beneficial haemodynamic effects, while the other found no benefits on PTS severity compared to placebo (very low-certainty evidence). There was very limited evidence available for adverse effects and quality of life (QoL). The two studies did not report on compliance rates during the study period.

Two trials studied the effects of intermittent mechanical compression devices. Both reported improvement in PTS severity (low-certainty evidence). Improvement of the severity of PTS was defined by treatment 'success' or 'failure'. Only one study comparing compression devices evaluated adverse effects and QoL. Although 9% of the participants experienced adverse effects such as leg swelling, irritation, superficial bleeding, and skin itching (moderate-certainty evidence), QoL was improved (moderate-certainty evidence). Studies did not assess compliance using intermittent mechanical compression devices.

None of the studies evaluated patient satisfaction.

Authors' conclusions

There is very low-certainty evidence regarding the use of GECS for treatment of PTS as assessed by two small studies of short duration. One study reported beneficial haemodynamic effects, while one found no benefits on PTS severity compared to control/placebo stockings. There is very limited evidence for adverse effects, patient satisfaction, QoL, and compliance rates. There is low-certainty evidence favouring use of intermittent pneumatic compression devices compared to a control device for the treatment of severity owing to different measurements used by the studies reporting on this outcome and small studies of short duration. There is moderate-certainty evidence of improved QoL but possible increased adverse effects related to compression device use owing to small studies of short duration. High-certainty evidence to support the use of compression therapy in prevention of PTS is lacking and any conclusions drawn from current evidence should be interpreted with care. Further research is needed to assess whether compression can result in long-term reduction and relief of the symptoms caused by PTS, or prevent deterioration and leg ulceration.

PLAIN LANGUAGE SUMMARY

Compression therapy for treating post-thrombotic syndrome of mild to moderate severity

Background

Deep vein thrombosis (DVT) occurs when a blood clot forms in a leg vein. The clot can break up and cause a potentially serious blockage in blood vessels. People who have had a DVT can develop post-thrombotic syndrome (PTS). This is characterised by problems such as leg pain, swelling ankles, and hardened discoloured skin. The symptoms are worsened with prolonged standing or sitting, and may limit lifestyle and day-to-day activities. In severe cases, venous ulcers, open sores that do not heal, also develop. Wearing compression bandages or graduated elastic compression stockings (GECS) after initial blood thinning (anticoagulant) treatment for DVT is used to reduce the likelihood of PTS and reduce symptoms. With severe swelling of the leg (oedema), a device or machine can be used to apply pressure to the leg to improve blood circulation (mechanical compression device or intermittent pneumatic compression device). There have been limited studies regarding the effectiveness of compression therapy for prevention or treatment of PTS. As a result, clinicians and guidelines differ in their assessment of the use of compression therapy during treatment of DVT and in the treatment of PTS.

Study characteristics and key results

The review authors identified four trials, with 116 participants, investigating the effectiveness of compressing therapies for PTS (most recent search 2 July 2018). Two trials studied the effect of GECS. One study showed an improvement of PTS symptoms and one showed no benefit. Two other trials studied the effect of an intermittent pneumatic compression device. Both reported an improvement in PTS severity. One study evaluated side effects and quality of life. Although 9% of the participants experienced side effects such as leg swelling, irritation, superficial bleeding, and skin itching, quality of life had positive outcomes. None of the studies assessed or reported on patient satisfaction or compliance rates.

Reliability of the evidence

The evidence for use of GECS or intermittent pneumatic compression device compared to control for the treatment of PTS severity is of very-low and low-certainty reliability. This is due to conflicting results, small studies of short duration, and differences in how the studies measured outcomes. Limited evidence was available for side effects, patient satisfaction, quality of life, and compliance.

Review Article

Phlebology

Phlebology
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Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement

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Abstract

Objective: Medical compression stockings are a standard, non-invasive treatment option for all venous and lymphatic diseases. The aim of this consensus document is to provide up-to-date recommendations and evidence grading on the indications for treatment, based on evidence accumulated during the past decade, under the auspices of the International Compression Club.

Methods: A systematic literature review was conducted and, using PRISMA guidelines, 51 relevant publications were selected for an evidence-based analysis of an initial 2407 unrefined results. Key search terms included: 'acute', CEAP', 'chronic', 'compression stockings', 'compression therapy', 'lymph', 'lymphatic disease', 'vein' and 'venous disease'. Evidence extracted from the publications was graded initially by the panel members individually and then refined at the consensus meeting.

Results: Based on the current evidence, 25 recommendations for chronic and acute venous disorders were made. Of these, 24 recommendations were graded as: Grade 1A (n = 4), 1B (n = 13), 1C (n = 2), 2B (n = 4) and 2C (n = 1). The panel members found moderately robust evidence for medical compression stockings in patients with venous symptoms and prevention and treatment of venous oedema. Robust evidence was found for prevention and treatment of venous leg ulcers. Recommendations for stocking-use after great saphenous vein interventions were limited to the first post-interventional week. No randomised clinical trials are available that document a prophylactic effect of medical compression stockings on the progression of chronic venous disease (CVD). In acute deep vein thrombosis, immediate compression is recommended to reduce pain and swelling. Despite conflicting results from a recent study to prevent post-thrombotic syndrome, medical compression stockings are still recommended. In thromboprophylaxis, the role of stockings in addition to anticoagulation is limited. For the maintenance phase of lymphoedema management, compression stockings are the most important intervention.

Conclusion: The beneficial value of applying compression stockings in the treatment of venous and lymphatic disease is supported by this document, with 19/25 recommendations rated as Grade 1 evidence. For recommendations rated with Grade 2 level of evidence, further studies are needed.

Keywords

Compression stockings, chronic venous disease, deep vein thrombosis, post-thrombotic syndrome, lymphoedema

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Section 6.0

New Discussion Items

Deletion of Pharmacist Prescribing Guideline

Question: Should the pharmacist prescribing guideline be deleted?

Question source: HERC staff, P&T staff

Issue: The pharmacist prescribing guideline has not been updated in many years. When this guideline was created, pharmacists could review medications and provide recommendations to providers regarding medication adjustments or changes. Pharmacists now have a much broader scope of practice and can by statute prescribe a variety of medication and immunizations independently. P&T staff have indicated to HERC staff that there are adequate OAR and pharmacy board rules governing pharmacist prescribing and that the guideline is no longer needed and is outdated. The CCO medical directors concur that they never refer to this guideline.

Current Oregon Board of Pharmacy rules regarding pharmacist prescribing:
https://www.oregon.gov/pharmacy/Imports/Laws_RulesPDF/OBOPCurrent_Laws_Rules.pdf

HERC staff recommendation:

1) Delete GN64

~~**GUIDELINE NOTE 64, PHARMACIST MEDICATION MANAGEMENT**~~

~~*Included on all lines with evaluation & management (E&M) codes*~~

~~Pharmacy medication management services must be provided by a pharmacist who has:~~

~~1) A current and unrestricted license to practice as a pharmacist in Oregon.~~

~~2) Documentation must be provided for each consultation and must reflect communication with the patient's primary care provider. Documentation should model SOAP charting; must include patient history, provider assessment and treatment plan; follow up instructions; be adequate so that the information provided supports the assessment and plan; and must be retained in the patient's medical record and be retrievable.~~

Intracardiac Echocardiogram

Question: Should intracardiac echocardiogram be moved to covered line(s) on the Prioritized List or to the Ancillary List?

Question source: Holly Jo Hodges, CCO medical director

Issue: Intracardiac echocardiogram (CPT 93662 Intracardiac echocardiography during therapeutic/diagnostic intervention, including imaging supervision and interpretation (List separately in addition to code for primary procedure)) is currently on line 662/Guideline Note 173. However, this procedure is considered standard of care during certain percutaneous cardiac interventions.

Intracardiac echocardiography involves the use of a catheter-based ECHO device that replaces transesophageal echocardiography (TEE) for certain transcutaneous cardiac procedures, such as valve replacement or ablation procedures [see Enriquez 2018].

Intracardiac echocardiography was reviewed in 2001 and recommended for the Ancillary File. It was again reviewed in January 2008. At that time, based on cardiologist consultation, intracardiac echocardiography was recommended for the Diagnostic Procedures List; however, the HOSC/HSC determined that it should be Never Covered. The HOSC/HSC minutes do not contain documentation as to the rationale for this decision.

CMS lists CPT 93662 as only billable as a secondary code to one of the following primary CPT codes:

CPT code	**CPT description**	**Current Placement**
92987	Percutaneous balloon valvuloplasty; mitral valve	39 lines
93453	Combined right and left heart catheterization including intraprocedural injection(s) for left ventriculography, imaging supervision and interpretation, when performed	Diagnostic Procedures File
93460-93462	Catheter placement in coronary artery(s) for coronary angiography, including intraprocedural injection(s) for coronary angiography, imaging supervision and interpretation; with right and left heart catheterization including intraprocedural injection(s) for left ventriculography, when performed	Diagnostic Procedures File
93532	Combined right heart catheterization and transseptal left heart catheterization through intact septum with or without retrograde left heart catheterization, for congenital cardiac anomalies	Diagnostic Procedures File
93580	Percutaneous transcatheter closure of congenital interatrial communication (ie, Fontan fenestration, atrial septal defect) with implant	118 ATRIAL SEPTAL DEFECT, SECUNDUM
93581	Percutaneous transcatheter closure of a congenital ventricular septal defect with implant	67 VENTRICULAR SEPTAL DEFECT
93621	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of	281 LIFE-THREATENING CARDIAC ARRHYTHMIAS 347 CARDIAC ARRHYTHMIAS

CPT code	CPT description	Current Placement
	arrhythmia; with left atrial pacing and recording from coronary sinus or left atrium (List separately in addition to code for primary procedure)	
93622	with left ventricular pacing and recording	281,347
93653	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with right atrial pacing and recording, right ventricular pacing and recording (when necessary), and His bundle recording (when necessary) with intracardiac catheter ablation of arrhythmogenic focus; with treatment of supraventricular tachycardia by ablation of fast or slow atrioventricular pathway, accessory atrioventricular connection, cavo-tricuspid isthmus or other single atrial focus or source of atrial re-entry	281,347
93654	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with right atrial pacing and recording, right ventricular pacing and recording (when necessary), and His bundle recording (when necessary) with intracardiac catheter ablation of arrhythmogenic focus; with treatment of ventricular tachycardia or focus of ventricular ectopy including intracardiac electrophysiologic 3D mapping, when performed, and left ventricular pacing and recording, when performed	281,347
93656	Comprehensive electrophysiologic evaluation including transseptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia including left or right atrial pacing/recording when necessary, right ventricular pacing/recording when necessary, and His bundle recording when necessary with intracardiac catheter ablation of atrial fibrillation by pulmonary vein isolation	281,347

<u>Similar codes</u>

1) Standard transthoracic echocardiogram (CPT 93303-93314, 93320-93352) are on the Diagnostic Procedures File
2) Transesophageal ECHO for congenital diseases (CPT 93315, 93316) are on the Diagnostic Procedures File
3) CPT 93355 (Echocardiography, transesophageal (TEE) for guidance of a transcatheter intracardiac or great vessel(s) structural intervention(s) (eg, TAVR, transcatheter pulmonary valve replacement, mitral valve repair, paravalvular regurgitation repair, left atrial appendage occlusion/closure, ventricular septal defect closure) (peri-and intra-procedural), real-time image

acquisition and documentation, guidance with quantitative measurements, probe manipulation, interpretation, and report, including diagnostic transesophageal echocardiography and, when performed, administration of ultrasound contrast, Doppler, color flow, and 3D) is on 26 lines

HERC staff recommendations:

1) Remove CPT 93662 (Intracardiac echocardiography during therapeutic/diagnostic intervention, including imaging supervision and interpretation (List separately in addition to code for primary procedure) from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
2) Strike the entry below from Guideline Note 173
3) Advise HSD to add CPT 93662 to the Diagnostic Procedure File
    a. Will be a secondary billing code to appropriate procedure codes

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~93662~~	~~Intracardiac echocardiography during therapeutic/diagnostic intervention~~		

Frequency Specific Microcurrent Therapy and Other TENS-like Therapies

Question: Should frequency specific microcurrent therapy, or similar types of therapy such as electro therapeutic point stimulation, microcurrent therapy, or microcurrent electrical nerve stimulation, be covered on the Prioritized List?

Question source: Primary Health CCO

Issue: Electrical stimulation therapy, such as TENS units, are included on line 662/GN173 which an entry that specifically mentions TENS therapy. Similar types of therapy, specifically frequency specific microcurrent therapy, have been requested for coverage. It appears that all of these types of therapy use the same CPT code, 97014 (Application of a modality to 1 or more areas; electrical stimulation (unattended)). Primary Health CCO is requesting clarification of the HERC coverage intent for these non-TENS electrical stimulation therapy.

Evidence review:
Medline was searched for microcurrent therapy, microcurrent, and frequency specific microcurrent therapy. The literature mostly consisted of case studies and small pilot studies of various types of microcurrent therapy on various soft tissue pain or dysfunction conditions.

1) **Page 2016**, Cochrane review of electrotherapy modalities for rotator cuff disease
    a. In single, small trials, no clinically important benefits of pulsed electromagnetic field therapy (PEMF), microcurrent electrical stimulation (MENS), acetic acid iontophoresis and microwave diathermy were observed (low or very low quality evidence).
    b. **Authors' conclusions:** We are uncertain whether TENS is superior to placebo, and whether any electrotherapy modality provides benefits over other active interventions (e.g. glucocorticoid injection) because of the very low quality of the evidence.
2) **Kwon 2014,** RCT of microcurrent therapy for infants with congenital muscular torticollis
    a. N=20 (10 ultrasound, 10 microcurrent therapy)
        i. All received standard PT
    b. The mean passive cervical rotational range of motion measured at three months posttreatment was significantly greater in the microtherapy group (101.1°) than that in the ultrasound group (86.4°) The mean duration of treatment was significantly shorter in the microcurrent group (2.6 months) than in the ultrasound group (6.3 months).
    c. **Conclusions:** Microcurrent therapy may increase the efficacy of therapeutic exercise with ultrasound for the treatment of congenital muscular torticollis involving the entire sternocleidomastoid muscle.

HERC staff recommendation:

1) Modify the GN173 entry for CPT 97014 (Application of a modality to 1 or more areas; electrical stimulation (unattended)) to reflect additional electrical stimulation types of therapies other than TENS
    a. No proven efficacy of any of these modalities

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
97014, 97032, 0278T, E0720, E0730, G0283	Transcutaneous electrical nerve stimulation (TENS), frequency specific microcurrent therapy, microcurrent electrical stimulation, and all similar therapies; Scrambler therapy; Cranial electrical stimulation; all similar transcutaneous electrical neurostimulation therapies	No clinically important benefit (CES) or insufficient evidence of effectiveness (all other) for chronic pain; insufficient evidence of effectiveness for all other indications	November 2019

Cochrane Library

Cochrane Database of Systematic Reviews

Electrotherapy modalities for rotator cuff disease (Review)

Page MJ, Green S, Mrocki MA, Surace SJ, Deitch J, McBain B, Lyttle N, Buchbinder R

Page MJ, Green S, Mrocki MA, Surace SJ, Deitch J, McBain B, Lyttle N, Buchbinder R.
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Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD012225.
DOI: 10.1002/14651858.CD012225.

www.cochranelibrary.com

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[Intervention Review]

Electrotherapy modalities for rotator cuff disease

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ABSTRACT

Background

Management of rotator cuff disease may include use of electrotherapy modalities (also known as electrophysical agents), which aim to reduce pain and improve function via an increase in energy (electrical, sound, light, or thermal) into the body. Examples include therapeutic ultrasound, low-level laser therapy (LLLT), transcutaneous electrical nerve stimulation (TENS), and pulsed electromagnetic field therapy (PEMF). These modalities are usually delivered as components of a physical therapy intervention. This review is one of a series of reviews that form an update of the Cochrane review, 'Physiotherapy interventions for shoulder pain'.

Objectives

To synthesise available evidence regarding the benefits and harms of electrotherapy modalities for the treatment of people with rotator cuff disease.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3), Ovid MEDLINE (January 1966 to March 2015), Ovid EMBASE (January 1980 to March 2015), CINAHL Plus (EBSCOhost, January 1937 to March 2015), ClinicalTrials.gov and the WHO ICTRP clinical trials registries up to March 2015, unrestricted by language, and reviewed the reference lists of review articles and retrieved trials, to identify potentially relevant trials.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-randomised trials, including adults with rotator cuff disease (e.g. subacromial impingement syndrome, rotator cuff tendinitis, calcific tendinitis), and comparing any electrotherapy modality with placebo, no intervention, a different electrotherapy modality or any other intervention (e.g. glucocorticoid injection). Trials investigating whether electrotherapy modalities were more effective than placebo or no treatment, or were an effective addition to another physical therapy intervention (e.g. manual therapy or exercise) were the main comparisons of interest. Main outcomes of interest were overall pain, function, pain on motion, patient-reported global assessment of treatment success, quality of life and the number of participants experiencing adverse events.

Data collection and analysis

Two review authors independently selected trials for inclusion, extracted the data, performed a risk of bias assessment and assessed the quality of the body of evidence for the main outcomes using the GRADE approach.

Main results

We included 47 trials (2388 participants). Most trials (n = 43) included participants with rotator cuff disease without calcification (four trials included people with calcific tendinitis). Sixteen (34%) trials investigated the effect of an electrotherapy modality delivered in isolation. Only 23% were rated at low risk of allocation bias, and 49% were rated at low risk of both performance and detection bias (for self-reported outcomes). The trials were heterogeneous in terms of population, intervention and comparator, so none of the data could be combined in a meta-analysis.

In one trial (61 participants; low quality evidence), pulsed therapeutic ultrasound (three to five times a week for six weeks) was compared with placebo (inactive ultrasound therapy) for calcific tendinitis. At six weeks, the mean reduction in overall pain with placebo was -6.3 points on a 52-point scale, and -14.9 points with ultrasound (MD -8.60 points, 95% CI -13.48 to -3.72 points; absolute risk difference 17%, 7% to 26% more). Mean improvement in function with placebo was 3.7 points on a 100-point scale, and 17.8 points with ultrasound (mean difference (MD) 14.10 points, 95% confidence interval (CI) 5.39 to 22.81 points; absolute risk difference 14%, 5% to 23% more). Ninety-one per cent (29/32) of participants reported treatment success with ultrasound compared with 52% (15/29) of participants receiving placebo (risk ratio (RR) 1.75, 95% CI 1.21 to 2.53; absolute risk difference 39%, 18% to 60% more). Mean improvement in quality of life with placebo was 0.40 points on a 10-point scale, and 2.60 points with ultrasound (MD 2.20 points, 95% CI 0.91 points to 3.49 points; absolute risk difference 22%, 9% to 35% more). Between-group differences were not important at nine months. No participant reported adverse events.

Therapeutic ultrasound produced no clinically important additional benefits when combined with other physical therapy interventions (eight clinically heterogeneous trials, low quality evidence). We are uncertain whether there are differences in patient-important outcomes between ultrasound and other active interventions (manual therapy, acupuncture, glucocorticoid injection, glucocorticoid injection plus oral tolmetin sodium, or exercise) because the quality of evidence is very low. Two placebo-controlled trials reported results favouring LLLT up to three weeks (low quality evidence), however combining LLLT with other physical therapy interventions produced few additional benefits (10 clinically heterogeneous trials, low quality evidence). We are uncertain whether transcutaneous electrical nerve stimulation (TENS) is more or less effective than glucocorticoid injection with respect to pain, function, global treatment success and active range of motion because of the very low quality evidence from a single trial. In other single, small trials, no clinically important benefits of pulsed electromagnetic field therapy (PEMF), microcurrent electrical stimulation (MENS), acetic acid iontophoresis and microwave diathermy were observed (low or very low quality evidence).

No adverse events of therapeutic ultrasound, LLLT, TENS or microwave diathermy were reported by any participants. Adverse events were not measured in any trials investigating the effects of PEMF, MENS or acetic acid iontophoresis.

Authors' conclusions

Based on low quality evidence, therapeutic ultrasound may have short-term benefits over placebo in people with calcific tendinitis, and LLLT may have short-term benefits over placebo in people with rotator cuff disease. Further high quality placebo-controlled trials are needed to confirm these results. In contrast, based on low quality evidence, PEMF may not provide clinically relevant benefits over placebo, and therapeutic ultrasound, LLLT and PEMF may not provide additional benefits when combined with other physical therapy interventions. We are uncertain whether TENS is superior to placebo, and whether any electrotherapy modality provides benefits over other active interventions (e.g. glucocorticoid injection) because of the very low quality of the evidence. Practitioners should communicate the uncertainty of these effects and consider other approaches or combinations of treatment. Further trials of electrotherapy modalities for rotator cuff disease should be based upon a strong rationale and consideration of whether or not they would alter the conclusions of this review.

PLAIN LANGUAGE SUMMARY

Electrotherapy modalities for rotator cuff disease

Background

Article

CLINICAL REHABILITATION

Clinical Rehabilitation
2014, Vol. 28(10) 983–991

DOI: 10.1177/0269215513511341
cre.sagepub.com
SAGE

Efficacy of microcurrent therapy in infants with congenital muscular torticollis involving the entire sternocleidomastoid muscle: a randomized placebo-controlled trial

Dong Rak Kwon and Gi Young Park

Abstract

Objective: To compare the effects of a combination of therapeutic exercise and ultrasound with or without additional microcurrent therapy in infants with congenital muscular torticollis involving the entire sternocleidomastoid muscle.

Design: Prospective, randomized, placebo-controlled trial.

Setting: An outpatient rehabilitation clinic in a tertiary university hospital.

Subjects: Infants (n = 20) with congenital muscular torticollis involving the entire sternocleidomastoid muscle.

Interventions: Group 1 comprised 10 infants who received therapeutic exercise with ultrasound alone and Group 2 comprised 10 infants who received the same treatment with microcurrent therapy.

Main measures: Passive cervical rotational range of motion was measured at before treatment and one, two, three, and six months after initial treatment. Thickness, cross-sectional area, and red pixel intensity on colour histograms, which were all assessed before treatment and at three months after initial treatment. Additionally, the duration of treatment was measured.

Results: The mean passive cervical rotational range of motion measured at three months posttreatment was significantly greater in Group 2 (101.1°) than that in Group 1 (86.4°), and the thickness, cross-sectional area, and red pixel intensity of the affected sternocleidomastoid muscle were all less in Group 2 (7.8 mm, 100.3 mm^2, and 126.1, respectively) than those in Group 1 (9.6 mm, 121.5 mm^2, and 140.5, respectively). The mean duration of treatment was significantly shorter in Group 2 (2.6 months) than in Group 1 (6.3 months).

Conclusions: Microcurrent therapy may increase the efficacy of therapeutic exercise with ultrasound for the treatment of congenital muscular torticollis involving the entire sternocleidomastoid muscle.

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Y90 Embolization and Mapping

Question: Should the coverage of mapping and embolization for Yttrium 90 therapy for hepatocellular carcinoma be modified?

Question source: Salem Radiology Clinic, Dr. Nicholas Hanson and Dr. Yama Kharoti; Dr. Hodges MVIPA

Issue: Drs. Hanson and Kharoti contacted Dr. Hodges regarding a denial for 37242 which is used in the mapping stages prior to treatment of Y90. This does not pair on the Prioritized List, rather the 37243 which is specific for tumors, pairs. Dr. Kharoti says both are necessary. The first mapping appointment is to determine if there are other nontumor areas that require embolization prior to administration of Y90. If they are identified then 37242 is used prophylactically to protect bowel and gallbladder. For example, they may embolize the right gastric branch so no Y90 beads would go there. There are sufficient collaterals that this does not cause bowel ischemia. The following appointment is when the Y90 is used for the liver cancer. Currently, only the code for liver cancer embolization (37243) pairs with liver cancer, but not this preventive embolization that is used to protect bowel and/or gallbladder (37242).

"The y90 treatment (37243) can NOT be done without the Y90 mapping (37242). It would be medical malpractice to do treatment without mapping."

From Ken Kolbeck, MD, Director of Y90 program at OHSU

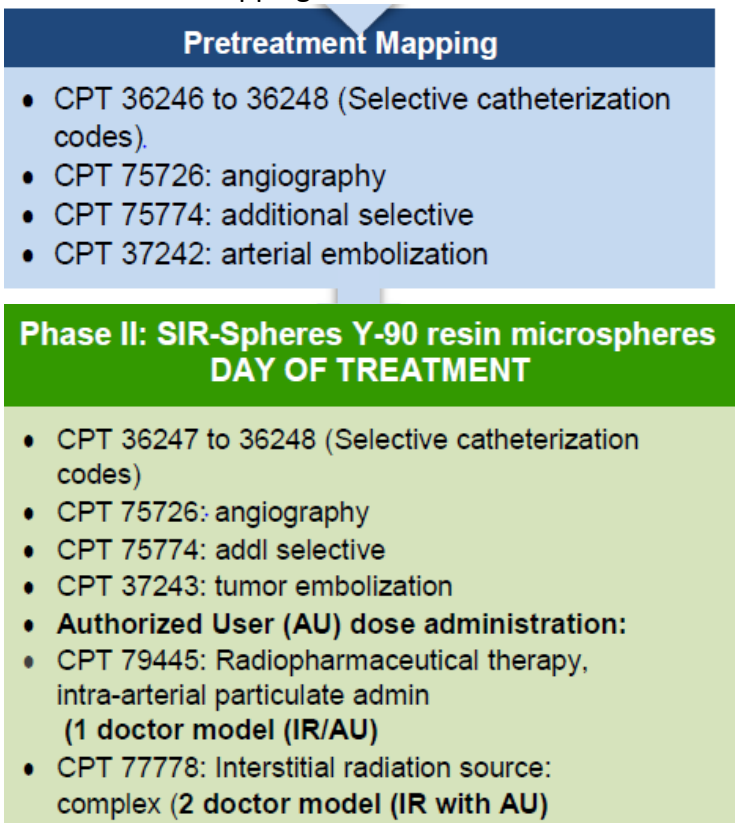
> When both of these products were developed, the biggest fear/complication risk was non-target embolization of the radioactive beads (either in right gastric, gastroduodenal, or cystic arterial distributions). A radiation induced GI ulcer can be very painful and require several additional hospitalizations. So the "instructions for use" and all the initial teaching included embolization of vessels "at risk". When we first started our Y90 program, we did embolize a few of these vessels, but with experience were able to find ways to avoid embolizing them (by using a different catheter position/split dose/modifying delivery techniques). I would say in the last few years, we coil embolize less than 5% of cases. When we did embolize—we purposefully chose to embolize on the day of the Y90 treatment – knowing full well that we would not be reimbursed for the coil (protective) embolization on the SAME DAY as the treatment embolization with the Y90. So our practice essentially "ate the cost" for the extra embolization—but it was a small percentage of the patients.
>
> From the insurance perspective-the key question will be balancing the risk/benefit. If I'm reading them correctly, the IFUs from both companies instruct to embolize/protect vessels at risk. If the IR sites reimbursement as the reason s/he didn't embolize it—the legal ramifications of a radiation induced gastric ulcer may be propagated beyond the IR / MD up to OHP.

So, at OHSU, we would rarely be impacted by the denials described below- because of our practice patterns. However, if other institutions routinely rely on the extra protection, there may be an increase in the amount of re-admissions/complications following the Y90 treatment.

Background for expectations around pre-treatment planning from manufacturer

Manufacturer coding guide https://www.sirtex.com/media/168654/2019-sirtex-coding-guide-final-approved-085-u-0119-0101019docx.pdf

Pre-treatment mapping includes



Background from Borggreve 2016

Nontarget embolization might subsequently result in complications, including gastrointestinal ulceration (0.7–28.6 %) and cholecystitis (0.6–6.0 %). Non-target embolization can be prevented through prophylactic embolization of hepaticoenteric arteries during a pretreatment angiography after which technetium-99m-labeled macroaggregated albumin (99mTc-MAA) can be injected as an additional screening procedure.

Experienced centers increasingly omit the occlusion of the vessels originating proximal to the microsphere injection site. Several studies have shown that collateralization and

recanalization of arteries can occur after occlusion of hepaticoenteric arteries, opposing the initial purpose of this procedure and bringing its benefit into question.

Current Prioritized List Status

Line: 315

Condition: CANCER OF LIVER (See Guideline Notes 7,11,12,64,65,78,185)

Treatment: MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10: C22.0-C22.9,C49.A9,C78.7,D37.6,D61.810,G89.3,Z51.0,Z51.11-Z51.12, Z85.05

CPT: 32553,36260-36262,37243,37617,43260-43265,43274-43277,47120-47130, 47370,47371,47380-47382,47533-47540,47542,47562,47600-47620,47711, 47712,48150,49411,77014,77261-77295,77300-77370,77385-77387,77402-77417,77424-77432,77469,77470,79005-79403,79445,93792,93793,96150-96155,96377,96405,96406,96420-96450,96542,96549,98966-98969,99051, 99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99451,99452,99468-99480,99487-99491,99495-99498,99605-99607

HCPCS: C2616,C9725,G0068,G0070,G0071,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514, G2010-G6017,S2095,S9537

Code	Code Description	Current Prioritized List Status
36246	Selective catheter placement, arterial system; initial second order abdominal, pelvic, or lower extremity artery branch, within a vascular family	ANCILLARY PROCEDURES
36247	Selective catheter placement, arterial system; initial third order or more selective abdominal, pelvic, or lower extremity artery branch, within a vascular family	ANCILLARY PROCEDURES
36248	Selective catheter placement, arterial system; additional second order, third order, and beyond, abdominal, pelvic, or lower extremity artery branch, within a vascular family (List in addition to code for initial second or third order vessel as appropriate)	ANCILLARY PROCEDURES
37242	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, **other than hemorrhage or tumor** (eg, congenital or acquired arterial malformations,	305 DISORDERS OF ARTERIES, OTHER THAN CAROTID OR CORONARY 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY

Code	Code Description	Current Prioritized List Status
	arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)	SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 547 SUBLINGUAL, SCROTAL, AND PELVIC VARICES 627 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; **for tumors, organ ischemia, or infarction**	315 CANCER OF LIVER 403 UTERINE LEIOMYOMA AND POLYPS
75726	Angiography, visceral, selective or supraselective (with or without flush aortogram), radiological supervision and interpretation	Diagnostic Procedures File
75774	Angiography, selective, each additional vessel studied after basic examination, radiological supervision and interpretation (List separately in addition to code for primary procedure)	Diagnostic Procedures File
78205	Liver imaging (SPECT)	Diagnostic Procedures File

GUIDELINE NOTE 185, YTTRIUM 90 THERAPY

Line 315

Yttrium 90 therapy is only included on this line for treatment of hepatocellular carcinoma (HCC) and only when recommended by a multidisciplinary tumor board or team in the following circumstances:

A) Downsizing tumors in patients who could become eligible for curative treatment (transplant, ablation, or resection), OR
B) Palliative treatment of incurable patients with unresectable or inoperable tumors that are not amenable to ablation therapy and
   1) who have good liver function (Child-Pugh class A or B) and
   2) good performance status (ECOG performance status 0-2), and
   3) who have intermediate stage disease with tumors > 5 cm OR advanced stage HCC with unilateral (not main) portal vein tumor thrombus.

Evidence

Borggreve, 2016

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821864/pdf/270_2016_Article_1310.pdf

- Systematic review of prophylactic embolization
- Authors with conflicts of interest
- 8 studies, 1237 patients, 456 received embolization of one or more arteries.
- No difference was seen in the incidence of gastrointestinal complications in patients with prophylactic embolization of the gastroduodenal artery (GDA), right gastric artery (RGA), cystic artery (CA) or hepatic falciform artery (HFA) compared to patients without embolization. The risk differences between patients in the embolized group and patients in the non-embolized group varied from 0 to 12%. None of the included studies showed evidence in favor of routine performance of prophylactic embolization.
- Few complications were reported when microspheres were injected distal to the origin of these arteries or when reversed flow of the GDA was present.
- A high risk of confounding by indication was present because of the nonrandomized nature of the included studies.
- Conclusion: It is advisable to restrict embolization to those hepaticoenteric arteries that originate distally or close to the injection site of microspheres. There is no conclusive evidence that embolization of hepaticoenteric arteries influences the risk of complications.
- Recommendation: According to the best available evidence, refraining from embolization of the GDA, RGA and CA is justified when the catheter tip can be placed distal to the origin of these arteries or when reversed flow is present in the GDA. The hepatic falciform artery can be embolized if a large uptake in the abdominal wall is seen.

Ward, 2017
https://www.jvir.org/article/S1051-0443(16)30519-X/fulltext

- Consecutive case series of 62 patients undergoing 69 treatments
- Planning angiography was performed and embolization most commonly performed of the right gastric and supradudoenal arteries. Only 2 patients received gastroduodenal artery prophylactic embolization.

Table 2. Procedural Details of Planning Angiography

Vessel Embolized	Mean or Percent	SD or Count
Right gastric artery	68%	42
Supraduodenal artery	10%	6
Left gastric artery	5%	3
Gastroduodenal artery	3%*	2*
Number of vessels embolized		
0	32%	20
1	54%	34
2	10%	6
3	2%	1
4	2%	1

*1 patient underwent gastroduodenal artery embolization at time of administration.

- Conclusions: Radioembolization without prophylactic embolization of the gastroduodenal artery can be performed safely

Other payers
Aetna, 2018 http://www.aetna.com/cpb/medical/data/200_299/0268.html

1. Intra-Hepatic Microspheres

   Aetna considers intra-hepatic microspheres (e.g., TheraSphere, MDS Nordion Inc.; SIR-Spheres, Sirtex Medical Inc.) medically necessary for any of the following:

   1. For treatment of neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver. For carcinoid tumors, intra-hepatic microspheres are considered medically necessary only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea); *or*
   2. For unresectable, primary HCC; *or*
   3. For unresectable liver tumors from primary colorectal cancer; *or*
   4. For unresectable and chemo-refractory intra-hepatic cholangiocarcinoma if member exhibits liver metastases only and has an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better with adequate liver function (serum total bilirubin of less than 2 mg/dL); *or*
   5. Pre-operative use as a bridge to orthotopic liver transplantation for HCC.

   Aetna considers intra-hepatic microspheres experimental and investigational for metastases from esophageal cancer and gallbladder cancer and other indications because of insufficient evidence in the peer-reviewed literature.

Selective Internal Radiation Therapy (SIRT), also known as radioembolization, is a procedure in which tiny radiation filled beads, called microspheres, are delivered directly to the tumor. The microspheres are delivered through a catheter placed in the femoral artery and threaded through the hepatic artery to the tumor site. The microspheres contain yttrium-90. Examples of this type of treatment include: SIR-Spheres, which are resin spheres that are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer; and Theraspheres, which are spheres made of glass, and are indicated for primary unresectable hepatocellular carcinoma (HCC).

Dancey et al (2000) indicated that the following criteria be used to select appropriate patients for administration of intra-hepatic microspheres as an adjuvant to chemotherapy, surgery or transplantation for persons with unresectable HCC. These criteria are based on the selection criteria for clinical studies of the TheraSphere

submitted for FDA approval, and contraindications to use of TheraSphere in the FDA-approved product labeling. These criteria may also be applied to persons with metastatic liver tumors from primary CRC (see discussion of SIR-Spheres below):

1. Histologically confirmed non-resectable lesion confined to the liver and at least 1 measurable lesion; *and*

    - Absolute granulocyte count greater than or equal to 2.0 x 10 9/L
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) less than 5 x upper normal limit [AST = 5 to 40 IU/L, ALT = 5 to 35 IU/L, ALP = 42 to 128 U/L]
    - Bilirubin less than 1.5 x upper normal limit [total bilirubin = 0.1 to 1.0 mg/dL or 5.1 to 17.0 mmol/L]
    - Estimated life expectancy greater than or equal to 12 weeks
    - Normal pulmonary function defined as within 30 % of the expected values for each parameter (e.g., forced vital capacity, forced expiratory volume in 1 second, maximal mid-expiratory flow, maximal voluntary ventilation, and arterial blood gases);
    - Platelet count greater than or equal to 100 x 109/L
    - Prothrombin time (PT) and activated partial prothrombin time (APTT) within normal limits [PT = 11.0 to 12.5 seconds; APTT = 30 to 40 seconds]; *and*
    - Eastern Cooperative Oncology Group (ECOG) performance status score less than or equal to 3

2. Adequate bone marrow and hepatic function; *and*
3. No contraindications to hepatic artery catheterization (e.g., vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis); *and*
4. No other concurrently planned oncotherapy; *and*
5. At least 1 month post other chemotherapy or surgery.

The following exclusion criteria apply:

1. Previous chemotherapy or radiation therapy for hepatoma; *or*
2. Potential absorbed dose to lungs greater than 30 Gy; *or*
3. Any uncorrectable angiographic flow to the gastrointestinal tract; *or*
4. Co-morbid disease that would preclude safe delivery of intra-hepatic microspheres treatment and place the member at undue risk.

Diagnostic work-up prior to the use of intra-hepatic microspheres includes:

1. Hepatic angiogram which entails placement of intra-hepatic catheter to assess vasculature and TheraSphere delivery route, and

2. Technetium-99 macroaggregated albumin (Tc-99 MAA) study to evaluate hepatic flow to gastrointestinal tract and/or pulmonary shunting.

These studies are medically necessary and thus are eligible for coverage.

In the United States, SIR-Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary CRC with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (floxuridine). The Food and Drug Administration (FDA) approval of SIR-Spheres was based on the results of a RCT involving 70 persons with CRC metastatic to the liver, 34 of whom received FUDR chemotherapy (control group), and 36 of whom received FUDR plus SIR-Spheres. Two of the patients receiving FUDR plus SIR-Spheres had a CR, and 16 had a partial response (PR). By comparison, 1 patient receiving FUDR alone achieved a CR and 7 had a PR. There is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres, when compared with the group treated with FUDR only.

The FDA-approved product labeling for SIR-Spheres states that treatment with SIR-Spheres may be indicated when the metastatic CRC in the liver is considered unresectable. According to the FDA-approved labeling, metastatic CRC may be considered non-resectable in any of the following circumstances:

1. Multiple liver metastases together with involvement of both lobes; *or*
2. Tumor invasion of the hepatic confluence where the 3 hepatic veins enter the inferior vena cava (IVC) such that none of the hepatic veins could be preserved if the metastases were resected; *or*
3. Tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; *or*
4. Widespread metastases such that resection would require removal of more liver than is necessary to maintain life.

The FDA-approved product labeling for SIR-Sphere's states that resectability may be evaluated via imaging with a triple phase contrast angio-portal CT scan or magnetic resonance imaging (MRI).

The FDA-approved labeling for SIR-Sphere states that the following tests are recommended before treatment.

1. A hepatic angiogram should be performed to establish arterial anatomy of the liver.
2. A nuclear medicine break-through scan (intra-hepatic technetium MAA Scan) to determine the percent lung shunting. If a port has been inserted, this test can be performed through the port.
3. Serologic tests of liver function should be performed to determine the extent of liver function/damage.

The FDA-approved product labeling for SIR-Spheres states that appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

The product labeling states that SIR-Spheres are contraindicated in patients who have:

- Ascites or are in clinical liver failure, *or*
- Been treated with capecitabine within the 2 previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres, *or*
- Disseminated extra-hepatic malignant disease, *or*
- Greater than 20 % lung shunting of the hepatic artery blood flow determined by technetium MAA scan, *or*
- Had previous external beam radiation therapy to the liver, *or*
- Markedly abnormal synthetic and excretory liver function tests (LTFs), *or*
- Portal vein thrombosis; *or*
- Pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel.

The manufacturer of SIR-Spheres recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres to confirm placement of the microspheres in the liver.

Both 37242 and 37243 are covered.

National Institute for Clinical Excellence, 2013. Excerpt from
https://www.nice.org.uk/guidance/ipg460/chapter/2-The-procedure

2.2 Outline of the procedure

2.2.1 Selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma involves infusion of microspheres loaded with yttrium-90, which aims to deliver radiation directly into the tumour, minimising the risk of radiation damage to healthy surrounding tissues.

2.2.2 Before undertaking the treatment, a nuclear medicine liver-to-lung shunt study is carried out to assess the risk of radioactive microspheres causing lung damage. Radiographic imaging and selective coil embolisation of arteries to the stomach and duodenum are also commonly carried out.

United Health Care, 2019
https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/implantable-beta-emitting-microspheres-treatment-malignant-tumors.pdf

Transarterial radioembolization (TARE) using yttrium-90 (90Y) microspheres is proven and medically necessary for the following indications:

- Unresectable metastatic liver tumors from primary colorectal cancer (CRC)
- Unresectable metastatic liver tumors from neuroendocrine tumors
- Unresectable primary hepatocellular carcinoma (HCC)
- Unresectable intrahepatic cholangiocarcinoma

Transarterial radioembolization (TARE) using yttrium-90 (90Y) microspheres is unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.

There is no menton of CPT code 37242.

CPT Code	Description
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

CPT® is a registered trademark of the American Medical Association

HCPCS Code	Description
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

Professional Society Guidelines
https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RMBD.pdf
Consensus Practice Parameter, 2019 - American College of Radiology (ACR), the American Brachytherapy Society (ABS), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), the Society of Interventional Radiology (SIR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI)

II. INDICATIONS AND CONTRAINDICATIONS

A. Indications for both agents include, but are not limited to, the following:

1. The presence of unresectable or inoperable primary or secondary liver malignancies (particularly CRC and NET metastases). The tumor burden should be liver dominant, not necessarily exclusive to the liver. Patients should also have a performance status that will allow them to benefit from such therapy.
2. A life expectancy of at least 3 months

B. Absolute contraindications include the following:
1. Inability to catheterize the hepatic artery
2. Fulminant liver failure
3. Initial mapping angiography and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating nontarget deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques.
4. Pretreatment hepatic arterial administration with technetium-99m MAA demonstrative of unfavorable (or unacceptable) shunt fraction between the liver and the pulmonary parenchyma. This shunt fraction must not be greater than acceptable limits specific to each brachytherapy device.
5. Active hepatic infection
6. Therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and considerations.

Article on costs

Steele, 2016 *https://ascopubs.org/doi/pdfdirect/10.1200/JOP.2014.001523*

Article on costs discussing different methods of intervention (balloon versus coil). Argues that pretreatment diagnostic visit is still necessary but balloon occlusion technique would be less expensive than coil embolization.

Gabr, 2019

https://www.techvir.com/article/S1089-2516(19)30016-2/fulltext

- Institutional description of same day preplanning and Y90 administration
- Possible model for decreased costs

HERC Staff Summary

Pre-treatment mapping appears to be commonly performed and may involve prophylactic embolization of vasculature to the bowel to avoid Y90 going to bowel, gallbladder, and abdominal wall. While the manufacturer recommends it, evidence supporting embolization is limited, however, with no evidence showing benefit. Expert opinion suggests pre-treatment embolization is necessary in less than 5% of cases. For surgeons accustomed to using older techniques including pre-embolization, it may be less safe to perform Y90 surgery without embolization. This may limit access to Y90 or differentially impact safety, since not all physicians are trained on the technique that allows Y90 to be delivered without embolization, and some providers or plans may be concerned about liability if embolization is not performed.

Pre-treatment mapping codes are in the Diagnostic File and would be covered, the relevant pre-treatment code that includes non-tumor embolization does not pair with liver cancer.

HERC Staff Recommendations:

1. **Do not add CPT 37242** *Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, other than hemorrhage or tumor (eg, congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)* **to Line 315**
    1) Alternatively, 37242 could be added to Line 315 without a guideline, due to the variation in practice standards across the state and some interventionists lack of comfort with proceeding without pre-treatment embolization and possible potential increased risks.

2. Modify Guideline Note 185 as follows:
   GUIDELINE NOTE 185, YTTRIUM 90 THERAPY

   Line 315

   Yttrium 90 therapy is only included on this line for treatment of hepatocellular carcinoma (HCC) and only when recommended by a multidisciplinary tumor board or team in the following circumstances:
   - A) Downsizing tumors in patients who could become eligible for curative treatment (transplant, ablation, or resection), OR
   - B) Palliative treatment of incurable patients with unresectable or inoperable tumors that are not amenable to ablation therapy and
     1) who have good liver function (Child-Pugh class A or B) and
     2) good performance status (ECOG performance status 0-2), and
     3) who have intermediate stage disease with tumors > 5 cm OR advanced stage HCC with unilateral (not main) portal vein tumor thrombus.

Pretreatment mapping is included on this line, however, pre-treatment embolization is not included on this line due to insufficient evidence of effectiveness.

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Radioembolization: Is Prophylactic Embolization of Hepaticoenteric Arteries Necessary? A Systematic Review

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Abstract
Purpose To study the effectiveness of prophylactic embolization of hepaticoenteric arteries to prevent gastrointestinal complications during radioembolization.
Methods A PubMed, Embase and Cochrane literature search was performed. We included studies assessing both a group of patients with and without embolization.
Results Our search revealed 1401 articles of which title and abstract were screened. Finally, eight studies were included investigating 1237 patients. Of these patients, 456 received embolization of one or more arteries. No difference was seen in the incidence of gastrointestinal complications in patients with prophylactic embolization of the gastroduodenal artery (GDA), right gastric artery (RGA), cystic artery (CA) or hepatic falciform artery (HFA) compared to patients without embolization. Few complications were reported when microspheres were injected distal to the origin of these arteries or when reversed flow of the GDA was present. A high risk of confounding by indication was present because of the non-randomized nature of the included studies.
Conclusion It is advisable to restrict embolization to those hepaticoenteric arteries that originate distally or close to the injection site of microspheres. There is no conclusive evidence that embolization of hepaticoenteric arteries influences the risk of complications.

Keywords Radioembolization · Yttrium · Embolization · Gastroduodenal artery · Right gastric artery · Cystic artery · Hepatic falciform artery · Complications

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Introduction

Radioembolization has gained widespread usage for the management of both primary and secondary, unresectable and chemotherapy refractory liver malignancies. Because healthy liver parenchyma is mostly supplied by the portal vein, hepatic tumors can be selectively targeted by injection of yttrium-90 (^{90}Y) microspheres in the hepatic arteries. Particles of resin or glass, containing millions of the radioactive ^{90}Y microspheres, are injected into the liver via the hepatic artery. These microspheres might disperse to surrounding organs through hepaticoenteric arteries, such as the gastroduodenal artery (GDA), right gastric artery (RGA),

cystic artery (CA) or hepatic falciform artery (HFA). Non-target embolization might subsequently result in complications, including gastrointestinal ulceration (0.7–28.6 %) [1–4] and cholecystitis (0.6–6.0 %) [5, 6]. Non-target embolization can be prevented through prophylactic embolization of hepaticoenteric arteries during a pretreatment angiography after which technetium-99m-labeled macroaggregated albumin (^{99m}Tc-MAA) can be injected as an additional screening procedure.

Experienced centers increasingly omit the occlusion of the vessels originating proximal to the microsphere injection site. Several studies have shown that collateralization and recanalization of arteries can occur after occlusion of hepaticoenteric arteries, opposing the initial purpose of this procedure [7–9] and bringing its benefit into question.

Therefore, the purpose of this review is to evaluate the evidence of prophylactic embolization of hepaticoenteric arteries (i.e. GDA, RGA, CA or HFA) to prevent non-target deposition of microspheres and subsequent complications in patients with liver malignancies undergoing hepatic radioembolization.

Methods

Reporting of this review was conducted according to the PRISMA guidelines [10].

Search Strategy

A PubMed, Embase and Cochrane literature search was performed on 22 May 2015 to identify all articles related to the use of embolization of hepaticoenteric arteries in patients with liver malignancies undergoing radioembolization. Search terms used to identify these articles were combinations of 'liver cancer', 'radioembolization', 'prophylactic embolization', all synonyms and MeSH or Emtree terms. After full text screening, references of reviews and identified articles were screened to find additional articles.

Study Selection

After the removal of duplicates, titles and abstracts were reviewed independently by two reviewers (the first group by A.B. and C.D., the second group by A.L. and C.V.). Full text was obtained if title and abstract met the predetermined in- and exclusion criteria. Disagreements were resolved on consensus-based discussion with all four reviewers. Articles were included in which: (1) patients with liver malignancies undergoing radioembolization were studied, (2) prophylactic embolization of hepaticoenteric arteries was reported, (3) gastrointestinal complications or non-target embolization on imaging was used as outcome, (4) both a group of patients with and without embolization were assessed and (5) the authors reported results in English, German or Dutch. Case reports, animal studies, in vitro studies, congress abstracts and reviews were excluded.

Risk of Bias

The quality of the studies was assessed by a critical appraisal that was specifically designed for our search and included studies. Studies were independently appraised on validity by four reviewers (A.B., A.L., C.D., C.V.) on the following items: (1) study design characteristics: study type, data collection, funding and potential role of funders in study; (2) standardization: sufficient description of indication for treatment, procedure of embolization, assessment of outcome and (3) loss to follow-up: routine imaging or endoscopy was preferred, but routine clinical assessment was also considered to be of value.

Data Extraction

Data extraction was performed by two independent reviewers. The following data were extracted from the studies: specification of the embolized arteries, the indication for embolization, study size, number of patients who were embolized or not, results of post-treatment imaging and the number and type of complications in each patient group.

No meta-analysis could be performed due to heterogeneity of the included study populations, the variety of indications used for embolization and the different methodologies used for the assessment of outcomes.

Results

The search strategy resulted in 1041 articles. Thirty-nine of these articles were screened on full-text. The check for references and related citations did not yield new articles. Eight studies fulfilled the eligibility criteria (Fig. 1) and were assessed for their quality (Fig. 2) [11–18].

The studies were all single-centered, retrospective and non-randomized in nature. There was one letter to the editor [11]. The risk of conflict of interest of all studies was low.

Paprottka et al. [17] and Powerski et al. [15] were considered to be of best quality: both studied a large cohort with even distribution between patients who were embolized or not, and both included a well-defined and extensive follow-up period (respectively 24 weeks and 12 months) (Fig. 2).

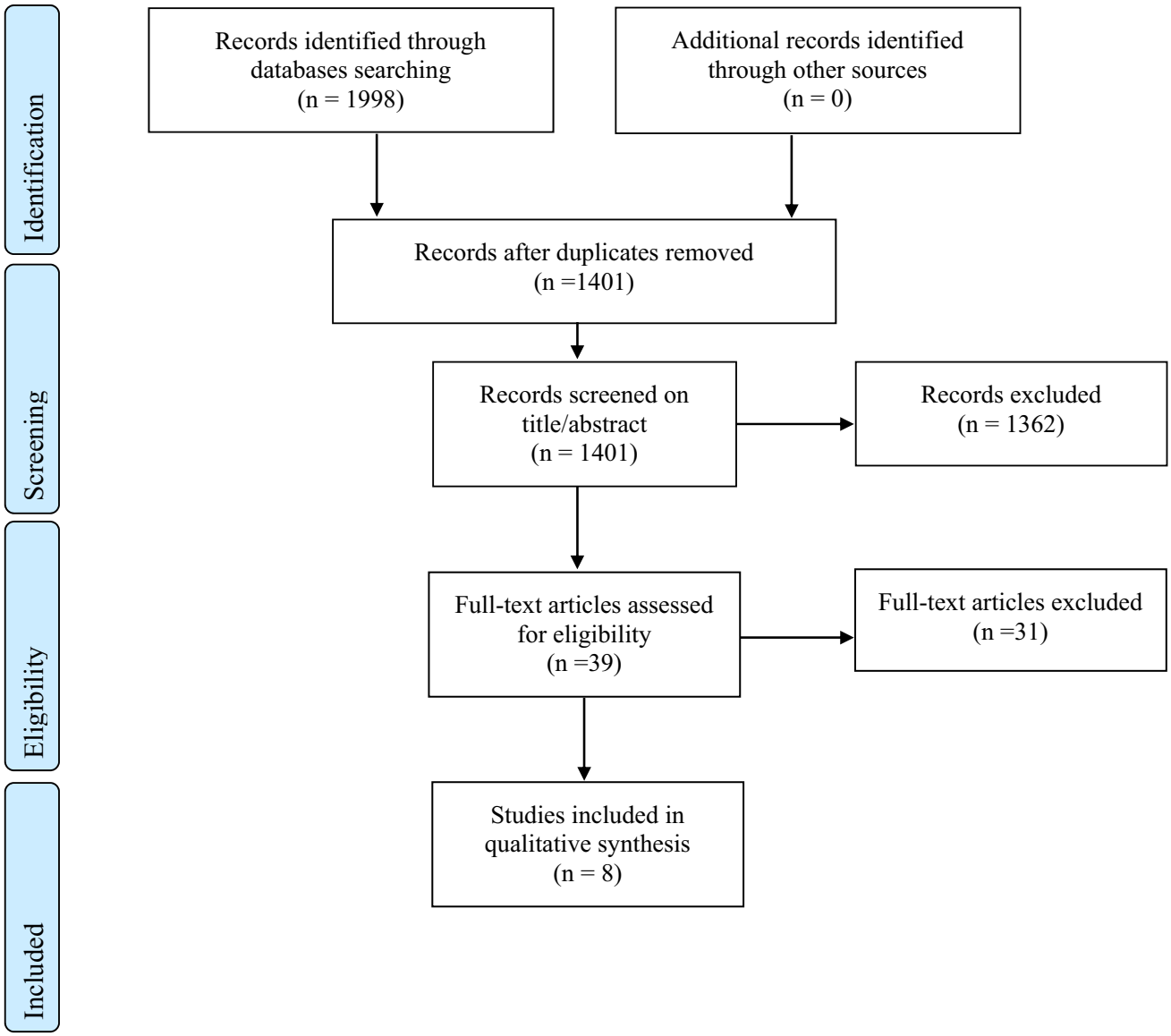

Fig. 1 Flow chart of literature search

Study characteristics and results are listed in Table 1. The included studies investigated a total of 1237 patients of whom 456 received embolization of one or more arteries. Overall, 55 out of 456 embolized patients experienced any type of complication (i.e. adverse events possibly, probably or definitely related to extrahepatic deposition of activity) after radioembolization, varying from pain in the right upper abdominal quadrant to gastrointestinal ulceration. In the non-embolized group, 34 out of 781 patients experienced complications of any kind. The risk differences between patients in the embolized group and patients in the non-embolized group varied from 0 to 12 %.

Indication for Embolization

The studies were subjected to confounding by indication (the determinant is present if a perceived high risk of poor prognosis is an indication for treatment) [19], because the decision to occlude hepaticoenteric arteries depended on specific clinical situations, e.g. the infusion of microspheres proximal to the origin of the hepaticoenteric arteries [11–18].

All studies gave a detailed description of the pretreatment preparations, the treatment itself and the equipment and materials used, except for Hamoui et al. [11] who specified only the type of microspheres used.

Author	Validity							
	Study characteristics				Standardization			
	Study type	Data collection	Study design	Funding	Indication for treatment	Procedure	Assessment of outcome	Loss to follow-up
Daghir[13]	±	–	–	±	+	+	±	+
Cosin[12]	–	–	–	–	+	+	±	–
Hamoui[11]	±	–	–	–	+	–	–	–
Theysohn[14]	±	–	–	+	+	+	+	–
Powerski[15]	±	–	–	±	+	+	+	–
Ahmadzedefar[18]	±	–	–	+	+	+	±	–
Schelhorn[16]	±	–	–	+	+	+	–	–
Paprottka[17]	±	–	–	+	+	+	±	–

Legend

Study type
+ Randomized controlled trial
± Cohort study
– Case series

Data collection
+ Prospective
– Retrospective

Study design
+ Multicenter
– Singlecenter

Funding and potential role of funders
+ No
± Yes
– Not reported

Indication for treatment
Criteria for occlusive therapy are
+ Well defined per protocol
– Not standardized or insufficiently reported

Procedure
Embolization therapy procedure was
+ Well defined per protocol
– Not standardized or insufficiently reported

Assessment of outcome
+ Routinely by imaging or endoscopy
± Routinely by clinical assessment
– Other

Loss to follow-up
+ <10 %
± 10-20%
– > 20% or not reported

Fig. 2 Critical appraisal of selected articles

Assessment of Outcome

Two studies [14, 15] used radiological follow-up, physical examination and blood tests to identify complications due to non-target radioembolization. Theysohn et al. [14] performed a CT-scan of the liver 28 days after radioembolization to detect changes like thickening of the gallbladder wall or free fluid in the gallbladder bed. In the study by Powerski et al. [15], patients received an MRI of the liver on three occasions to assess gallbladder wall thickness and free fluid adjacent to the gallbladder: before pretreatment angiography, immediately after treatment and 6 weeks after treatment. Additionally, bremsstrahlung SPECT was used to detect radioactive microspheres in gallbladder tissue [15].

Five studies used clinical and/or laboratory parameters during follow-up [12, 13, 16–18]. Paprottka et al. [17] was the only study that classified the clinical complications of non-target embolization using standardized criteria, namely the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3.0) [20] and differentiated between early complications (within a week after treatment) and late complications (up to 6 months). Complications of grade ≥ 3 were considered clinically relevant.

Hamoui et al. did not specify their follow-up procedure, but did seek for histologic evidence of microsphere deposition in patients with gastric ulcers [11].

Timing of Follow-Up

Follow-up consisted of frequent clinical assessment in five studies [12, 13, 15, 17, 18]: every 2–6 weeks, up to 2 [13], 3 [12], 6 [17] or 12 months [15, 18] after treatment. Other

Table 1 Overview of studies comparing complication rates between patients in whom hepaticoenteric arteries were embolized or not

Author	Artery	Indication for embolization	*n*	Embolized *n* (%)	Imaging post treatment	Complications	Not embolized *n* (%)[b]	Imaging post treatment	Complications	Risk difference (95 % CI)[e]
Daghir [13]	GDA	Antegrade flow in GDA and injection position close to GDA. Other arteries, including the RGA, were also embolized	82	71 (87)[c]	*NR*	2 (3 %) duodenal ulceration 1 (1 %) prepyloric ulceration and bleeding	11 (13)	*NR*	0	+3 % (−29 to 11) +1 % (−31 to 9 %)
Cosin [12]	RGA	If visible on angiography and in or close to vascular territory or uptake of ^{99m}Tc-MAA	27	9 (33)	*NR*	0	18 (67)	*NR*	0	0 % (−22 to 37 %)
Hamoui[a] [11]	RGA or GDA	Injection proximal to GDA or RGA	134	42 (31)	*NR*	*NR*	92 (69)	*NR*	2 (1 %) gastrointestinal ulcers[d]	*NA*
Theysohn [14]	Cystic artery	Increased ^{99m}Tc-MAA accumulation in the gallbladder wall	295	20 (10)	*NR*	1 (5 %) clinical signs of cholecystitis[d]	275 (93)	*NR*	0	+5 % (0 to 46 %)
Powerski [15]	Cystic artery	If it could be entered swiftly with the wire/catheter	105	68 (65)	3.3 % uptake in gallbladder wall	22 % pain in upper right quadrant 2 (3 %) cholecystitis	37 (35)	8.8 % uptake in gallbladder wall	10 % pain in upper right quadrant 1 (3 %) cholecystitis	+12 % (*NA*) 0 % (−13 to 9 %)
Ahmadzadehfar [18]	Falciform artery	*NR*	17	1 (6)	0	*NR*	16 (94)	9 (56 %) uptake in abdominal wall	1 (6 %) abdominal muscle pain	*NA*
Schelhorn [16]	Falciform artery	If technically possible	11	5 (45)	*NR*	0	6 (55)	*NR*	0	0 % (−48 to 54 %)
Paprottka [17]	*NR*	If catheter could not be placed distally with sufficient safety margin (even if no ^{99m}Tc-MAA uptake was present)	566	240 (42)	*NR*	31 (13 %) CTCAE ≥3 within 7 days 3 (1 %) CTCAE ≥3 within 6 months	326 (58)	*NR*	14 (4 %) CTCAE ≥ 3 within 7 days 3 (1 %) CTCAE ≥ 3 within 6 months	+9 % (4 to 14 %) 0 % (−2 to 3 %)

CI confidence interval, *RGA* right gastric artery, *GDA* gastroduodenal artery, *NR* not reported, *NA* not applicable

[a] Letter to the editor

[b] Relates to the specific artery, others arteries may be embolized

[c] Not only GDA was embolized, also RGA, cystic and hepatic arteries

[d] Healed after conservative therapy

[e] Risk difference was calculated for the incidence of complications in the embolized group compared to the non-embolized group, i.e. a positive risk difference indicates more complications occurred in the embolized group and vice versa (Wilson procedure with continuity correction)

studies did not specify the frequency of post-procedural follow-up visits or instructed patients to contact the hospital in case of complaints [11, 14, 16]. One study [13] mentioned loss to follow-up of patients, but did not take this into account during analysis or interpretation of the data.

Resin and Glass Microspheres

Two studies [11, 14] used glass microspheres while all other studies used resin microspheres [12, 13, 15–18].

Gastrointestinal Complications

Three studies investigated embolization of the GDA or RGA [11–13] when applying specific criteria (Fig. 3). None found a significant difference in the occurrence of complications between the study arms.

The first study, Daghir et al. [13], reported on a cohort of 82 patients in whom the GDA was not embolized if it had reversed (i.e., hepatofugal) flow. None of the 11 patients with reversed flow developed complications related to extrahepatic deposition (gastroduodenal bleeding, ulceration or pancreatitis), but 7 out of those 11 patients experienced early toxicity of the treatment, including liver derangement, radiation hepatitis, anemia, nausea or postembolization syndrome. Within the group of patients with antegrade flow ($n = 71$), two cases of gastroduodenal ulceration and one case of gastroduodenal bleeding were reported. In two of these three cases, a culprit vessel could be found.

The second, Cosin et al. [12], embolized the RGA when it was visible on angiography and close to the injection position (distance not specified). Neither one of the nine embolized nor one of the 18 non-embolized patients showed any complications.

The third, Hamoui et al. [11], posed that injection distal to the GDA or RGA does not require embolization, since the complication rate was low ($n = 2$, 1 % gastrointestinal ulcers). After endoscopic biopsy, microspheres were present in the gastric wall of one patient, but not in the other, who had a history of peptic ulcer disease. The complication rate of the embolized group was not reported.

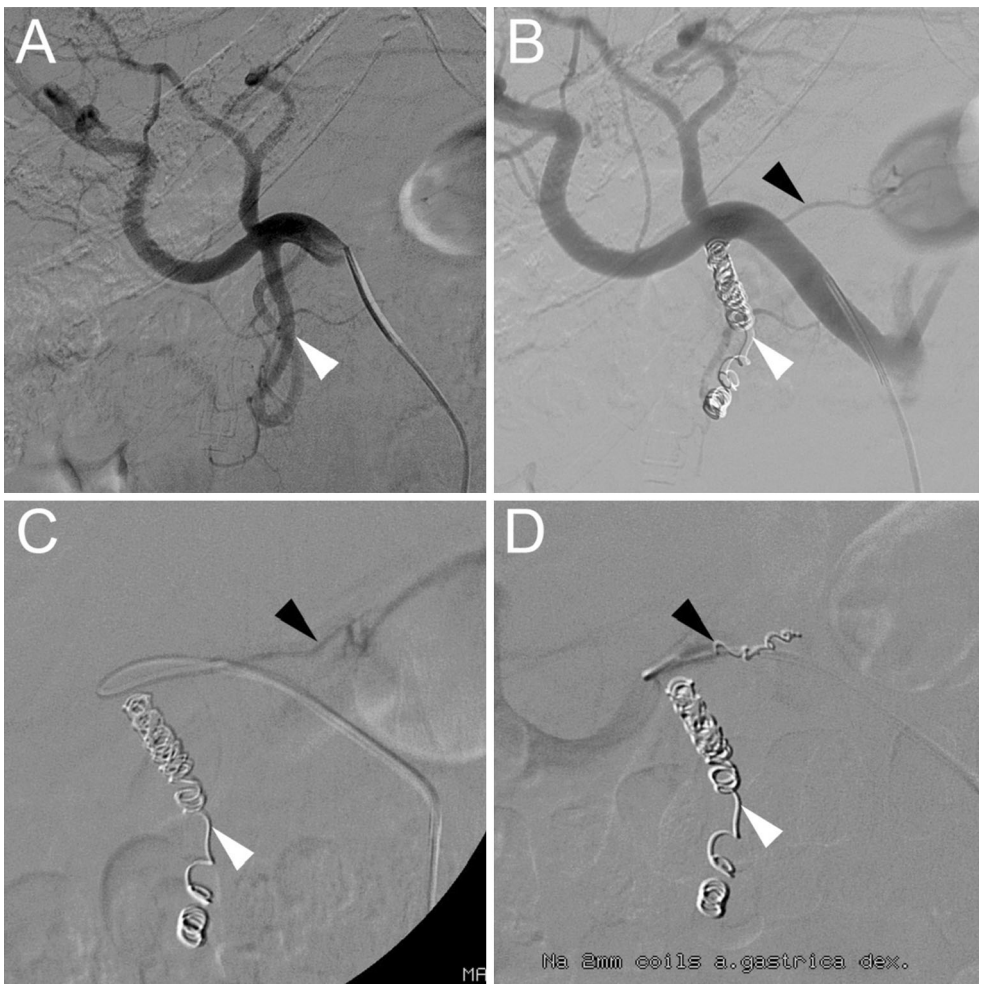

Fig. 3 Typical angiography in a patient who underwent coil-embolization of the gastroduodenal artery (GDA) and right gastric artery (RGA). **A** Digital subtraction angiography (DSA) of the GDA (*white arrowhead*) on pre-treatment angiography. **B** DSA with appearance of the RGA (*black arrowhead*) after coil-embolization of the GDA. **C** DSA with catheter placement in the RGA. **D** DSA after successful coil-embolization of the GDA and RGA

Biliary Complications

Three studies [13–15] reported on the need to embolize the cystic artery. In the first, Theysohn et al. [14] embolized patients' cystic artery if the uptake of ^{99m}Tc-MAA in the gallbladder was larger than in the liver and found one complication in the group that was embolized ($n = 20$).

In the second, Powerski et al. [15] performed embolization if the catheter could easily enter the cystic artery. The amount of ^{90}Y uptake in the gallbladder wall was lower after embolization, but more patients complained of right upper quadrant pain (22 vs. 10 %). Two patients developed cholecystitis in the embolized subgroup ($n = 68$), and one in the non-embolized subgroup ($n = 37$).

In the third, Daghir et al. [13] mentioned they did not routinely embolize the cystic artery; however, they did not specify the number of patients in whom the cystic artery was embolized or which precautions they undertook to avoid the cystic artery during delivery of the radioembolic material. No signs of gallbladder inflammation or infarction were seen in both patient groups.

Hepatic Falciform Artery

Embolization of the hepatic falciform artery was evaluated in two small studies [16, 18]. In these studies, the hepatic falciform artery could be identified in only 28 out of 798 patients (3.5 %).

In the first, by Ahmadzadehfar et al. [18], tracer accumulation in the anterior abdominal wall was seen in 17 (9.3 %) patients. The hepatic falciform artery could be identified and embolized in only one patient, who subsequently did not show ^{90}Y uptake in the anterior abdominal wall on bremsstrahlung SPECT/CT. Out of the 16 other patients that showed tracer accumulation in the anterior abdominal wall on ^{99m}Tc-MAA images prior to radioembolization, only 9 (56 %) showed uptake in the abdominal wall on post-treatment imaging. One of those nine patients developed abdominal muscular pain above the umbilicus. Furthermore, all other hepaticoenteric arteries were also embolized, but the occurrence of complications, other than abdominal muscular pain, was not reported.

In the second, Schelhorn et al. [16] embolized the hepatic falciform artery with coils or gelfoam in a subgroup of five patients. In six patients no embolization was performed, but neither subgroup of patients developed complications. However, unlike Ahmadzadehfar et al. [18], they used ice packs to induce vasoconstriction in the anterior abdominal wall during ^{90}Y administration to prevent complications in patients showing a persistently patent HFA that could not be embolized.

Other

Paprottka et al. [17] embolized all hepaticoenteric branches originating distal to the injection position during the radioembolization procedure. There were significantly less early toxicities (including nausea, vomiting, abdominal pain and fever) in the group without embolization (4 %) compared to the group with embolization (13 %). The milder (grade 1 and 2) complications also occurred significantly less in the group without embolization (35 vs. 60 %).

Discussion

The purpose of this literature review was to summarize the evidence for prophylactic embolization of hepaticoenteric arteries to prevent complications after radioembolization. We identified eight comparative, non-randomized, retrospective studies. In general, the rate of gastro-intestinal complications after radioembolization was low in both the embolized and non-embolized group. None of the included studies showed evidence in favor of routine performance of prophylactic embolization. However, they did state that when using certain criteria for embolization (Table 1) it appears to be safe to refrain from prophylactic embolization. For example, Paprottka et al. [17] states that coiling might be abandoned if the catheter for applying the microspheres has a distance of at least 2 cm to the first proximal extra-hepatic artery.

The most important limitation of this review is the lack of randomized controlled trials and prospective studies. Embolization of hepaticoenteric arteries was only performed in patients who are at higher risk for complications, which was determined by the hepaticoenteric vascular anatomy. The risk differences that appear to be in favor of non-embolized patients are distorted by confounding by indication, as the study groups are not comparable. Therefore, the evidence is limited and it is only possible to draw conclusions regarding the necessity of prophylactic embolization to decrease the risk of complications in specific situations.

Also, complications may have been underestimated because most studies did not routinely perform follow-up, post-treatment imaging or endoscopy [11–14, 17]. Even though we developed a quality scoring system specifically for this review to assess these kinds of methodological aspects, this may not have captured all the relevant aspects adequately.

Furthermore, the incidence of complications in both embolized and non-embolized patients may partly be explained by the fact that the occurrence of gastrointestinal complications does not only depend on extrahepatic microsphere deposition, but also on patient characteristics such as a history of gastro-intestinal ulcerative disease. One study

[11] took histologic evidence of the affected organs into account and could, and thus, proved that the gastro-intestinal complications were attributable to extrahepatic microsphere deposition, rather than other causes. This implicates that the outcome measures used were prone to bias. Furthermore, it is questionable whether symptoms such as pain are truly attributable to non-target radioembolization when they could also be caused by, for example, ischemia of tumor or liver tissue: post-radioembolization syndrome. Misidentification of hepaticoenteric arteries on pre-treatment angiography or the inability to occlude hepaticoenteric arteries due to small size may also have contributed to the incidence of complications in the non-embolized group [11, 13].

Prophylactic embolization might not always be sufficient to prevent non-target deposition of microspheres as four studies reported complications in embolized patients. A possible explanation for this problem is the occurrence of recanalization of embolized arteries, collateral formation or opening of formerly hypoperfused vessels. Several studies report an incidence of recanalization and collateral development of 11–44 % in coiled patients [7–9]. Perhaps timing of prophylactic embolization during the radioembolization procedure itself, rather than during pretreatment angiography, might reduce the incidence of recanalization and collateral development. Of the studies selected in this review, only Paprottka et al. [17] and Theysohn et al. [14] described this approach. Lastly, extrahepatic deposition could occur because of stasis during administration, but the included studies did not investigate this [21].

Compared to glass microspheres, resin micropsheres have a significant embolic effect, which often leads to arterial occlusion, which, in turn, increases the risk of non-target radioembolization through backflow of microspheres [22, 23]. Theoretically, prophylactic embolization might be less important when using glass microspheres, but our study does not provide sufficient data to support this hypothesis. Two studies directly comparing both microspheres show no significant differences in toxicity and survival rates [24, 25].

A significant improvement in the detection of hepaticoenteric shunting can be achieved by using cone beam CT before radioembolization in addition to digital subtraction angiography [26–28]. The potential role and impact of cone beam CT are not assessed in this review, because none of the included studies mentioned the use of cone beam CT for pre-treatment planning. It is expected that using a cone beam CT will reduce the incidence of hepaticoenteric complications.

Future research could provide a higher level of evidence for the criteria to be used for prophylactic embolization. The most important aspect is the comparability of patient groups. There is no need for further studies comparing patients with an indication for embolization to patients without, but there is a need for a study comparing embolization within those groups. For this, a prospective study that uses a pre-defined protocol that defines the indication to embolize is advisable (e.g. minimal distance between catheter tip and hepaticoenteric arteries).

Lastly, the need to embolize hepaticoenteric arteries before radioembolization may be further eliminated in the future since promising results of alternative techniques to prevent non-target deposition of microspheres, such as temporary balloon occlusion and anti-reflux catheters, have been published recently [29–35].

Conclusion

There is no conclusive evidence supporting prophylactic embolization of hepaticoenteric arteries directly influences the risk of complications. According to the best available evidence, refraining from embolization of the GDA, RGA and CA is justified when the catheter tip can be placed distal to the origin of these arteries or when reversed flow is present in the GDA. The hepatic falciform artery can be embolized if a large uptake in the abdominal wall is seen. Using these criteria, the risk of complications is low.

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Compliance with Ethical Standards

Conflict of interest Marnix G. E. H. Lam is an advisor for BTG and Bayer Healthcare and is a speaker for Sirtex Medical. None of the other authors declares a conflict of interest.

Ethical approval For this type of study, formal consent is not required.

Informed consent None.

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SIR-Spheres®
(Yttrium-90 Microspheres)

1. DESCRIPTION

SIR-Spheres® consists of biocompatible microspheres containing yttrium-90 with a size between 20 and 40 microns in diameter. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission. The maximum energy of the beta particles is 2.27MeV with a mean of 0.93MeV. The maximum range of emissions in tissue is 11mm with a mean of 2.5mm. The half-life is 64.1 hours. In therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. The average number of particles implanted is $30 - 60 \times 10^6$. SIR-Spheres® is a permanent implant.

SIR-Spheres® is implanted into a hepatic tumor by injection into either the common hepatic artery or the right or left hepatic artery via the chemotherapy catheter port. The SIR-Spheres® distributes non-uniformly in the liver, primarily due to the unique physiological characteristics of the hepatic arterial flow, the tumor to normal liver ratio of the tissue vascularity, and the size of the tumor. The tumor usually gets higher density per unit distribution of SIR-Spheres® than the normal liver. The density of SIR-Spheres® in the tumor can be as high as 5 to 6 times of the normal liver tissue. Once SIR-Spheres® is implanted into the liver, it is not metabolized or excreted and it stays permanently in the liver.

2. INDICATIONS FOR USE

SIR-Spheres® is indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

3. CONTRAINDICATIONS

SIR-Spheres® is contraindicated in patients who have

- had previous external beam radiation therapy to the liver,
- ascites or are in clinical liver failure,
- markedly abnormal synthetic and excretory liver function tests (LTFs),
- greater than 20% lung shunting of the hepatic artery blood flow determined by Technetium MAA scan,
- pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel,
- disseminated extra-hepatic malignant disease,
- been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres®,
- portal vein thrombosis.

4. WARNINGS

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- Inadvertent delivery of SIR-Spheres® to the gastrointestinal tract or pancreas will cause acute abdominal pain, acute pancreatitis or peptic ulceration.
- High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis.
- Excessive radiation to the normal liver parenchyma may result in radiation hepatitis.

5. PRECAUTIONS

- No studies have been done on the safety and effectiveness of this device in pregnant women, nursing mothers or children.
- Due to the radioactivity of this device and the significant consequences of misplacing the microspheres in situ, this product must be implanted by doctors with adequate training in the handling and implantation technique for this device.
- Sirtex Medical Inc recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres®. The SPECT scan will detect the Bremsstrahlung radiation from the yttrium-90 to confirm placement of the microspheres in the liver.
- This product is radioactive. The use of this device is regulated under Title10 of the Code of Federal Regulations Part 35. These regulations must be followed when handling this device.
- All persons handling, dispensing and implanting this device must be familiar with and abide by all Local, State and Federal regulatory requirements governing therapeutic radioactive materials. Accepted radiation protection techniques should be used to protect staff when handling both the isotope and the patient.
- Some patients may experience gastric problems following treatment but H-2 blocking agents may be used the day before implantation of SIR-Spheres® and continued as needed to reduce gastric complications.
- Many patients may experience abdominal pain immediately after administration of SIR-Spheres® and pain relief may be required.
- SIR-Spheres® demonstrated a mild sensitization potential when tested dermally in an animal model.

6. CLINICAL TRIAL RESULTS

In a randomized, controlled clinical trial, a total of 70 patients were studied in two arms, 34 patients with FUDR chemotherapy (control group), and 36 patients with FUDR plus SIR-Spheres®. The results are shown in the following tables.

Table 1. Tumor response by volume

Response	CR	PR	NC	PD	Others
FUDR only (N = 34)	**1**	**7**	12	9	5
FUDR plus SIR-Spheres® (N = 36)*	**2**	**16**	10	5	3

* (P=0.033)

Tumor response was measured by two consecutive CT scans in a 3-month interval period.
CR = Complete Response, PR = Partial Response, NC = No Change, PD = Progressive Disease
Others = No follow up, or unmeasurable

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Table 1 indicates that there is a statistically significant improvement of the tumor response rates (CR+PR) in the group treated with FUDR plus SIR-Spheres®, when compared with the group treated with FUDR only.

Table 2. Time to first progressive disease in the liver

	FUDR Only	FUDR plus SIR-Spheres®
Number of Patients	34	36
Mean Time in Days +/- SD*	312 Days +/- 330	510 Days +/- 516
Median Time in Days*	233 Days	366 Days

* (P=0.05)

Progressive Disease was defined as more than 25 % increase of tumor volume, or development of new lesion(s) in the follow up CT scan, when compared to the pre-treatment CT scan.

Table 2 indicates that there is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres®, when compared with the group treated with FUDR only.

7. ADVERSE EVENTS

When the patient is treated with proper technique, without excessive radiation to any organ, the common adverse events after receiving the SIR-Spheres® are fever, transient decrease of hemoglobin, mild to moderate abnormality of liver function tests (mild increase in SGOT, alkaline phosphatase, bilirubin), abdominal pain, nausea, vomiting, and diarrhea.

In the phase III randomized controlled clinical trial with 70 patients, there was a minimal increase of Grade 1 and 2 events, mostly transient abnormal LFTs and nausea and vomiting in the patients who received SIR-Spheres®. There was no difference in the number of patients who developed Grade 3 and 4 adverse events between the two groups. No patient died due to the adverse events directly related to SIR-Spheres®.

Table 3. Adverse Events

	Grade 1 and 2		Grade 3 and 4	
Events	**FUDR**	**FUDR + SIR-Spheres®**	**FUDR**	**FUDR+ SIR-Spheres®**
Hemoglobin	4	5	1	0
Bilirubin	7	2	0	1
AST (SGOT)	110	109	14	7
Alk. Phos.	90	188	5	14
Nausea/vomiting	5	13	2	1
Diarrhea	6	3	1	0
Total	**222**	**320**	**23**	**23**

The data are from a clinical trial with 34 patients on chemotherapy only, and 36 patients on chemotherapy plus SIR-Spheres®.

Potential serious adverse events due to high radiation:

- **Acute pancreatitis** ---- causes immediate severe abdominal pain. Verify by SPECT imaging of the abdomen (Yttrium-90 Bremsstrahlung image) and test for serum amylase.
- **Radiation Pneumonitis** ---- causes excessive nonproductive cough. Verify by X-ray evidence of pneumonia.
- **Acute Gastritis** ---- causes abdominal pain. Verify by standard methods to diagnosis gastric ulceration.
- **Radiation Hepatitis** ---- causes unexplained progressive deterioration of liver function. Verify by transcutaneous core biopsy of the liver.

8. PATIENT SELECTION and PRETREATMENT TESTING

- Patients are indicated for treatment with SIR-Spheres® when the metastatic colorectal cancer in the liver is considered non-resectable. In any of the following circumstances, patients would generally be considered non-resectable:
    1. multiple liver metastases together with involvement of both lobes;
    2. tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the metastases were resected;
    3. tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; and
    4. widespread metastases such that resection would require removal of more liver than is necessary to maintain life.
- Resectability may be evaluated via imaging with a triple phase contrast angio-portal CAT scan or MRI.

Patient Tests Before Treatment with SIR-Spheres®

The following tests are recommended before treatment.

- A hepatic angiogram should be performed to establish arterial anatomy of the liver.
- A nuclear medicine break-through scan (Intrahepatic Technetium MAA Scan) to determine the percent lung shunting. If a port has been inserted, this test can be performed through the port.
- Serologic tests of liver function should be performed to determine the extent of liver function damage.

Appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

9. RADIATION SAFETY

The preparation and implant procedure must be regarded as being a potentially serious radiation hazard to the staff and a serious contamination hazard. Regulatory and local radiation usage guidelines should be followed concerning implantation and post-implantation care.

The following are sample measured thermoluminescent dosimetry (TLD) exposures to personnel.

Table 4. Exposure dose per patient for implant preparation (Technologist)

	Trunk mSv (mrem)	**Lens of the eye MSv (mrem)**	**Hands mSv (mrem)**

Shallow dose (0.07 mm)	0.027 (2.7)	0.026 (2.6)	0.35 (35)
Deep dose (10 mm)	0.003 (0.3)	0.004 (0.4)	

Assuming handling of a 3 GBq device and dose preparation time of 30 minutes. TLDs were worn near the pelvis, on the shirt's lapel, and on the working finger.

Table 5. Exposure dose per patient for implant procedure (Physician)

	Trunk mSv (mrem)	**Lens of the eye MSv (mrem)**	**Hands mSv (mrem)**
Shallow Dose (0.07mm)	0.038 (3.8)	0.12 (12)	0.32 (32)
Deep Dose (10 mm)	0.004 (0.4)	0.054 (5.4)	

Assuming average patient dose of approximately 2 GBq and dose injection time of 20 minutes.

Post-Implant Exposure

Exposure data from patients implanted with an average of 2.1GBq at approximately 5-6 hours post implantation at the following distances from the patient's abdomen:

0.25m	18.8 μSv/hr
0.5m	9.2 μSv/hr
1m	1.5 μSv/hr
2m	0.4 μSv/hr
4m	<0.1 μSv/hr

(1 mSv= 100 mrem)

10. HOW SUPPLIED

SIR-Spheres® is provided in a vial with water for injection. Each vial contains 3 GBq of yttrium-90 (at the time of calibration) in a total of 5 cc water for injection. Each vial contains 40 – 80 million microspheres. The vial is shipped within a 6.4mm thick, lead pot. The package consists of a crimp sealed SIR-Spheres® glass vial within a lead pot, and a package insert within Type A packing bucket.

The vial and its contents should be stored inside its transportation container at room temperature (15-25° C, 59-77° F).

The calibration date (for radioactive contents) and the expiration information are quoted on the vial label. The useful life of the SIR-Spheres® is 24 hours from the time of calibration. The particle size has been validated before shipment, as 32.5 μ +/- 2.5 μ.
Less than 10% will be > 30 μ and < 35 μ.

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Appendices

I. General Information
II. Dose Preparation Procedure
III. Calculation of Individual Dose
IV. Radiation Dosimetry
V. Technique for Performing the Intra-hepatic Technetium MAA Scan
VI. Correction for Decay

Appendix I

GENERAL INFORMATION

Restricted to Accredited Facilities
SIR-Spheres® may only be dispatched to a duly licensed or accredited facility capable of handling therapeutic medical isotopes.
Restricted to Licensed Physicians
Only doctors qualified and licensed under Title 10 Code of Federal Regulations Part 35 (NuclearRegulatory Commission) may order and implant SIR-Spheres®.

Appendix II

Dose Preparation Procedure:

- Unpack SIR-Spheres®, leaving shipping vial lead pot and place on the bench top lead shielded box. As an option, you can place the lead pot behind your own lead-shielded glass, if you have one.
- Remove the center of aluminum seal from sterile glass v-vial with forceps, and clean the rubber top with alcohol swap.
- Place the glass v-vial in an empty lead pot (10 cm x 6 cm) for stability and shielding.
- Open the shipping vial lead pot; remove the SIR-Spheres® shipping vial.
- Using a qualified dose calibrator, calibrate the activity in the shipping vial to current time and record the activity. Use the Table 1., Decay Factor Chart, or accompanying decay graph. Make sure the pre-shipping calibration time zone is converted to current local time zone.
- Remove partially the aluminum seal of the SIR-Spheres® delivery vial, clean with alcohol swap.
- Draw 2 mL room air into a shielded 5 mL syringe attached with a 20 gauge Huber point needle, and puncture through the rubber top of the SIR-Spheres® delivery vial, and quickly draw back and forth several times in order to mix the SIR-Spheres® thoroughly.
- Lay lead pot containing the SIR-Spheres® vial at approximately 45° angle, withdraw quickly a pre-calculated specific amount of patient dose, and transfer into the glass-v vial in the other lead pot. Make sure to withdraw the required amount quickly, before the content of the shipping vial starts to settle.
- Verify the patient dose in the glass-v vial by re-measuring the activity in the shipping vial with dose calibrator, and correct, if necessary.
- Put the glass-v vial, containing the confirmed patient dose into the dedicated Perspex shield.

Now, the patient dose is ready for transport to the SIR-Spheres® implantation room.

Appendix III

CALCULATION OF INDIVIDUAL DOSE

There are generally two acceptable methods in calculating the individual patient dose; the partition model (individual dose calculation), and empirical model. The empirical model accepts the safety margins of the dose known from the previously published clinical data and chooses the most safe and effective dose from it. The empirical model has been used in the pivotal clinical trial of the SIR-Spheres®.

The patient dose can be determined according to the following table 1.

Table 1. The Recommended Patient Dose

The % involvement by the tumor in the liver	Recommended Y-90 Dose*
> 50 %	3.0 GBq
25 % - 50 %	2.5 GBq
< 25 %	2.0 GBq

CAUTION: The recommended implanted activities are specific to SIR-Spheres®. They are not applicable and should not be extrapolated to other implanted Y-90 sources.

* When there is 10 % or more lung shunting, the patient dose would be further reduced, according to the following table 2.

Table 2. Dose Reduction Factors for Patients with Lung Shunting

% Lung shunting	Reduction Factor
< 10 %	No reduction
10 % - 15 %	20 % reduction
15 % - 20 %	40 % reduction
> 20 %	No Treatment

Lung Shunt Calculation Procedure:

- Inject 4 mCi (150MBq) of Tc-99m MAA into the hepatic artery via a port or catheter
- Use a large FOV gamma camera, and obtain anterior and posterior images of the chest and abdomen (with 700k to 1 million counts on abdomen, and the same count on the chest),
- Take right lateral abdomen, using same count,
- Draw ROI around the whole liver and the whole lung and get the total counts for the lung and the liver,
- Calculate the % shunt using following formula:

  % Shunt = (Lung Counts / Liver Counts + Lung Counts) x 100

Appendix IV

RADIATION DOSIMETRY

The radiation dosimetry of the SIR-Spheres® can be a complex and difficult task due to the non-uniform distribution of the particles in the normal liver and the tumors. In general, 1 GBq (27 mCi) of Yttrium-90/kg of tissue provides 50 Gy of radiation dose.* However, because of the non-uniform distribution of the dose between the tumor and the normal liver tissue, a proportionally larger amount of radiation will be delivered to the tumor tissue, and less amount to the liver.

* Russell, Carden, Herron: 'Dosimetry Calculations of Yttrium-90 used in the treatment of liver cancer.' Endocurietherapy/Hypertherm Oncol. 1988;4:171-186

In example, a patient, who has a liver weighing 1500 g, and has two tumor nodules,
A 4 cm size tumor in the right lobe, and a 3 cm size nodule in the left lobe. The post-injection images suggest that there is 5:1 density ratio for unit volume between the tumor and the liver. The patient received 2 GBq of SIR-Spheres®. In such case, the calculated radiation dose to the tumor is 294 Gy and the dose to the liver tissue is 58.5 Gy.

The radiation dose for other organs would be minimal or negligible, except for the organs adjacent to the liver, such as the stomach, large intestine, gall bladder, and the lung. The radiation dose may increase significantly, when there is a shunting of the arterial blood to the lung, stomach, or small intestine.

Appendix V

Technique for Performing the Intra-hepatic Technetium MAA Scan

Purpose:	To assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs.
Agent:	Technetium-99 labeled MAA (Macro-Aggregated Albumin)
Dose:	150MBq (4 mCi)
Equipment:	Any large FOV gamma camera
Administration:	The patient needs to have a surgically implanted port or trans-femoral catheter placed in the hepatic artery. The Technitium-99 labeled MAA is injected into the port or catheter.
Imaging:	The patient is positioned supine under the gamma camera and the images recorded. * Anterior and posterior images of abdomen and thorax. Collect 700k –1000k cts for abdomen and same time for thorax * Right lateral abdomen - same time acquisition as for anterior
Analysis:	Draw ROI around whole of liver and whole of lung fields. Calculate G mean for liver region and lung region. Calculate Lung/Liver ratio using the following formula. % lung shunting = (counts of total lung/counts of total lung plus counts of liver) x 100
Interpretation:	If percent lung shunting is >10% then there is need for dose reduction of SIR-Spheres® (see *Table 1* below)

Table 1. Dose Reduction Recommendations

Percent Lung Shunting	Activity of SIR-Spheres®
< 10%	Deliver full amount of SIR-Spheres®
10% to 15%	Reduce amount of SIR-Spheres® by 20%
15% to 20%	Reduce amount of SIR-Spheres® by 40%
> 20 %	Do not give SIR-Spheres®

Appendix VI

CORRECTION FOR DECAY

The physical half-life of yttrium-90 is 64.1 hours. Radioactive decay factors should be applied at the time of patient dose preparation, in order to calculate the true value of radioactivity present.

Table 1. Decay Factors of Yttrium-90 Sir-Spheres

Hours	Decay Factor
0.5	0.995
1	0.989
2	0.979
3	0.968
4	0.956
5	0.947
6	0.937
7	0.927
8	0.917
9	0.907
10	0.898
11	0.888
12	0.878
24	0.772
36	0.678
48	0.595
72	0.459

* Caution: The time of the initial calibration must be converted to the user's local time.

SIR-Spheres®
Y-90 resin microspheres

January 2019

Coding Guide

Pretreatment Mapping and Microspheres Administration

Hospital Outpatient, ASC OBIS and Physician Services

SIRTeX

SIR-Spheres®
Y-90 resin microspheres

What are SIR-Spheres® yttrium-90 resin microspheres?

SIR-Spheres® Y-90 resin microspheres are microscopic spheres that are delivered via Selective Internal Radiation Therapy (SIRT) to liver tumors. The polymer microspheres with an average diameter of approximately 32.5 microns, are loaded with yttrium-90 (Y-90). After administration to the hepatic artery, SIR-Spheres yttrium-90 resin microspheres lodge preferentially in the vasculature of the tumor. The beta radiation remains localized, penetrating a mean of 2.5 mm in the tissue, destroying the tumor cells. Due to the half-life of 64.1 hours, most radiation (94%) is delivered in 11 days. The microspheres are biologically inert, and are not metabolized or excreted. Each vial is for a single patient use.

SIR-Spheres yttrium-90 resin microspheres are the ONLY fully FDA PMA approved yttrium-90 microspheres for the treatment of mCRC in the liver. The only yttrium-90 microspheres backed by randomized controlled trial (RCT) data, SIR-Spheres yttrium-90esin microspheres can be used alone or in combination with chemotherapy.[1,2,3]

SIR-Spheres yttrium-90 resin microspheres are the ONLY yttrium-90 microspheres administered using contrast imaging, ensuring visualization, and confirmation of distribution. Coupled with personalized dosing, and precise infusion, complete procedural control is assured.

Delivered through the hepatic artery, SIR-Spheres yttrium-90 resin microspheres directly target liver tumors with yttrium-90 beta radiation, minimizing healthy tissue exposure. Because these are the ONLY microspheres with a specific gravity similar to blood, infusion efficiency is enhanced, resulting in a homogeneous distribution, optimizing tumor coverage.

SIR-Spheres Y-90 resin microspheres

Microsphere material	Biocompatible Polymer
Isotope	Yttrium-90 permanently bound to the microspheres
Diameter	~32.5 µm
Penetration in tissue	2.5mm mean; 11mm maximum range
Half life	64.1 hours; 94% of the radiation decayed in 11 days
How supplied	3 GBq or 81 mCi per vial +/- 10% at the time of calibration
Number of particles per vial	40-80 million

1. Gray et al. *Ann Oncol* 2001;**12**:1711–20 2. van Hazel et al. J *Surg Oncol* 2004;**88**:78–85 3. Hendlisz et al. *J Clin Oncol* 2010;**28**:3687–94

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. SIR-Spheres Y-90 resin microspheres may only be distributed to a duly licensed or accredited facility capable of handling therapeutic medical isotopes. This product is radioactive and should thus be handled in accordance with all applicable standards and regulations. **Intended Use / Indications For Use:** SIR-Spheres Y-90 resin microspheres are approved for use in Argentina, Australia, Brazil, Canada, the European Union (CE Mark), Switzerland, Turkey, and several countries in Asia for the treatment of unresectable liver tumors. In the US, SIR-Spheres Y-90 resin microspheres have a Pre-Market Approval (PMA) from the FDA and are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine). **Warnings / Precautions:** Inadvertent delivery of the microspheres to locations other than the intended hepatic tumor may result in local radiation damage. Due to the radioactivity and the significant consequences of misplacing the microspheres in situ, this product must be implanted by physicians who have completed the Sirtex TEC training program. A SPECT scan of the upper abdomen immediately after implantation is recommended. Patients may experience abdominal pain immediately after administration and pain relief may be required. H-2 blocking agents may be administered the day before implantation and continued as needed to reduce gastric complications. **Side Effects**: Common side effects are fever, transient decrease of hemoglobin, mild to moderate abnormality of liver function tests, abdominal pain, nausea, vomiting, and diarrhea. Potential serious effects due to exposure to high radiation include acute pancreatitis, radiation pneumonitis, acute gastritis, radiation hepatitis, and acute cholecystitis. **Contraindications:** SIR-Spheres Y-90 resin microspheres should not be implanted in patients who have either had previous external beam radiation therapy to the liver, ascites, or are in clinical liver failure. This device is contraindicated in patients with markedly abnormal synthetic and excretory liver function tests, greater than 20% lung shunting of the hepatic artery blood flow, disseminated extra-hepatic malignant disease, and portal vein thrombosis. This device should not be implanted in patients determined via angiogram to have an abnormal vascular anatomy that would result in significant reflux of the hepatic arterial blood flow to the stomach, pancreas or bowel. **Reference the Package Insert (www.sirtex.com) for a complete listing of indications, contraindications, side effects, warnings, and precautions.**

SIR-Spheres® yttrium-90 resin microspheres Patient Flow and Coding Reference Guide

The following patient flow and coding reference for SIR-Spheres yttrium-90 resin microspheres treatment

Phase I: PRETREATMENT

Patient Referral to Interventional Radiology

Insurance Authorization (Pre-determination or Prior authorization Recommended for commercial plans)

- CPT 74175: CTA of abdomen W&WO contrast

Pretreatment Mapping

- CPT 36246 to 36248 (Selective catheterization codes)
- CPT 75726: angiography
- CPT 75774: additional selective
- CPT 37242: arterial embolization

Nuclear Medicine

- CPT 78201: planar or CPT 78205: SPECT
- CPT 78801 : Radiopharmaceutical locatlization of tumor
- CPT 78580 Lung Shunt Assessment
  - Advanced Imaging based upon provider preference

Treatment Planning:
(Performed by Authorized User (AU)

- CPT 77263: Treatment planning: complex
- CPT 77262: Treatment planning: intermediate
- CPT 77290: Simulation: complex
- CPT 77300: Basic dosimetry
- CPT 77295: Complex dosimetry (DVH) *
- CPT 77370: Physics consult
- CPT 77470: Special Treatment Procedure

SIR-Spheres Y-90 resin microspheres dose order
(Ordered same week or one week prior to treatment)

Phase II: SIR-Spheres Y-90 resin microspheres DAY OF TREATMENT

- CPT 36247 to 36248 (Selective catheterization codes)
- CPT 75726: angiography
- CPT 75774: addl selective
- CPT 37243: tumor embolization
- **Authorized User (AU) dose administration:**
- CPT 79445: Radiopharmaceutical therapy, intra-arterial particulate admin **(1 doctor model (IR/AU)**
- CPT 77778: Interstitial radiation source: complex (**2 doctor model (IR with AU)**

SIR-Spheres Y-90 Resin Microspheres Coding:

- HCPCS code: C2616: yttrium-90 (non-stranded) used for Medicare
- HCPCS Code C2616, S2095, Q3001 used with commercial plans
- HCPCS code Q3001:Brachytherapy elements used for Medicare (service site 11)

Post-Treatment Imaging (Provider preference)

- CPT 78201: planar or CPT 78205: SPECT
- CPT 78814: PET/CT limited
- CPT 77399: unlisted procedure (fusion)
- CPT 78801 Radiopharmaceutical locatlization of tumor

This is provided to as a guideline of typical practice and does not encompass all possible coding options. Coding for these procedures and services will vary by site of service and provider.

Key:
IR - Interventional Radiologists
AU - Authorized User
DVH - Dose Volume histogram* in conjunction with a physicist
CT - Computed tomography
CPT - Current Procedural Terminology
HCPCS - Healthcare Common Procedure Coding

SIR-Spheres® yttrium-90 resin microspheres
Coding and Medicare National Average Reimbursement
2019 Hospital Outpatient (OPPS), Ambulatory Surgery Center (ASC) and
2019 Physician Services (MPFS)

The SIR-Spheres yttium-90 resin microspheres coding guide is designed to assist you with coding and billing for the SIRT yttrium-90 procedures. The codes and national average payments are based upon CY2019 Medicare OPPS Final Rule, Addendum B, published November 2, 2018. Medicare physician payment rates included in this coding guide are based on current law, including the Pathway for SGR Reform Act of 2013 and the MPFS payment rates reflecting policies adopted in CY2019 Medicare Physician Fee Schedule Final Rule that appeared in the Federal Register on November 2, 2018. Medicare physician payment rates are based on conversion factor $36.0391 through December 31, 2019.

Coding for administration of SIR-Spheres yttrium-90 microspheres can be complex. There is no consensus or consistency in the Coding/billing for the administration of SIR-Sphere microspheres. This coding guide provides SIR-Spheres resin microspheres Pre-Treatment and Day of Treatment coding options. Payer policies should be reviewed for coverage & coding guidelines.

FDA LABELED INDICATIONS FOR USE
SIR-Spheres yttrium-90 resin microspheres: Colorectal cancer metastasized to the liver in combination with hepatic arterial chemotherapy (FUDR) – Full PMA approval

Payment:

Centers for Medicare and Medicaid Services (CMS)
SIR-Spheres yttrium-90 resin microspheres are eligible for payment under the Medicare Hospital Outpatient Prospective Payment System (OPPS). Effective, January 1st each year, the OPPS reimbursement rate may be adjusted based upon hospital cost reports. SIR-Spheres Y-90 resin microspheres are paid separately from the facility technical charges as mandated by the 2003 Medicare Modernization Act.

HCPCS	Descriptor	APC / Status Indicator	Hospital Outpatient APC Payment (Jan 1, 2019)	Ambulatory Surgery Center Payment (Jan 1, 2019)
C2616	Yttrium-90 non-stranded	2616 / U	$16,626.00	$16,626.00

Medicare Overview and Coverage Policies:
Medicare patients have the option of enrolling in either traditional fee-for-service Medicare or Medicare Advantage plans. Traditional fee-for-service Medicare provides eligible beneficiaries with medical benefits through Medicare Parts A and B. Medicare Part B covers medically necessary services rendered in hospital outpatient facilities and freestanding physician offices. Medicare's managed care option, or Medicare Advantage (MA), is also known as Medicare Part C.
Commercial plans contract with the Medicare program to offer coverage to Medicare enrollees. MA plans must provide coverage that is equal to or greater than the coverage offered by the beneficiary's local traditional fee-for-service Medicare Administrative Contractor (MAC). SIR-Spheres ® resin microspheres are eligible for Medicare reimbursement. Local Medicare contractors have the ability to approve or deny coverage based on medical necessity, coding, and appropriate procedural documentation.

Commercial Payers:
Reimbursement for SIR-Spheres® yttrium-90 resin microspheres by private payers will depend upon the payers coverage policy, medical necessity criteria and by your facilities contracted rates for individual plans. Private or commercial insurance coverage varies between payers and their respective health plans. Coverage, coding, and reimbursement for SIR-Spheres ® Y-90 resin microspheres and related procedures should be confirmed with the payer to determine any applicable coverage policies or criteria prior to performing a procedure. Many national, regional, and local companies have determined SIR-Spheres ® Y-90 resin microspheres to be medically necessary. Pre-determination / prior authorization is recommended for most private insurance plans.

Medicaid:
Medicaid is a public insurance program funded jointly by federal and state governments that provides safety-net coverage mainly to low-income and disabled Americans. Medicaid is run at the state level, and coverage and benefit requirements vary from state to state. Some states structure Medicaid as a fee-for-service program or contract with private companies that administer individual Medicaid managed care plans. Medicaid coverage for SIR-Spheres ® Y-90 resin microspheres and actual coverage amounts will vary by state and plan type (Managed Medicaid vs. State Medicaid). Many states publish fee schedules on their websites for fee for service plans. Most Managed Medicaid plans will determine reimbursement based upon the terms of the contracts with individual providers. You will need to contact your patient's state or Managed Medicaid plan to determine the actual reimbursement for the office or facility.

Hospital Pre-determination Process / Prior Authorization:
Medicare Advantage, private commercial, and Medicaid plans may require providers to obtain a pre-determination or prior authorization for SIR-Spheres ® Y-90 resin microspheres coverage and related procedures. It is recommended that the coverage policies of your payer mix be researched and that applicable pre-determination requirements be understood prior to treating the patient. **Note: Obtaining a pre-determination / prior authorization is not a guarantee of coverage or payment. Coverage and payment determination can only be made at the time a claim is adjudicated.**

Medicare Place of Service Payment Methodology

Provider of Service	Place of Service Code	Medicare Payment Methodology
Hospital Outpatient	22	Hospital Outpatient Prospective Payment System (OPPS) payments made based on CPT codes under Ambulatory Payment Classifications (APC)
Ambulatory Surgery Center (ASC)	24	ASC Payment System is linked to the OPPS, paying ~65% of the APC payment
Office Based Interventional Suite	11	Medicare Physician Fee Schedule (MPFS) payments are based on relative values assigned to CPT codes (work, practice and malpractice expense)

ICD-10 Diagnosis Codes:
The following diagnosis code range is specific to colorectal cancer (SIR-Spheres microspheres is approved for colorectal cancer that has metastasized to the liver). If the cancer is other than colorectal metastases, consult your ICD-10-CM codebook for appropriate coding.

C18.0 – C18.9	Malignant neoplasm of colon
C19.0 – C21.1	Malignant neoplasm of rectum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

Microspheres Revenue Code:
Revenue Code: 0278 (Medical/Surgical Supplies – Other Implants)

Microspheres Coding:

The HCPCS codes used to report use of SIR-Spheres® Y-90 resin microspheres to payers, may vary by plan type and the site of service where treatment is rendered. The following codes may be appropriate depending on payer

HCPCS	Descriptor	Payer(s)	Place of Service
C2616	Brachytherapy source, non-stranded, Yttrium-90, per source	Medicare; some private payers	Hospital outpatient 22 ASC 24
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres	**Not used by Medicare;** Used by Blue Cross and Blue Shield and some UHC plans	Hospital outpatient 22 ASC 24 Office Based Interventional Suite 11
Q3001	Radioelements for brachytherapy, any type, each	Medicare; some private payers	Office Based interventional Suite 11

Important Provider Notice:

National Correct Coding Initiative (CCI) Edits may result in coding conflicts for various treatments and procedures. Providers should carefully review each quarter's CCI edit updates. CCI edits may be downloaded from the CMS website at: http://www.cms.gov/NationalCorrectCodInitEd/. Questions, concerns or comments regarding specific NCCI edits, may be submitted in writing to:

National Correct Coding Initiative
Correct Coding Solutions LLC (Fax #: 317-571-1745)
P.O. Box 907
Carmel, IN 46082-0907
Attention: Niles R. Rosen, MD, Medical Director

Coding Options for SIR-Spheres® yttrium90 resin microspheres Therapy

Pretreatment and Mapping – Medicare January 2019

CPT	APC	CPT Description[1] *See 2018 CPT Guide for full descriptions*	Facility Payment: Hospital Outpatient	Facility Payment: Ambulatory Surgery Center	Physician Payment: Physician (Facility)[2]	Physician Payment: Physician (Non-Facility)[3]
E&M CODES – E&M codes will vary; consult your most recent CPT Coding Guide for E&M coding options and guidelines						
PHASE I: PRE-PLANNING – MAPPING CODING[4]						
Selective Catheterizations for Diagnostic Procedure						
36246	NA	Selective catheter placement; initial second order	$00	$00	$266	$858
36247	NA	; initial third order or more	$00	$00	$316	$1,535
36248	NA	; addl second order, third order and beyond	$00	$00	$51	$148
Hepatic Angiogram						
75726	5184	Angiography, visceral, radiological S&I	$4,377	$00	$56	$147
75774	NA	Angiography, selective, radiological S&I	$0	$00	$18	$84
Embolization *(if indicated)*						
37242	5193 **(J1*)**	Arterial embolization or occlusion, inclusive of all radiological S&I; arterial other than hemorrhage or tumor	$9,669.00	$5,787	$500	$7,622
		NOTE:** The APC J1 status indicator for CPT 37242 provides one bundled payment for all services provided in the facility setting considered integral, ancillary, supportive and/or adjunctive to the primary service (CPT 37242). **If embolization is performed, all services provided on the same day of service will be packaged into the J1 APC payment for 37242.				
Treatment Planning – AU (Authorized User) Work						
77262[5]	NA	Treatment Planning; intermediate OR	$0	$0	$110	$110
77263[6]	NA	Treatment Planning; complex	$0	$0	$172	$172
77290	5612	Complex Simulation	$322	$166	$84	$520
77300	5611	Basic Dosimetry Calculation	$124	$34	$34	$68
77370[6]	5611	Special Medical Radiation Physics Consultation	$124	$64	$0	$127
77470[7]	5623	Special Treatment Procedure	$520	$26	$109	$135
77295[8]	5613	3D Rad plan	$1,192	$270	$231	$502
77399	5611	External radiation dosimetry	$124	$64	Carrier Determined	
78814	5594	PET/CT limited	$1,376	$708	$109	$109
78811	5594	PET limited (if PET/MRI) *MRI code provider dependent*	$1,376	$633	$77	$77

[1] Some CPT descriptors have been shortened for purposes of brevity. See your CPT Guide for full descriptors and coding guidelines.
[2] "Facility payment" refers to professional services rendered in a facility setting such as hospital or ASC.
[3] "Non-Facility payment" refers to professional services provided in the physician freestanding office, surgical or cancer center.
[4] The possible coding options listed in this section are based on Medicare guidelines and society recommendations. Medicare base case coding scenarios typical for one mapping and one treatment in the hospital outpatient or ASC setting follow this section.
[5] Treatment planning should be billed and dictated separately prior to microspheres administration,
[6] Use of this code requires a written order by the physician.
[7] Used for brachytherapy and in circumstances requiring extra work over and above basic dosimetry calculation: Patient with previous chemo, is receiving concurrent chemo, or external beam radiation to the body/liver. AU must review current CT scan, liver function studies and ECOG performance status to determinate % yttrium-90 dose to be adjusted taking into account previous treatments. Often used as a re-treatment code. Should be supported by clinical treatment note.
[8] 3 DVH calculations may be performed for the procedure with a Physicist.

Pretreatment and Mapping (continued) – Medicare January 2019

CPT	APC	CPT Description[9] *See 2018 CPT Guide for full descriptions*	Facility Payment: Hospital Outpatient	Facility Payment: Ambulatory Surgery Center	Physician Payment: Physician (Facility)[2]	Physician Payment: Physician (Non-Facility)[3]
3-D Post-Processing (for liver volume)						
76376	N	3D Post Scan, not requiring image post-processing	$0	$0	$10	$23
76377	N	Cone Beam CT (*Medicare NCCI edit with 78580)*	$0	$0	$41	$72
CT Acquisition *(may be billed in conjunction with CPT code 76377)*						
74150	5522	CTA without contrast material	$113	$58	$61	$152
74160	5571	CTA; with contrast material(s)	$202	$104	$65	$242
74170	5571	CTA; with and without contrast	$202	$104	$72	$275
74175	5571	CTA; abdomen & pelvis, with & without contrast	$202	$104	$93	$320
Pre-Treatment Imaging (*coding options will vary based on provider preference)*						
78201	5593	Liver imaging, static	$1,229	$633	$22	$198
78205	5593	Liver imaging (SPECT) **(Medicare NCCI edit with C2616)*	$1,229	$633	$34	$219
78215	5591	Liver Spleen Imaging	$353	$182	$25	$202
78580	5591	Pulmonary perfusion imaging *(Medicare NCCI edit 76377)*	$353	$182	$37	$248
78800	5591	Radiopharmaceutical localization of tumor; limited are	$353	$182	$35	$202
78801	5591	Radiopharmaceutical locatioization of tumor	$353	$182	$40	$267
78802	5593	Radiopharmaceutical localization whole body, single day	$1,229	$633	$43	$335
78803	5592	Radiopharmaceutical localization of tumor (SPECT)	$455	$235	$53	$354
78811	5593	Optional Procedure - PET; limited area	$1,229	$633	$77	$77
A9540[10]		Technetium 99m macroaggregated albumin	$0	$0	NA	$0

[9] Some CPT descriptors have been shortened for purposes of brevity. See your CPT Guide for full descriptors and coding guidelines.
[10] Do NOT code CPT 79445 for the injection of TC99 MAA on the mapping day as this is considered part of the nuclear medicine exam.

Coding Options for SIR-Spheres® yttium-90 resin microspheres Therapy

Day of Treatment - Medicare January 2019

CPT	APC	CPT Description[11] *See 2018 CPT Guide for full descriptions*	Facility Payment: Hospital Outpatient	Facility Payment: Ambulatory Surgery Center	Physician Payment: Physician (Facility)[2]	Physician Payment: Physician (Non-Facility)[3]
PHASE II: Day of Treatment (Administration / Implant)						
Selective Catheterizations						
36247	NA	Selective catheter placement; initial third order or more	$00	$00	$316	$1,535
36248	NA	; additional second order, third order and beyond	$00	$00	$51	$148
Hepatic Angiogram						
75726	5183	Angiography, visceral, radiological S&I	$4,377	$00	$56	$147
75774	NA	Angiography, selective, radiological S&I	$0	$00	$18	$84
Coding Options for Billing of Sources (Yttrium-90 Microspheres – non stranded)						
C2616	2616	Brachytherapy source (yttrium-90 non stranded) *(Medicare - billed in OPPS/ASC)*	$16,626	$16,626	NA	Invoice
S2095	NA	Transcatheter embo for tumor destruction using yttrium-90 microspheres (*Private payer; billed in OPPS/ASC/OBIS)*	Private Payer Contract Price	Private Payer Contract Price	NA	Private Payer Contract Price
Q3001	NA	Brachytherapy Radioelements, any type *(billed In OBIS)*	NA	NA	NA	Invoice
Microspheres Administration						
37243	5193 **(J1*)**	Tumor embolization or occlusion, inc of all radiological S&I; venous, for tumors, organ ischemia, or infarction	$9,669	$4,056	$589	$9,861
		***Note:** APC J1 status indicator for CPT 37243 provides one bundled payment for all services provided in the facility setting considered integral, ancillary, supportive and/or adjunctive to the primary service (CPT 37243).				
Microspheres Administration: Authorized User Codes						
77262[5]	NA	Treatment Planning; intermediate OR	$0	$0	$110	$110
77263[6]	NA	Treatment Planning; complex	$0	$0	$172	$172
77290	5612	Simulation: complex	$322	$166	$84	$520
77300	5611	Basic Dosimetry Calculation	$125	$34	$35	$68
77295[8]	5613	3D Rad plan	$1,187	$270	$231	$502
77370[6]	5611	Special Medical Radiation Physics Consultation	$124	$64	$0	$127
77470[12]	5623	Special Treatment Procedure	$520	$26	$109	$135
79445	5661	Radiopharmaceutical therapy, intra-arterial particulate Admin ***(1 doctor model (IR/AU) or 2 doctor model IR with separate AU) OR***	$231	$119	$117	$117
77778[13]	5624	Interstitial radiation source application; complex ***(2 Doctor model IR with separate AU)***	$705	$363	$471	$867
77790[14]	N	Supervision, handling, loading of radiation source	$0	$0	$15	$15

[11] Some CPT descriptors have been shortened for purposes of brevity. See your CPT Guide for full descriptors and coding guidelines.

[12] Used in circumstances requiring extra work over and above basic dosimetry calculation: Patient with previous chemo, is receiving concurrent chemo, or external beam radiation to the body/liver. AU must review current CT scan, liver function studies and ECOG performance status to determinate % yttrium-90 dose to be adjusted taking into account previous treatments. Often used as a re-treatment code.

[13] Medicare NCCI edit with 37243

[14] Medicare packages this service with CPT 79445

Coding Options for SIR-Spheres® yttrium-90 resin microspheres Therapy

Day of Treatment (continued) – Medicare January 2019

CPT	APC	CPT Description[1] *See 2018 CPT Guide for full descriptions*	Hospital Outpatient	Ambulatory Surgery Center	Physician Payment: Physician (Facility)[2]	Physician Payment: Physician (Non-Facility)[3]
Post Treatment Imaging *(coding options will vary based on provider preference)*						
74170	5571	CTA; with and without contrast	$202	$104	$72	$275
74175	5571	CTA abdomen & pelvis, with & without contrast	$202	$104	$93	$320
78201	5593	Liver imaging, static	$1,229	$633	$22	$198
78205	5593	Liver imaging (SPECT)* *(Medicare NCCI edit with C2616)*	$1,229	$633	$34	$219
78215	5591	Liver Spleen Imaging	$353	$182	$25	$202
78580	5591	Pulmonary perfusion imaging *(Medicare NCCI edit 76377)*	$349	$182	$37	$248
78800	5591	Radiopharmaceutical localization of tumor; limited area	$353	$182	$35	$202
78801	5591	Radiopharmaceutical locatlization of tumor	$353	$182	$40	$267
78802	5593	Radiopharmaceutical localization whole body, single day	$1,229	$633	$43	$335
78803	5592	Radiopharmaceutical localization of tumor (SPECT)	$456	$235	$53	$354

HOSPITAL CHARGE MASTER REMINDER

- The hospital's charge master should reflect the following codes for the microspheres
  - C2616 (Brachytherapy source, yttrium-90 – non-stranded) mapped to Revenue Code 0278 and/or
  - S2095 (Trans-catheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres: BC/BS)
  - Q3001 (radioelements for brachytherapy, any type, each)
    - *For Use In Office Based Interventional Suite*
- Coding of SIR-Spheres Y-90 resin microspheres is dependent upon the patient's health insurance coverage. Private payer guidelines should be consulted for appropriate coding and payment.

NOTE: It is important to consult with the hospital finance department to determine the appropriate charges for the microspheres.

Sirtex Medical Inc. | 300 Unicorn Park Drive | Woburn, MA 01801
Tel: 888.4.Sirtex (888.474.7839) | Fax: 877-642-7888

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Tel: +61 2 9964 8400 | Fax: +61 2 9964 8410

www.sirtex.com

Vitamin D

Question: How should coverage of vitamin D testing be clarified on the Prioritized List?

Question source: Oregon Health Leadership Council, OHA Staff

Issue: The Oregon Health Leadership Council http://www.orhealthleadershipcouncil.org/about/ is looking at opportunities to reduce health care waste. One of the identified areas by the Evidence-Based Best Practice Committee is on vitamin D screening. Vitamin D screening is considered broadly overused.

This is the agreed upon OHLC guideline:
25 OH Vitamin D: Screening is medically necessary and covered for patients with the following risk factors for Vitamin D Deficiency:

A. Chronic kidney disease stage III or greater
B. Cirrhosis
C. Hypocalcemia
D. Hypercalcemia
E. Hypercalciuria
F. Hypervitaminosis D
G. Parathyroid disorders
H. Malabsorption states
I. Obstructive jaundice
J. Osteomalacia
K. Osteoporosis if:
    1. T score on DEXA scan <-2/5; **or**
    2. History of fragility fractures; or
    3. FRAX >3% (any fracture) with T-score <-1.5; **or**
    4. Initiating bisphosphonate therapy (vitamin D level should be determined and managed as necessary before bisphosphonate is initiated)
L. Osteosclerosis/petrosis
M. Rickets
N. Vitamin D deficiency on replacement therapy related to a condition listed above; to monitor the efficacy of treatment.

1,25-OH Vitamin D: This is a *more expensive* test, and is only considered medically necessary and covered for patients in the setting of the following conditions:

A. Unexplained hypercalcemia (suspected granulomatous disease or lymphoma)
B. Unexplained hypercalciuria (suspected granulomatous or lymphoma)
C. Suspected genetic childhood rickets
D. Suspected tumor induced osteomalacia
E. Nephrolithiasis or hypercalciuria
F. End stage renal disease

Current Prioritized List Status:

Code	Code Description	Prioritized List Placement	Fee Schedule
82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed	Diagnostic Procedures File	23.02
82652	Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed	Diagnostic Procedures File	29.95

OHP utilization. Paid CPT only

Procedure Code	Procedure Description	Claim Indicator	Cnt
82306	Vitamin D 25 Hydroxy	CCO	85,253
82306	Vitamin D 25 Hydroxy	FFS	12,212
82652	Vit D 1 25-Dihydroxy	CCO	2,219
82652	Vit D 1 25-Dihydroxy	FFS	199

At OHP fee-for-service rates:
Vitamin D 25 hydroxy expenditures = (85253 +12212)*23.02 = **$2,243,644**
Vitamin D 1,25 dihydroxy expenditures = (2219+199)*29.95 = **$72,419**

Many of the primary diagnoses with which the blood tests are paired appearing to be for screening purposes, for example:

- Encntr for general adult medical exam w/o abnormal findings
- Encntr screen for dis of the bld/bld-form org/immun mechnsm
- Encntr for routine child health exam w/o abnormal findings
- Encounter for general adult medical exam w abnormal findings
- Encounter for screening for lipoid disorders
- Essential (primary) hypertension

Evidence review

USPSTF, 2014 https://www.ncbi.nlm.nih.gov/books/NBK263419/

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.

"I" recommendation

USPSTF, 2018

Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: Preventive Medication

https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/vitamin-d-calcium-or-combined-supplementation-for-the-primary-prevention-of-fractures-in-adults-preventive-medication

Population	Recommendation	Grade
Men and premenopausal women	The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in men and premenopausal women.	I
Postmenopausal women	The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.	I
Postmenopausal women	The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.	D

USPSTF, 2018
https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/falls-prevention-in-older-adults-interventions1

Population	Recommendation	Grade
Adults 65 years or older	The USPSTF recommends against vitamin D supplementation to prevent falls in community-dwelling adults 65 years or older.	D

Recommendations from professional societies

American Society of Clinical Pathology (ASCP), 2013
http://www.choosingwisely.org/clinician-lists/american-society-clinical-pathology-population-based-screening-for-vitamin-d-deficiency/

Don't perform population based screening for 25-OH-Vitamin D deficiency.

Vitamin D deficiency is common in many populations, particularly in patients at higher latitudes, during winter months and in those with limited sun exposure. Over the counter Vitamin D supplements and increased summer sun exposure are sufficient for most otherwise healthy patients. Laboratory testing is appropriate in higher risk patients

when results will be used to institute more aggressive therapy (e.g., osteoporosis, chronic kidney disease, malabsorption, some infections, obese individuals).

Endocrine Society, 2013
https://www.choosingwisely.org/clinician-lists/endocrine-society-vitamin-d-testing/

Don't routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function.

Holick, 2011, Endocrine Society clinical practice guideline.
https://academic.oup.com/jcem/article/96/7/1911/2833671

1.1 We recommend screening for vitamin D deficiency in individuals at risk for deficiency. We do not recommend population screening for vitamin D deficiency in individuals who are not at risk (1|⊕⊕⊕⊕).

1.2 We recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter). We recommend against using the serum 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] assay for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism (1|⊕⊕⊕⊕).

4.1 We recommend prescribing vitamin D supplementation for fall prevention. We do not recommend prescribing vitamin D supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (2|⊕⊕⊕⊕).

Other Payer Policies
CMS LCD, 2018 Revision
https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34051&ver=27&Date=&DocID=L34051&bc=iAAAABAAAAAA&
Indications:

Measurement of 25-OH Vitamin D, CPT 82306, level is indicated for patients with:

- chronic kidney disease stage III or greater
- cirrhosis
- hypocalcemia
- hypercalcemia
- hypercalciuria
- hypervitaminosis D

- parathyroid disorders
- malabsorption states
- obstructive jaundice
- osteomalacia
- osteoporosis if

  i. T score on DEXA scan <-2.5 or
  ii. History of fragility fractures or
  iii. FRAX > 3% 10-year probability of hip fracture or 20% 10-year probability of other major osteoporotic fracture or
  iv. FRAX > 3% (any fracture) with T-score <-1.5 or
  v. Initiating bisphosphanate therapy (Vit D level should be determined and managed as necessary *before* bisphosphonate is initiated)

- osteosclerosis/petrosis
- rickets
- vitamin D deficiency on replacement therapy related to a condition listed above; to monitor the efficacy of treatment.

Measurement of 1, 25-OH Vitamin D, CPT 82652, level is indicated for patients with:

- unexplained hypercalcemia (suspected granulomatous disease or lymphoma)
- unexplained hypercalciuria (suspected granulomatous disease or lymphoma)
- suspected genetic childhood rickets
- suspected tumor-induced osteomalacia
- nephrolithiasis or hypercalciuria

Limitations:

Testing may not be used for routine or other screening.

Both assays of vitamin D need not be performed for each of the above conditions. Often, one type is more appropriate for a certain disease state than another. The most common type of vitamin D deficiency is 25-OH vitamin D. A much smaller percentage of 1,25-dihydroxy vitamin D deficiency exists; mostly, in those with renal disease. Although it is not the active form of the hormone, 25-OH vitamin D is much more commonly measured because it better reflects the sum total of vitamin D produced endogenously and absorbed from the diet than does the level of the active hormone 1, 25 -dihydroxy vitamin D. Deficiency of 1,25-dihydroxy vitamin D, which is present at much lower concentrations, does not necessarily reflect deficiency of 25-OH vitamin D and its measurement should be limited to the indications listed. Documentation must justify the test(s) chosen for a particular disease entity. Various component sources of 25-OH vitamin D, such as stored D or diet-derived D, should not be billed separately.

Once a beneficiary has been shown to be vitamin D deficient, further testing may be

medically necessary only to ensure adequate replacement has been accomplished. If Vitamin D level is between 20 and 50 ng/dl and patient is clinically stable, repeat testing is often unnecessary; if performed, documentation most clearly indicate the necessity of the test. If level <20 ng/dl or > 60 ng/dl, a subsequent level(s) may be reimbursed until the level is within the normal range.

HERC Staff Summary

USPSTF has found insufficient evidence for vitamin D screening and has recommended against vitamin D supplementation for fall prevention and for fracture prevention. The Oregon Health Leadership Council is working on a coordinated effort to improve appropriate utilization of vitamin D testing in Oregon across payers. There appears to be significant use of vitamin D testing in the OHP population, with a proportion of it for screening purposes which is not supported by the evidence.

HERC Staff Recommendations:

1) Advise HSD to remove 82306 *Vitamin D; 25 hydroxy* and **82652** *Vitamin D; 1, 25 dihydroxy***, from the Diagnostic File**

2) Add 82306 to the following lines:

- 24 ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN
- 55 COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS
- 102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS
- 117 NUTRITIONAL DEFICIENCIES
- 151 DISORDERS OF MINERAL METABOLISM, OTHER THAN CALCIUM
- 195 ACUTE PANCREATITIS
- 224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM
- 227 INTESTINAL MALABSORPTION
- 239 SHORT BOWEL SYNDROME - AGE 5 OR UNDER
- 248 METABOLIC BONE DISEASE
- 250 CHRONIC PANCREATITIS
- 259 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
- 288 OSTEOPETROSIS
- 293 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER
- 307 CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE
- 334 ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER
- 339 CHRONIC KIDNEY DISEASE

- 352 URINARY SYSTEM CALCULUS

3) Add 82652 *Vitamin D; 1, 25 dihydroxy* to the following lines

- 224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM
- 151 DISORDERS OF MINERAL METABOLISM, OTHER THAN CALCIUM
- 248 METABOLIC BONE DISEASE
- 352 URINARY SYSTEM CALCULUS

3) **Add R82.994** Hypercalciuria (currently in the Diagnostic Workup File) to Lines 224 and 352

Fetal Repair of Myelomeningocele

Question: Should fetal repair of myelomeningocele be added to the Prioritized List?

Question source: HSD Hearings Division

Issue: HSD Hearings recently had a case in which a patient with a fetus with myelomeningocele requested fetal repair. The HCPCS code S2404 (Repair, myelomeningocele in the fetus, procedure performed in utero) is not listed on the Prioritized List, and the surgery is not included in Guideline Note 2, Fetoscopic Surgery. Several other HCPCS codes for fetal repair of congenital conditions are included on line 1 PREGNANCY and in GN2.

Myelomeningocele is the most severe form of spina bifida, in which the lower portion of the spine is open and the spinal cord and spinal nerves protrude out of the opening. It is frequently accompanied by hydrocephalus and other intracranial abnormalities. It frequently results in bowel and bladder control loss, and partial or complete lower extremity paralysis. The standard treatment for myelomeningocele is to repair the defect shortly after birth.

The Management Of Myelomeningocele Study (MOMS) study, published in 2011, established fetal repair of myelomeningocele as a viable alternative option for treatment of myelomeningocele. However, this surgery is only offered at a few centers in the US and carries considerable risk for both mom and baby.

GUIDELINE NOTE 2, FETOSCOPIC SURGERY

Line 1

Fetal surgery is only covered for the following conditions: repair of urinary tract obstructions via placement of a urethral shunt, repair of congenital cystic adenomatoid malformation, repair of extralobal pulmonary sequestration, repair of sacrococcygeal teratoma, and therapy for twin-twin transfusion syndrome.

Fetoscopic repair of urinary tract obstruction (S2401) is only covered for placement of a urethral shunt. Fetal surgery for cystic adenomatoid malformation of the lung, extralobal pulmonary sequestration and sacrococcygeal teratoma must show evidence of developing hydrops fetalis.

Certification of laboratory required (76813-76814).

Evidence

1) **Grivell 2014,** Cochrane review of fetal surgery for spina bifida
    a. N=1 trial of 158 women (MOMS trial—see below)
        i. Low risk of bias
    b. For the primary infant outcome of neonatal mortality, there was no clear evidence of a difference identified for prenatal versus postnatal repair (one study, 158 infants, risk ratio (RR) 0.51, 95%confidence interval (CI) 0.05 to 5.54), however event rates were uncommon and so the analysis is likely to be underpowered to detect differences.
    c. Prenatal repair was associated with an earlier gestational age at birth (one study, 158 infants, mean difference (MD) -3.20 weeks, 95% CI -3.93 to -2.47) and a corresponding increase in both the risk of preterm birth before 37 weeks (one study, 158 infants, RR 5.30, 95% CI 3.11 to 9.04) and preterm birth before 34 weeks (one study, 158 infants, RR 9.23, 95% CI 3.45 to 24.71). Prenatal repair was associated with a reduction in shunt dependent hydrocephalus and moderate to severe hindbrain herniation. For women, prenatal repair was associated with increased preterm ruptured membranes (one study, 158 women, RR 6.15, 95% CI 2.75 to 13.78), although there was no clear evidence of difference in the risk of chorioamnionitis or blood transfusion, although again, event rates were uncommon.
    d. A number of this review's secondary infant and maternal outcomes were not reported. For the infant: days of hospital admission; survival to discharge; stillbirth; need for further surgery (e.g. skin grafting); neurogenic bladder dysfunction; childhood/infant quality of life. For the mother: admission to intensive care; women's emotional wellbeing and satisfaction with care.
    e. **Authors' conclusions:** This review is based on one small well-conducted study. There is insufficient evidence to recommend drawing firm conclusions on the benefits or harms of prenatal repair as an intervention for fetuses with spina bifida. Current evidence is limited by the small number of pregnancies that have been included in the single conducted randomized trial to date.

1) **Adzick 2011**, MOMS trial
    a. N=158 patients
        i. trial was stopped for efficacy of prenatal surgery after the recruitment of 183 of a planned 200 patients.
        ii. This paper reports on the 158 patients with a child evaluation of 12 months
        iii. Inclusion criteria: singleton gestation, myelomeningocele with an upper boundary between T1 and S1, evidence of hindbrain herniation of fetal MRI, gestation age between 19 0/7 weeks and 25 6/7 weeks at randomization, normal karyotype
        iv. Exclusion criteria: fetal anomalies unrelated to the myelomeningocele, risk of preterm birth, placental abruption, contraindication to surgery, and a maternal body mass index of 35 or more
    b. There were 2 perinatal deaths in each group
    c. Need for cerebrospinal fluid shunt by 12 months occurred in 68% of the infants in the prenatal-surgery group and in 98% of those in the postnatal surgery group (relative risk, 0.70; 97.7% confidence interval [CI], 0.58 to 0.84; P<0.001). Actual rates of shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group (relative risk, 0.48; 97.7% CI, 0.36 to 0.64; P<0.001).
    d. At 12 months of age, the proportion of infants who had no evidence of hindbrain herniation was higher in the prenatal-surgery group (36%) than in the postnatal-surgery

group (4%). Similarly, at 12 months, the prenatal-surgery group had a lower rate of moderate or severe hindbrain herniation (25%) than the postnatal-surgery group (67%), as well as lower rates of brain-stem kinking, abnormal fourth-ventricle location, and syringomyelia

e. Infants in the prenatal-surgery group underwent more procedures for delayed spinal cord tethering
f. Prenatal surgery resulted in improvement in the composite score for mental development and motor function at 30 months (P = 0.007) and in improvement in several secondary outcomes, including hindbrain herniation by 12 months and ambulation by 30 months.
g. However, prenatal surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery.
h. Conclusions Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks.

2) **Johnson 2016**, MOMS study complications
    a. N=183 women (91 prenatal, 92 postnatal surgery)
    b. prenatal surgery was associated with an increased risk for membrane separation, oligohydramnios, spontaneous membrane rupture, spontaneous onset of labor, and earlier gestational age at birth.
    c. Gestational age at birth was significantly lower in the fetal surgery group (34.0 vs 37.3 weeks, P<0.001). Overall, 74 (81.3%) in the fetal surgery group were preterm vs 11 (11.9%) in the post natal surgery group.
        i. Risk of deliver at <30 weeks was significantly greater in the fetal surgery group (10 vs 0, P<0.001)
    a. CONCLUSION: Despite the confirmed benefits of prenatal surgery, considerable maternal and fetal risk exists compared with postnatal repair. Early gestational age at surgery and development of chorioamniotic membrane separation are risk factors for ruptured membranes. Oligohydramnios is a risk factor for preterm delivery and nulliparity is a risk factor for nonintact hysterotomy at delivery.
3) **Farmer 2018**, maternal and fetal/infant outcomes at 30 months for entire MOMS cohort
    a. N=183 maternal/fetal pairs
    b. prenatal repair improves the primary outcome composite score of mental development and motor function (199.4 ± 80.5 vs 166.7 ± 76.7,P=.004). Prenatal surgery also resulted in improvement in the secondary outcomes of independent ambulation (44.8% vs 23.9%, P = .004), WeeFIM self-care score (20.8 vs 19.0, P = .006), functional level at least 2 better than anatomic level (26.4% vs 11.4%, P=.02), and mean Bayley Scales of Infant Development, Second Edition, psychomotor development index (17.3% vs 15.1%, P = .03), but does not affect cognitive development at 30 months.
    c. CONCLUSION: The full cohort data of 30-month cognitive development and motor function outcomes validate in utero surgical repair as an effective treatment for fetuses with myelomeningocele. Current data suggest that outcomes related to the need for shunting should be counseled separately from the outcomes related to distal neurologic functioning.

Fetal Repair of Myelomeningocele

Expert guidelines

1) **ACOG 2017**, committee opinion on fetal surgery for myelomeningocele
    a. ACOG and the Society for Maternal-Fetal Medicine make the following recommendations:
        i. Open maternal-fetal surgery for myelomeningocele repair has been demonstrated to improve a number of important pediatric outcomes at the expense of procedure-associated maternal and fetal risks
        ii. Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in nondirective fashion regarding all management options, including the possibility of open maternal-fetal surgery
        iii. Interested candidates for fetal myelomeningocele repair should be referred for further assessment and consultation to a fetal therapy center that offers this intervention and possesses the expertise, multi-disciplinary team, services, and facilities to provide detailed information regarding maternal-fetal surgery and the intensive care required for patients who choose to undergo open maternal-fetal surgery

Other payer policies

1) Aetna 2019 and United Health Care 2019 cover fetal repair of myelomeningocele

Expert input

Mark Tomlinson, Maternal Fetal Medicine and Director of Obstetrics for Providence

> There are fetal benefits to in utero myelomeningocele repair and I would recommend coverage. These [patients] require a lot of counseling though because of the maternal morbidity associated with the uterine scar. This is particularly important for young mothers who plan future children. The rate of rupture in subsequent pregnancies is significant, 10-30% depending on definitions used. There is an article presented at the annual meeting in [February] and recently published in the AJOG in the last couple of months looking at a registry of maternal outcomes suggesting a risk of rupture at the lower end of the range. There are some groups doing the surgery fetoscopically, but currently that is controversial. It decreases adverse maternal outcomes, however the fetal outcomes are uncertain at this time.

Fetal Repair of Myelomeningocele

HERC staff summary

Fetal repair of myelomeningocele improves infant outcomes, based on one good quality RCT. However, there are significant risks to both mother and baby. ACOG recommends that fetal repair be offered as one option to women with a fetus affected by myelomeningocele who meet the inclusion criteria to the MOMS trial. Cochrane cautions that the evidence base for this procedure includes only 1 trial conducted at highly specialized centers. Our expert consultant also recommends coverage for patients who have been appropriately counseled.

HERC staff recommendations

1) Add HCPCS S2404 (Repair, myelomeningocele in the fetus, procedure performed in utero) to line 1 PREGNANCY
2) Modify GN2 as shown below

GUIDELINE NOTE 2, ~~FETOSCOPIC~~ FETAL SURGERY

Line 1

Fetal surgery is only covered for the following conditions: repair of urinary tract obstructions via placement of a urethral shunt, repair of congenital cystic adenomatoid malformation, repair of extralobal pulmonary sequestration, repair of sacrococcygeal teratoma, ~~and~~ therapy for twin-twin transfusion syndrome, and repair of myelomeningocele.

Fetoscopic repair of urinary tract obstruction (S2401) is only covered for placement of a urethral shunt. Fetal surgery for cystic adenomatoid malformation of the lung, extralobal pulmonary sequestration and sacrococcygeal teratoma must show evidence of developing hydrops fetalis.

Certification of laboratory required (76813-76814).

Prenatal versus postnatal repair procedures for spina bifida for improving infant and maternal outcomes (Review)

Grivell RM, Andersen C, Dodd JM

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WILEY

[Intervention Review]

Prenatal versus postnatal repair procedures for spina bifida for improving infant and maternal outcomes

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ABSTRACT

Background

Spina bifida is a fetal neural tube defect (NTD), which may be diagnosed in utero and is compatible with life postnatally, albeit often with significant disability and morbidity. Although postnatal repair is possible, with increasing in utero diagnosis with ultrasound, the condition has been treated during pregnancy (prenatal repair) with the aim of decreased morbidity for the child. The procedure that is performed during pregnancy does have potential morbidities for the mother, as it involves maternal surgery to access the fetus.

Objectives

To compare the effects of prenatal versus postnatal repair and different types of repair of spina bifida on perinatal mortality and morbidity, longer term infant outcomes and maternal morbidity.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 July 2014).

Selection criteria

All published, unpublished, and ongoing randomised controlled trials comparing prenatal and postnatal repair of meningomyelocele for fetuses with spina bifida and different types of prenatal repair.

Data collection and analysis

Two review authors independently evaluated trials for inclusion and methodological quality without consideration of their results according to the stated eligibility criteria and extracted data.

Main results

Our search strategy identified six reports for potential inclusion. Of those, we included one trial (four reports) involving 158 women, which was at low risk of bias.

The one included trial examined the effect of prenatal repair versus postnatal repair. For the primary infant outcome of neonatal mortality, there was no clear evidence of a difference identified for prenatal versus postnatal repair (one study, 158 infants, risk ratio (RR) 0.51, 95% confidence interval (CI) 0.05 to 5.54), however event rates were uncommon and so the analysis is likely to be underpowered to detect differences.

Prenatal repair was associated with an earlier gestational age at birth (one study, 158 infants, mean difference (MD) -3.20 weeks, 95% CI -3.93 to -2.47) and a corresponding increase in both the risk of preterm birth before 37 weeks (one study, 158 infants, RR 5.30, 95% CI 3.11 to 9.04) and preterm birth before 34 weeks (one study, 158 infants, RR 9.23, 95% CI 3.45 to 24.71). Prenatal repair was associated with a reduction in shunt dependent hydrocephalus and moderate to severe hindbrain herniation. For women, prenatal repair was associated with increased preterm ruptured membranes (one study, 158 women, RR 6.15, 95% CI 2.75 to 13.78), although there was no clear evidence of difference in the risk of chorioamnionitis or blood transfusion, although again, event rates were uncommon.

A number of this review's secondary infant and maternal outcomes were not reported. For the infant: days of hospital admission; survival to discharge; stillbirth; need for further surgery (e.g. skin grafting); neurogenic bladder dysfunction; childhood/infant quality of life. For the mother: admission to intensive care; women's emotional wellbeing and satisfaction with care.

Authors' conclusions

This review is based one small well-conducted study. There is insufficient evidence to recommend drawing firm conclusions on the benefits or harms of prenatal repair as an intervention for fetuses with spina bifida. Current evidence is limited by the small number of pregnancies that have been included in the single conducted randomised trial to date.

PLAIN LANGUAGE SUMMARY

Spina bifida repair and infant and maternal health

Spina bifida is the term used to describe a group of neural tube conditions where the fetal spinal cord does not close properly during the first month of pregnancy. With open spina bifida some of the vertebrae are not completely formed but are split or divided and the spinal cord and its coverings (the meninges) protrude through the opening. The most severe is where the spinal cord and meninges come out of the child's back (myelomeningocele). Open spina bifida is often associated with hindbrain herniation, where the cerebellum and brainstem tissue extend into the large opening in the base of the skull, and hydrocephalus (enlargement of the fluid filled cavities in the brain). Resulting disabilities include bladder and bowel incontinence, difficulties in moving about due to limb weakness, paralysis, deformity and loss of sensation. Conventional treatment of spina bifida is surgical repair within two days of birth, which may include the placement of a shunt between the ventricles of the baby's brain and the belly (peritoneum) to relieve hydrocephalus. Spina bifida can be diagnosed with prenatal ultrasound or maternal serum alpha-feto protein and in utero treatment could improve outcomes; although it involves surgical incision into the mother's abdomen and uterus to access the unborn baby.

This review aimed to compare the effects of in utero repair versus repair as a newborn. We included one randomised controlled trial involving 158 women who were from 19 to 27 weeks pregnant with a baby with severe spina bifida and evidence of hindbrain herniation. For neonatal mortality, there was no clear difference identified for prenatal versus postnatal repair. However, the numbers of neonates who died were low and so the review was likely underpowered to detect any difference. Prenatal repair was associated with reduced need for shunt placement and a reduction in the risk of moderate to severe hindbrain herniation after birth. No direct complications of the repair procedure were evident, including orthopaedic deformities. Prenatal repair was associated with an increased risk of the women experiencing preterm ruptured membranes and subsequent preterm birth (both before 34 and 37 weeks). Severe maternal illness (infection and need for blood transfusion) were not clearly different; although the review was underpowered to detect any difference in these important, less common outcomes. The included trial was of high quality (low risk of bias) but included a small number of pregnancies. There is currently insufficient evidence to recommend in utero repair for unborn babies with spina bifida.

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A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele

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ABSTRACT

BACKGROUND

Prenatal repair of myelomeningocele, the most common form of spina bifida, may result in better neurologic function than repair deferred until after delivery. We compared outcomes of in utero repair with standard postnatal repair.

METHODS

We randomly assigned eligible women to undergo either prenatal surgery before 26 weeks of gestation or standard postnatal repair. One primary outcome was a composite of fetal or neonatal death or the need for placement of a cerebrospinal fluid shunt by the age of 12 months. Another primary outcome at 30 months was a composite of mental development and motor function.

RESULTS

The trial was stopped for efficacy of prenatal surgery after the recruitment of 183 of a planned 200 patients. This report is based on results in 158 patients whose children were evaluated at 12 months. The first primary outcome occurred in 68% of the infants in the prenatal-surgery group and in 98% of those in the postnatal-surgery group (relative risk, 0.70; 97.7% confidence interval [CI], 0.58 to 0.84; P<0.001). Actual rates of shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group (relative risk, 0.48; 97.7% CI, 0.36 to 0.64; P<0.001). Prenatal surgery also resulted in improvement in the composite score for mental development and motor function at 30 months (P=0.007) and in improvement in several secondary outcomes, including hindbrain herniation by 12 months and ambulation by 30 months. However, prenatal surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery.

CONCLUSIONS

Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT00060606.)

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* Additional investigators in the Management of Myelomeningocele Study (MOMS) are listed in the Supplementary Appendix, available at NEJM.org.

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OBSTETRICS

The Management of Myelomeningocele Study: obstetrical outcomes and risk factors for obstetrical complications following prenatal surgery

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BACKGROUND: The Management of Myelomeningocele Study was a multicenter randomized trial to compare prenatal and standard postnatal closure of myelomeningocele. The trial was stopped early at recommendation of the data and safety monitoring committee and outcome data for 158 of the 183 randomized women published.

OBJECTIVE: In this report, pregnancy outcomes for the complete trial cohort are presented. We also sought to analyze risk factors for adverse pregnancy outcome among those women who underwent prenatal myelomeningocele repair.

STUDY DESIGN: Pregnancy outcomes were compared between the 2 surgery groups. For women who underwent prenatal surgery, antecedent demographic, surgical, and pregnancy complication risk factors were evaluated for the following outcomes: premature spontaneous membrane rupture ≤34 weeks 0 days (preterm premature rupture of membranes), spontaneous membrane rupture at any gestational age, preterm delivery at ≤34 weeks 0 days, nonintact hysterotomy (minimal uterine wall tissue between fetal membranes and uterine serosa, or partial or complete dehiscence at delivery), and chorioamniotic membrane separation. Risk factors were evaluated using χ^2 and Wilcoxon tests and multivariable logistic regression.

RESULTS: A total of 183 women were randomized: 91 to prenatal and 92 to postnatal surgery groups. Analysis of the complete cohort confirmed initial findings: that prenatal surgery was associated with an increased risk for membrane separation, oligohydramnios, spontaneous membrane rupture, spontaneous onset of labor, and earlier gestational age at birth. In multivariable logistic regression of the prenatal surgery group adjusting for clinical center, earlier gestational age at surgery and chorioamniotic membrane separation were associated with increased risk of spontaneous membrane rupture (odds ratio, 1.49; 95% confidence interval, 1.01—2.22; and odds ratio, 2.96, 95% confidence interval, 1.05—8.35, respectively). Oligohydramnios was associated with an increased risk of subsequent preterm delivery (odds ratio, 9.21; 95% confidence interval, 2.19—38.78). Nulliparity was a risk factor for nonintact hysterotomy (odds ratio, 3.68; 95% confidence interval, 1.35—10.05).

CONCLUSION: Despite the confirmed benefits of prenatal surgery, considerable maternal and fetal risk exists compared with postnatal repair. Early gestational age at surgery and development of chorioamniotic membrane separation are risk factors for ruptured membranes. Oligohydramnios is a risk factor for preterm delivery and nulliparity is a risk factor for nonintact hysterotomy at delivery.

Key words: fetal myelomeningocele, fetal spina bifida, fetal therapy, prenatal surgery

Introduction

The National Institutes of Health-sponsored Management of Myelomeningocele Study (MOMS) was initiated in 2003 to compare the safety and efficacy of prenatal repair of myelomeningocele with that of standard postnatal repair. The trial was stopped in 2010 before reaching the target sample size, at the recommendation of its data and safety monitoring committee according to prespecified stopping rules for the efficacy of prenatal surgery. Results of the trial were reported[1] based on 158 women who had undergone randomization before July 1, 2009, as this was the cohort analyzed for the data and safety monitoring committee. Findings in that report demonstrated a significant improvement in the primary outcomes at 12 and 30 months of age, and in multiple secondary outcomes, including reversal of hindbrain herniation and ambulation by 30 months, in the prenatal repair group. However, prenatal surgical intervention was associated with significantly higher rates of oligohydramnios and chorioamniotic separation, as well as spontaneous membrane rupture (SROM) and preterm delivery (PTD) ($P < .001$). Moreover, of those in the prenatal surgery group, only 64% had an intact, well-healed hysterotomy site from the prenatal repair surgery observed at cesarean delivery.

The initial MOMS report summarized the pregnancy outcomes of 86% of the 183 randomized women. The primary objective of the current report is to update the final pregnancy outcome results from the MOMS trial, as well as to analyze risk factors for preterm premature rupture of membranes (PPROM), SROM at any gestation, early preterm delivery (PTD), and uterine dehiscence among those women who underwent prenatal repair. It is the authors' view that these additional components are anticipated to enhance the knowledge of benefits, risk assessment, and informed consent process for future families considering fetal myelomeningocele repair, where maternal and fetal characteristics match those set forth in the inclusion and exclusion criteria of the trial.

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0002-9378/$36.00

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OBSTETRICS

The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes

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BACKGROUND: Previous reports from the Management of Myelomeningocele Study demonstrated that prenatal repair of myelomeningocele reduces hindbrain herniation and the need for cerebrospinal fluid shunting, and improves motor function in children with myelomeningocele. The trial was stopped for efficacy after 183 patients were randomized, but 30-month outcomes were only available at the time of initial publication in 134 mother-child dyads. Data from the complete cohort for the 30-month outcomes are presented here. Maternal and 12-month neurodevelopmental outcomes for the full cohort were reported previously.

OBJECTIVE: The purpose of this study is to report the 30-month outcomes for the full cohort of patients randomized to either prenatal or postnatal repair of myelomeningocele in the original Management of Myelomeningocele Study.

STUDY DESIGN: Eligible women were randomly assigned to undergo standard postnatal repair or prenatal repair <26 weeks gestation. We evaluated a composite of mental development and motor function outcome at 30 months for all enrolled patients as well as independent ambulation and the Bayley Scales of Infant Development, Second Edition. We assessed whether there was a differential effect of prenatal surgery in subgroups defined by: fetal leg movements, ventricle size, presence of hindbrain herniation, gender, and location of the myelomeningocele lesion. Within the prenatal surgery group only, we evaluated these and other baseline parameters as predictors of 30-month motor and cognitive outcomes. We evaluated whether presence or absence of a shunt at 1 year was associated with 30-month motor outcomes.

RESULTS: The data for the full cohort of 183 patients corroborate the original findings of Management of Myelomeningocele Study, confirming that prenatal repair improves the primary outcome composite score of mental development and motor function (199.4 ± 80.5 vs 166.7 ± 76.7, $P = .004$). Prenatal surgery also resulted in improvement in the secondary outcomes of independent ambulation (44.8% vs 23.9%, $P = .004$), WeeFIM self-care score (20.8 vs 19.0, $P = .006$), functional level at least 2 better than anatomic level (26.4% vs 11.4%, $P = .02$), and mean Bayley Scales of Infant Development, Second Edition, psychomotor development index (17.3% vs 15.1%, $P = .03$), but does not affect cognitive development at 30 months. On subgroup analysis, there was a nominally significant interaction between gender and surgery, with boys demonstrating better improvement in functional level and psychomotor development index. For patients receiving prenatal surgery, the presence of in utero ankle, knee, and hip movement, absence of a sac over the lesion and a myelomeningocele lesion of ≤L3 were significantly associated with independent ambulation. Postnatal motor function showed no correlation with either prenatal ventricular size or postnatal shunt placement.

CONCLUSION: The full cohort data of 30-month cognitive development and motor function outcomes validate in utero surgical repair as an effective treatment for fetuses with myelomeningocele. Current data suggest that outcomes related to the need for shunting should be counseled separately from the outcomes related to distal neurologic functioning.

Key words: ankle, knee, and hip movement, fetal surgery, long-term follow-up, Management of Myelomeningocele Study, motor outcomes, myelomeningocele, postnatal motor function, shunt, ventricular size, ventriculomegaly

Introduction

Myelomeningocele (MMC) is a life-altering birth defect resulting from incomplete closure of the neural tube during the fourth week of gestation. The exposed spinal cord sustains intrauterine trauma, leaving children with lifelong paralysis, incontinence, and cognitive disabilities. MMC is a devastating disease for patients and families, not only physically and psychologically, but also financially: MMC health costs are 13 times greater than those of unaffected children.[1,2]

With the improvement of prenatal diagnostics and prenatal surgical techniques, surgeons began to repair the lesion before birth with the hope of preventing in utero spinal cord trauma. Preliminary studies indicated that prenatal intervention resulted in more desirable outcomes than postnatal repair.[3-7]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Management of Myelomeningocele Study (MOMS) compared prenatal closure of the MMC defect with postnatal repair in a multicenter randomized trial. MOMS was stopped for efficacy after recruitment of 183 patients from a planned sample size of 200. The original article reported 30-month neurodevelopmental, self-care, and mobility outcomes from 134 of those patients.[8] Initial publication demonstrated that prenatal repair of the MMC defect decreased hindbrain herniation, decreased the need for cerebrospinal fluid (CSF) shunting, and improved distal neurologic function.[8] The full cohort data on maternal outcomes and the reduced need for CSF shunting have been previously published.[9,10] Urologic outcomes at 30

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The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

ACOG COMMITTEE OPINION

Number 720 • September 2017

(Replaces Committee Opinion Number 550, January 2013)

Committee on Obstetric Practice
Society for Maternal–Fetal Medicine

The North American Fetal Therapy Network endorses this document. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee member Russell S. Miller, MD, and the Society for Maternal–Fetal Medicine in collaboration with member Jeffrey A. Kuller, MD.

Maternal–Fetal Surgery for Myelomeningocele

ABSTRACT: Myelomeningocele, a severe form of spina bifida, occurs in approximately 1 in 3,000 live births in the United States. The extent of disability is generally related to the level of the myelomeningocele defect, with a higher upper level of lesion generally corresponding to greater deficits. Open maternal–fetal surgery for myelomeningocele repair is a major procedure for the woman and her affected fetus. Although there is demonstrated potential for fetal and pediatric benefit, there are significant maternal implications and complications that may occur acutely, postoperatively, for the duration of the pregnancy, and in subsequent pregnancies. Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in a nondirective fashion regarding all management options, including the possibility of open maternal–fetal surgery. Maternal–fetal surgery for myelomeningocele repair should be offered only to carefully selected patients at facilities with an appropriate level of personnel and resources.

Recommendations

The American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine make the following recommendations:

- Open maternal–fetal surgery for myelomeningocele repair has been demonstrated to improve a number of important pediatric outcomes at the expense of procedure-associated maternal and fetal risks.
- Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in nondirective fashion regarding all management options, including the possibility of open maternal–fetal surgery.
- Interested candidates for fetal myelomeningocele repair should be referred for further assessment and consultation to a fetal therapy center that offers this intervention and possesses the expertise, multidisciplinary team, services, and facilities to provide detailed information regarding maternal–fetal surgery and the intensive care required for patients who choose to undergo open maternal–fetal surgery.

Introduction

Myelomeningocele, a severe form of spina bifida, occurs in approximately 1 in 3,000 live births in the United States (1) and is complicated by hydrocephalus, need for ventriculoperitoneal shunt placement, motor and cognitive defects, bowel and bladder dysfunction, and social and emotional challenges. The extent of disability generally is related to the level of the myelomeningocele defect, with a higher upper level of lesion generally corresponding to greater deficits. Among newborns prenatally diagnosed with myelomeningocele, lesions are usually surgically repaired in the early neonatal period.

Fetal surgery has historically been considered a heroic intervention reserved for severe fetal presentations in which in utero therapy might favorably alter a natural history expected to result in fetal or neonatal death or severe disability. However, significant maternal and fetal risks prompted concern regarding the appropriateness of such treatments. Although open maternal–fetal surgery was originally limited to life-threatening conditions, it was considered for fetal myelomeningocele repair because results of laboratory and animal studies

iStent Inject for Glaucoma with Cataract Removal

Question: Should iStent Inject (CPT 0376T) be added to the Prioritized List for treatment of glaucoma?

Question source: Glaukos

Issue: In October and November, 2018, iStent (CPT 0191T) was added to the open angle glaucoma line with a new guideline restricting use to concurrent cataract removal. Glaukos, the manufacturer of iStent has requested that the HERC consider their newly FDA approved product, iStent Inject. Per the manufacturer materials, iStent inject has two channels, rather than the one channel in iStent and is designed to work in either eye (iStent is eye specific). It is also smaller than the iStent.

Per the FDA memo from June, 2018, "This device is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma."

IStent uses CPT 0191T (Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; initial insertion) while iStent Inject uses CPT 0376T (Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; each additional device insertion).

From Glaukos:

> On behalf of Glaukos, your contracted Ophthalmic Surgeons, and patients in Oregon with Mild to Moderate Open Angle Glaucoma our hope is to provide an update regarding your recent decision to add 0191T to line 139 Glaucoma, Other Than Primary Angle-Closure of the Prioritized Health List, which is effective on 10/1/19. Thank you for the addition of 0191T and our current request is based on the 2018 FDA approval of a second generation stent commercially named iStent Inject. Though relatively new to the market, iStent Inject has received strong commercial acceptance in many Oregon Ophthalmic Surgeon's treatment algorithm and is supported by strong data that is in line with your standards for supporting evidence. We respectfully ask the Commission to consider adding 0376T to support coverage for iStent Inject to line 139 Glaucoma, Other Than Primary Angle-Closure of the Prioritized Health List due to the rapid acceptance of iStent Inject into the marketplace and providing Oregon Medicaid patients access to this advancement in technology.

Other relevant codes:
HCPCS C1783 (Ocular implant, aqueous drainage assist device): never reviewed
HCPCS L8612 (Aqueous shunt): never reviewed

iStent Inject for Glaucoma with Cataract Removal

Evidence

1) **Samuelson 2019**, RCT of iStent Inject vs no stent for glaucoma patients undergoing cataract surgery
    a. Eyes were randomized 3:1 intraoperatively to implantation of iStent inject (Model G2-M-IS; treatment group, n = 387) or no stent implantation (control group, n = 118). Subjects were followed through 2 years postoperatively
    b. At 24 months, 75.8% of treatment eyes versus 61.9% of control eyes experienced ≥20% reduction from baseline in unmedicated DIOP ($P < 0.005$), and mean reduction in unmedicated DIOP from baseline was greater in treatment eyes (7.0 ± 4.0 mmHg) than in control eyes (5.4 ± 3.7 mmHg; $P < 0.001$). Of the responders, 84% of treatment eyes and 67% of control eyes were not receiving ocular hypotensive medication at 23 months.
    c. The overall safety profile of the treatment group was favorable and similar to that in the control group throughout the 2-year follow-up.
    d. Conclusions: Clinically and statistically greater reductions in IOP without medication were achieved after iStent inject implantation with cataract surgery versus cataract surgery alone, with excellent safety through 2 years.
    e. No notation of study funding in paper
1) **Paletta Guedes 2019**, retrospective cohort study of iStent and iStent inject
    a. Funded by Glaukos Corp.
    b. N=73 eyes with open angle glaucoma and cataract (38 iStent, 35 iStent Inject)
    c. At 6 months after surgery, mean IOP had fallen from 16.5 ± 3.9 to 13.9 ± 2.3 mmHg in eyes with the iStent implant ($p<0.001$), and from 17.3 ± 3.0 to 12.7 ± 1.8 mmHg in those with the iStent inject implant ($p<0.001$). This reduction was significantly greater in the iStent inject eyes than in the iStent eyes (26.6 vs. 15.8%) ($p = 0.005$). Significantly more eyes receiving the iStent inject device compared to the iStent device achieved an IOP of <18 mmHg at 6 months post surgery (100 vs. 86.8%) ($p = 0.033$). Average medication usage was reduced from 1.8 to 0.4 medications in iStent eyes ($p<0.001$) and from 2.3 to 0.4 medications in iStent inject eyes ($p<0.001$). Over 70% of eyes in both groups became medication- free by 6 months post implantation.
    d. Adverse events in iStent eyes were mild and resulted in no sequelae; two iStent eyes underwent non-penetrating deep sclerectomy during follow-up. No complications or secondary surgeries were noted in iStent inject eyes.
    e. Conclusion: Significant and safe IOP and medication reductions were observed after iStent or iStent inject implantation with concomitant cataract surgery. Trends toward greater effectiveness and fewer adverse events were observed with the iStent inject device compared with the iStent device

Other payer policies:

1) **Aetna 2019** covers both CPT 0191T and 0376T for glaucoma in conjunction with cataract surgery
    a. Unclear of 0376T refers to a second iStent or to iStent Inject in their policy
    b. Also cover Hydrus Microstent (same CPT codes)

Cost:

1) CPT 0191T: $2680-3640
2) CPT0376T: bundled into other service (presumably 0191T or cataract surgery codes)

HERC staff summary: There is limited literature regarding iStent Inject, but based on the one published RCT comparing iStent Inject to no stent and a cohort study comparing to iStent Inject to iStent, the iStent Inject appears to be equally effective to iStent at reducing intraocular pressure with a similar safety profile.

HERC staff also found that there is more than one product on the market that provides anterior segment aqueous drainage. The CPT code requested for addition (CPT 0376T) can also be used for insertion of a second iStent. There appears to be no additional cost for CPT 0376T at this time.

HERC staff recommendations:

1) Add CPT 0376T (Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; each additional device insertion) to line 139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE
2) Add HCPCS C1783 (Ocular implant, aqueous drainage assist device) and L8612 (Aqueous shunt) to line 139
3) Modify Guideline Note 184 as shown below
    a. Remove brand name as other devices are FDA approved. IStent Inject would be allowable with current guideline wording

GUIDELINE NOTE 184, ANTERIOR SEGMENT AQUEOUS DRAINAGE DEVICE INSERTION

Line 139

Anterior segment aqueous drainage device ~~(e.g. iStent©)~~ insertion is only included on this line when done at the same time as cataract removal and when the two procedures are billed together as a bundled service.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Prospective, Randomized, Controlled Pivotal Trial of an *Ab Interno* Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract

Two-Year Results

Thomas W. Samuelson, MD,[1] Steven R. Sarkisian, Jr., MD,[2] David M. Lubeck, MD,[3] Michael C. Stiles, MD,[4] Yi-Jing Duh, PhD,[5] Eeke A. Romo, DSc,[6] Jane Ellen Giamporcaro, MS,[7] Dana M. Hornbeak, MD, MPH,[7] L. Jay Katz, MD,[7,8] for the iStent inject *Study Group**

Purpose: Evaluate the safety and effectiveness of an *ab interno* implanted (iStent *inject*) Trabecular Micro-Bypass System (Glaukos Corporation, San Clemente, CA) in combination with cataract surgery in subjects with mild to moderate primary open-angle glaucoma (POAG).

Design: Prospective, randomized, single-masked, concurrently controlled, multicenter clinical trial.

Participants: Eyes with mild to moderate POAG and preoperative intraocular pressure (IOP) ≤24 mmHg on 1 to 3 medications, unmedicated diurnal IOP (DIOP) 21 to 36 mmHg, and cataract requiring surgery.

Methods: After uncomplicated cataract surgery, eyes were randomized 3:1 intraoperatively to *ab interno* implantation of iStent *inject* (Model G2-M-IS; treatment group, n = 387) or no stent implantation (control group, n = 118). Subjects were followed through 2 years postoperatively. Annual washout of ocular hypotensive medication was performed.

Main Outcome Measures: Effectiveness end points were ≥20% reduction from baseline in month 24 unmedicated DIOP and change in unmedicated month 24 DIOP from baseline. Safety measures included best spectacle-corrected visual acuity (BSCVA), slit-lamp and fundus examinations, gonioscopy, pachymetry, specular microscopy, visual fields, complications, and adverse events.

Results: The groups were well balanced preoperatively, including medicated IOP (17.5 mmHg in both groups) and unmedicated DIOP (24.8±3.3 mmHg vs. 24.5±3.1 mmHg in the treatment and control groups, respectively, $P = 0.33$). At 24 months, 75.8% of treatment eyes versus 61.9% of control eyes experienced ≥20% reduction from baseline in unmedicated DIOP ($P = 0.005$), and mean reduction in unmedicated DIOP from baseline was greater in treatment eyes (7.0±4.0 mmHg) than in control eyes (5.4±3.7 mmHg; $P < 0.001$). Of the responders, 84% of treatment eyes and 67% of control eyes were not receiving ocular hypotensive medication at 23 months. Furthermore, 63.2% of treatment eyes versus 50.0% of control eyes had month 24 medication-free DIOP ≤18 mmHg (difference 13.2%; 95% confidence interval, 2.9−23.4). The overall safety profile of the treatment group was favorable and similar to that in the control group throughout the 2-year follow-up.

Conclusions: Clinically and statistically greater reductions in IOP without medication were achieved after iStent *inject* implantation with cataract surgery versus cataract surgery alone, with excellent safety through 2 years. *Ophthalmology 2019;126:811-821 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Glaucoma is the leading cause of irreversible blindness worldwide, currently affecting more than 44.7 million people and increasing to 58.6 million by 2020.[1,2] Most therapies target intraocular pressure (IOP) reduction, the only clinically proven method to slow progression of optic nerve damage. Even modest IOP reductions have benefit, as shown by an 11% to 19% decreased disease progression risk for each 1 mmHg IOP reduction.[3,4]

Recently, micro-invasive glaucoma surgery (MIGS) procedures have been shown to provide sustained IOP reduction without the disadvantages of ocular hypotensive medication (e.g., poor compliance, ocular surface disease,

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ORIGINAL RESEARCH

Intermediate Results of iStent or iStent *inject* Implantation Combined with Cataract Surgery in a Real-World Setting: A Longitudinal Retrospective Study

Ricardo Augusto Paletta Guedes · Daniela Marcelo Gravina · Jonathan Clive Lake · Vanessa Maria Paletta Guedes · Alfredo Chaoubah

Received: December 12, 2018 / Published online: February 5, 2019

ABSTRACT

Introduction: In this real-world, retrospective, comparative study we evaluated 6-month performance and safety in consecutive eyes following implantation of the iStent® or iStent *inject*® trabecular micro-bypass device with concomitant cataract surgery.

Methods: Performance outcomes included intraocular pressure (IOP) reduction; glaucoma medication reduction; proportions of eyes achieving an IOP of < 18, < 16, < 14, or < 12 mmHg; and proportions of eyes on 0, 1, 2, or ≥ 3 medications. Safety outcomes included adverse events, secondary surgeries, and best-corrected visual acuity (BCVA).

Results: A total of 73 eyes with open-angle glaucoma and cataract were included in the study; of these, 38 eyes were implanted with the iStent device and 35 were implanted with the iStent *inject* device. The two groups of patients had similar baseline characteristics, with the exception of mean age and medication burden (both higher in patients receiving the iStent *inject* device); over 90% of eyes in both groups had early glaucoma. At 6 months after surgery, mean IOP had fallen from 16.5 ± 3.9 to 13.9 ± 2.3 mmHg in eyes with the iStent implant ($p < 0.001$), and from 17.3 ± 3.0 to 12.7 ± 1.8 mmHg in those with the iStent *inject* implant ($p < 0.001$). This reduction was significantly greater in the iStent *inject* eyes than in the iStent eyes (26.6 vs. 15.8%) ($p = 0.005$). Significantly more eyes receiving the iStent *inject* device compared to the iStent device achieved an IOP of < 18 mmHg at 6 months post surgery (100 vs. 86.8%) ($p = 0.033$). Average medication usage was reduced from 1.8 to 0.4 medications in iStent eyes ($p < 0.001$) and from 2.3 to 0.4 medications in iStent *inject* eyes ($p < 0.001$). Over 70% of eyes in both groups became medication-free by 6 months post implantation. Adverse events in iStent eyes were mild and resulted in no sequelae; two iStent eyes underwent non-penetrating deep sclerectomy during follow-up. No complications or secondary surgeries were noted in iStent *inject* eyes. All eyes in both groups maintained or showed improved BCVA versus baseline.

Conclusion: Significant and safe IOP and medication reductions were observed after iStent or iStent *inject* implantation with concomitant

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cataract surgery. Trends toward greater effectiveness and fewer adverse events were observed with the iStent *inject* device compared with the iStent device.

Funding: Article processing charges were provided by Glaukos Corporation.

Keywords: Cataract; Glaucoma; Intraocular pressure; iStent; iStent *inject*; Microinvasive glaucoma surgery; Second-generation; Stent; Trabecular micro-bypass

INTRODUCTION

The permanent optic nerve damage associated with glaucoma makes it the leading cause of irreversible blindness worldwide. All existing therapies, both medical and surgical, aim to lower intraocular pressure (IOP), which remains the primary risk factor linked to glaucoma progression and visual field decline. Indeed, considerable data support the strong relationship between reduced IOP and reduced glaucoma progression and vision loss [1–4]; this was quantified in the landmark Early Manifest Glaucoma Trial (EMGT) to be approximately 10% decreased risk of glaucoma progression per every 1 mmHg IOP reduction [1].

Historically, the glaucoma treatment landscape has consisted of medications and/or laser trabeculoplasty as initial treatment, while incisional filtering surgeries, such as trabeculectomy, non-penetrating deep sclerectomy, and tube implants, have rounded out the more invasive end of the treatment spectrum [5]. The effectiveness of medications may be limited by local and systemic side effects, poor adherence rates, difficulty with instillation, complex dosing regimens, and ocular surface hypersensitivities [6–10], while the utility of laser trabeculoplasty is curbed by its waning treatment effect over time [11]. Filtering surgeries yield considerable IOP reduction, but carry risks that include hypotony, infection, bleb-related complications, and/or choroidal detachment [12–14]. Over the past two decades, micro-invasive glaucoma surgery (MIGS) has gained an increasing role in glaucoma treatment, and it may be particularly useful in patients whose disease lies between the aforementioned two extremes on the treatment spectrum.

A substantial body of peer-reviewed evidence has been amassed on the iStent implant (Glaukos Corp., San Clemente, CA, USA), which is the first MIGS device to be approved by the U.S. Food and Drug Administration, and its more recent iteration, the iStent *inject* implant (Glaukos Corp.) [15–43]. These studies have demonstrated sizable, durable reductions in IOP and medication burden, combined with favorable safety. Results have been achieved in a variety of clinical settings, including with and without cataract surgery, in mild to severe glaucoma, in primary open-angle glaucoma as well as pseudoexfoliative glaucoma and ocular hypertension, in controlled clinical trials and single-surgeon case series, in comparative and non-comparative studies, and in evaluations of single or multiple stents.

Either the iStent (containing one stent) or iStent *inject* (containing two stents, each with the newer design) devices (Fig. 1) were implanted in the eyes included in the present study. Both devices are designed to decrease IOP by creating a patent pathway for aqueous humor to exit the anterior chamber through the

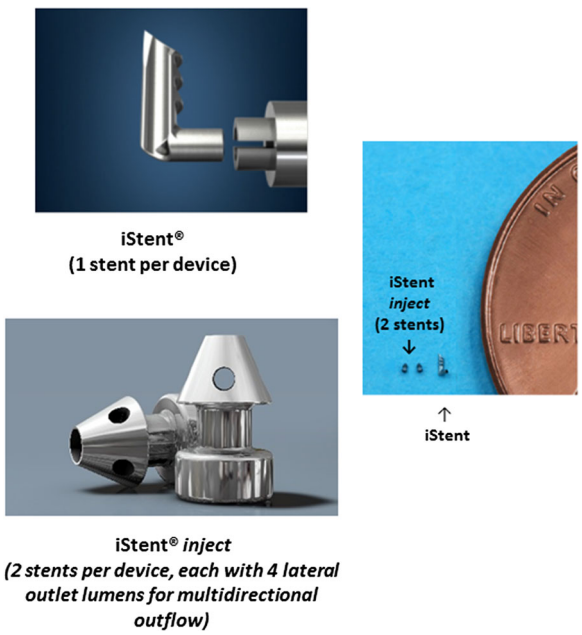

Fig. 1 The iStent® and iStent® *inject* trabecular microbypass stents, with relative dimensions

Spinal Cord Stimulators

Question: Should spinal cord stimulators continue to be included on a covered back surgery line? If so, are there any guidelines or limitations which should apply?

Question source: Multiple CCOs

Issue: Spinal cord stimulation is a technology that can help manage chronic back pain, most commonly used to treat failed back surgery syndrome. The device consists of an electrode connected to a generator. By placing a stimulating electrode over the spinal cord, the pain signal cannot be sent up from the spine to the brain. The stimulation is a very mild electrical pulse that the patient usually does not feel. These electrical pulses mask the pain signal and can be adjusted over the course of the trial to get the greatest improvement in pain. Patients generally have a two week trial before permanent insertion of the spinal cord stimulation system. Trials are considered successful if they can remove half of a patient's pain.

Currently, the CPT codes for placement of spinal cord stimulators are on all three surgical back lines.

This topic was nominated for a coverage guidance; however, the Center for Evidence Based Policy found insufficient evidence for all outcomes (long term pain, function and quality of life) and concluded that the evidence base for this intervention is very poor. HERC staff recommended that this be brought directly to VbBS for discussion.

CODES	DESCRIPTION	
CPT Codes		
63650	Percutaneous implantation of neurostimulator electrode array, epidural	292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS 361 SCOLIOSIS 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural	292,346,361,529
63661	Removal of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed	285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
63662	Removal of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed	285,424
63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed	285,424
63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed	285,424
63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling	292,346,361,529
63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver	285,424
95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by	DIAGNOSTIC PROCEDURES

	physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming	
95971	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (e.g., sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional	DIAGNOSTIC PROCEDURES
HCPCS Level II Codes		
C1767	Generator, neurostimulator (implantable), non-rechargeable	174,249,292,327,346,361,441,455, 538, 529
C1778	Lead, neurostimulator (implantable)	Multiple lines
C1787	Patient programmer, neurostimulator	327,455,528
C1816	Receiver and/or transmitter, neurostimulator (implantable)	174,249,292,346,361,441,529
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system	174,249,292,346,361,441,529
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system	174,249,292,346,361,441,529
C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads	174,249,292,346,361,441,529
C1883	Adapter/extension, pacing lead or neurostimulator lead (implantable)	Ancillary
C1897	Lead, neurostimulator test kit (implantable)	Multiple Lines
L8679	Implantable neurostimulator, pulse generator, any type	327,455,528
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only	327,455,528
L8682	Implantable neurostimulator radiofrequency receiver	327,455,528
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver	327,455,528
L8684	Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement	327,455,528

L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension	327,455,528
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension	327,455,528
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension	327,455,528
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension	327,455,528
L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only	327,455,528
L8695	External recharging system for battery (external) for use with implantable neurostimulator, replacement only	Ancillary

Coding specification for line 292
Spinal cord stimulation (63650-63688) is not included on this line when paired with ICD-10-CM category G90.5 Complex regional pain syndrome/reflex sympathetic dystrophy.

Rationale for the above coding specification: an evidence review by the Health Services Commission from August, 2009 found spinal cord stimulation to be harmful when used for complex regional pain syndrome. This review included 4 Cochrane reviews and 3 systematic reviews that found minimal pain relief and a high (>35%) rate of complications.

Evidence

1) **Mekhail 2018**, systematic review and meta-analysis of spinal cord stimulator RCTs
    a. CEBP rated this review poor quality
    b. N=7 RCTs examining trunk and limb pain (includes failed back surgery syndrome)
    c. there was significant heterogeneity in the specific devices used for SCS, as well as the comparators. Two of the included trials had sham control arms and two had active control arms (one with repeat surgery as the comparator and one with conventional medical management as the comparator). The remaining 3 trials compared one mode of SCS to another mode of SCS.
    d. For pain outcomes, a variety of measures were used across the studies including the visual analog scale (VAS), numeric rating scale (NRS), and the percentage of patients reporting >50% reduction in pain. Because of the heterogeneity of interventions, comparators, and outcomes in this population, the authors report results narratively.
    e. For pain outcomes, all but one of the studies found improvements in a pain measure for patients treated with SCS compared to controls. Two of the studies (one comparing SCS to repeat surgery for FBSS and one comparing SCS to conventional medical management) found that the proportion of patients reporting improvement in pain of >50% increased by approximately 35% to 40% in the SCS groups at 6 months to two years of mean follow-up. The latter study also found that SCS improved VAS scores for back pain (mean improvement of 11 mm) and leg pain (mean improvement of 26.7 mm). One trial with three arms compared Medtronic SCS at 5 kHz to Medtronic SCS at 40 to 50 Hz and to a sham control; this study found no significant differences between the groups in VAS pain scores. A second sham controlled trial of the St Jude burst SCS compared to tonic 500 Hz SCS and to sham control found that burst stimulation resulted in statistically significant decreases in VAS pain scores (2.4 mm for burst SCS vs. tonic SCS and 3.6 for burst SCS vs. sham control).
        i. Mean clinically significant difference for VAS scores is 10-15 mm
    f. Functional and quality of life (QoL) outcomes were more sparsely reported in the included studies. One of the sham controlled studies found no statistically significant differences in the Oswestry disability index (ODI) when comparing St Jude burst stimulation to tonic 500 Hz SCS to sham control. The other sham controlled study did not report functional outcomes. One trial comparing Medtronic SCS to conventional medical management found a mean reduction in ODI of 11.2 favoring SCS. The trial comparing high-frequency 10 kHz stimulation to conventional stimulation found a small improvement in ODI with high-frequency stimulation (mean difference of -3.5), but no statistically significant difference in the Global Assessment of Functioning (GAF) score. Only two of the included studies reported quality of life outcomes. The trial comparing SCS to conventional medical management found significant improvements for SCS treated patients in QoL scores in 7 of 8 SF-36 domains with improvements ranging from 9.5 to 21.8 points. The trial comparing 5 kHz SCS to 40 to 50 Hz SCS to sham control found no differences between the groups in QoL as assessed by the EuroQoL-5D instrument.
    g. The authors note that while none of the included trials had pre-specified outcomes related to analgesic use, four studies reported on this outcome. While the studies comparing SCS to repeat operation and laminectomy electrodes to percutaneous

electrodes found reductions in analgesic use with SCS and laminectomy electrodes, the remaining two trials (SCS vs. conventional medical management and 5 kHz SCS vs. 40 to 50 Hz SCS vs. sham control) found no statistically significant differences in opioid use.

h. Overall, the authors conclude that there is "moderately strong" evidence of that SCS improves pain, function, and patient satisfaction when compared to conventional medical management. When compared with repeat surgery, pain and patient satisfaction improved, but the functional gains were not significant.

2) **Rigoard 2019**, PROMISE study RCT of spinal cord stimulator plus optimal medical therapy vs optimal medical therapy alone for failed back surgery syndrome
    a. CEBP rated this study as poor quality
    b. N=218 patients
        i. OMM included both non-invasive and invasive treatments including acupuncture, behavioral therapies, physical therapy, spinal epidural injections, adhesiolysis, and neurotomies. Patients randomized to OMM alone were allowed to crossover to SCS after six months.
    c. The primary outcome of greater than 50% reduction in low back pain in the ITT analysis was achieved in 15 patients in the SCS plus OMM group (13.6%) and 5 patients in the OMM alone group (4.6%) (absolute risk difference 9%, 95% CI 0.6% to 17.5%, p = 0.036). Notably, the SCS group responder rate ranged from 0% to 50% across the study sites. In the ITT analysis the between group difference in ODI at 6 months was 6.3 (95% CI 2.5 to 10.2, p < 0.001) favoring the SCS plus OMM arm. In the ITT analysis the between group difference in SF-36 physical component score at 6 months was 3.9 (95% CI 2.0 to 5.9, p < 0.001) favoring the SCS plus OMM arm.
    d. The between group difference in morphine milligram equivalents (MME) was 8.3 MME (95% CI -3.1 to 19.6, p = 0.031) with lower MME observed in in the SCS group.
    e. There were 13 serious and 21 total adverse events in the SCS arm (17.6% of patients experienced any adverse event). The most common adverse event reported in the SCS arm was implant site infection occurring in 7 patients (6.9%); five of these patients required surgical intervention. Other adverse events included device stimulation issues, paresthesias, implant site pain, pulmonary edema, and urinary tract infection.
    f. The study was limited by the inability to blind patients or investigators as well as the heterogeneous treatments that were available as OMM in both arms of the trial. The study was funded by Medtronic.
    g. Author's conclusions: Adding multicolumn SCS to OMM improved pain relief, HRQoL, and function in a traditionally difficult-to-treat population of failed back surgery syndrome patients with predominant LBP. Improvements were sustained at 12 and 24 months.

<u>Evidence of harms</u>

1) Labaran 2019
    a. Medicare database retrospective cohort study
    b. N=12,297 patients

c. The most common indications for SCS placement were postlaminectomy syndrome (25.2%) and chronic pain syndrome (20.2%).
d. There was a 4.2 and 17.2% incidence of postoperative back or spine emergency department (ED) visits, and a 0.3 and 3.4% incidence of SCS electrode removal or reimplantation within 90 days and 1 year, respectively. Other reported surgical complications were wound infection (4.3%), hematoma (0.5%), and seroma (0.4%) at one year postoperatively. Within 90 days after SCS implantation, the rate of subsequent spine surgery or revision was 0.9%. This incidence was 7.1, 11.7, and 15.5% at one, two, and three years, respectively.
e. Conclusions: In our retrospective analysis of Medicare patients, the most common indication for SCS implantation was postlaminectomy syndrome. Common postoperative complications included wound infection, and removal of SCS electrodes at one year postoperatively. About 17% patients had an ED visit for spine-related symptoms within one year of device implantation, and 15.5% underwent subsequent spinal decompression and/or fusion within 3 years after primary SCS placement.

2) Falowski 2019

a. Retrospective cohort study of MarketScan® Databases
b. N=6615 patients
c. 12 month device-related infection rate was 3.11%.
d. Conclusions: The 3.11% SCS-related infection rate within 12 m of implant emphasizes the need for improved infection control practices. Research is needed to limit SCS infections in younger patients and those with infection history.

Other payer policies

Medicare National Coverage Determination (NCD)

Covers spinal cord stimulators for chronic back pain under certain conditions. This procedure is covered only as a late resort for patients with chronic intractable pain. Patients must undergo screening and evaluation by a multidisciplinary team, including psychological and physical evaluation. Successful trial associated with at least a 50% reduction of target pain, or 50% reduction of analgesic medications, and show some element of functional improvement. There should be no active substance abuse issues

Aetna

A trial of percutaneous dorsal column stimulation is medically necessary to predict whether a dorsal column stimulator will induce significant pain relief for:

- Low back pain and significant radicular pain due to failed back surgery syndrome
- Last resort treatment of moderate to severe (5 or more on a 10-point VAS scale) chronic neuropathic pain of certain origins (i.e., lumbosacral arachnoiditis, phantom limb/stump pain, peripheral neuropathy, post-herpetic neuralgia, intercostal neuralgia, cauda equina injury, incomplete spinal cord injury, or plexopathy) that is refractory to 12 or more months of standard therapy (including non-steroidal anti-inflammatory drugs, tricyclic antidepressants, and anticonvulsants).

Coverage is provided when all these criteria are met:

- Member has undergone careful screening, evaluation and diagnosis by a multidisciplinary team prior to implantation (Note: screening must include psychological as well as physical evaluations)
- Member does not have any untreated existing drug addiction problems (per American Society of Addiction Medicine guidelines)
- Member has obtained clearance from a psychiatrist, psychologist, or other qualified mental health professional
- Other more conservative methods of pain management have been tried and failed
- There is documented pathology, i.e., an objective basis for the pain complaint

Implantation of a dorsal column stimulator is medically necessary when the trial criteria are met and the patient experienced significant pain reduction (50% or more) with a 3 to 7 day trial of percutaneous spinal stimulation.

High-frequency dorsal column stimulators (also known as BurstDR spinal cord stimulators) are an equal effective alternative to standard dorsal column stimulators. Replacement of a functioning standard dorsal column stimulator with a high-frequency dorsal column stimulator is considered not medically necessary.

Replacement of a cervical, lumbar or thoracic dorsal column stimulator or battery/generator is medically necessary for individuals who meet medical necessity criteria for dorsal column stimulation and the existing stimulator or battery/generator are no longer under warranty and cannot be repaired.

Up to 16 electrodes/contacts, 2 percutaneous leads, or 1 paddle lead is medically necessary for a trial of a dorsal column stimulator. An additional 16 electrodes/contacts, 2 percutaneous leads, or 1 paddle lead are considered medically necessary for implantation of a dorsal column stimulator.

The use of intra-operative motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP) experimental and investigational for implantation of spinal cord stimulators.

The use of cervical dorsal column stimulation is experimental and investigational for the treatment of cervical trauma, disc herniation, failed cervical spine surgery syndrome presenting with arm pain, neck pain, cervicogenic headache, because its effectiveness for these indications has not been established.

Dorsal root ganglion stimulators (e.g., Axium Neurostimulator System) are medically necessary for moderate to severe chronic intractable pain of the lower limbs in persons with complex regional pain syndrome, and Aetna's policy does not mention dorsal root ganglion stimulators for back pain.

Cigna

A short-term trial (i.e., greater than 48 hours) of spinal cord stimulation (i.e., non-high-frequency, high-frequency) is considered medically necessary for the treatment of chronic intractable pain secondary to failed back surgery syndrome with intractable neuropathic leg pain when all the following criteria are met:

- Failure of at least six consecutive months of physician-supervised conservative medical management (e.g., pharmacotherapy, physical therapy, cognitive therapy, and activity lifestyle modification)

- Surgical intervention is not indicated or the individual does not wish to proceed with spinal surgery
- An evaluation by a mental health provider (e.g., a face-to-face assessment with or without psychological questionnaires and/or psychological testing) reveals no evidence of an inadequately controlled mental health problem (e.g., alcohol or drug dependence, depression, psychosis) that would impact perception of pain and/or negatively impact the success of a SCS or contraindicate placement of the device.

Permanent implantation of a spinal cord stimulator is considered medically necessary for the treatment of chronic intractable pain secondary to failed back surgery syndrome with intractable neuropathic leg pain when at least 50% reduction in pain has been demonstrated during a short-term trial of SCS.

The replacement of an existing high frequency or non-high-frequency dorsal column spinal cord stimulator, battery, or generator is considered medically necessary for an individual when the existing stimulator, battery, or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

Replacement of a functioning non high-frequency dorsal column spinal cord stimulator with a high frequency spinal cord stimulator is considered not medically necessary.

Dorsal root ganglion stimulation is considered experimental, investigational or unproven for all indications

Moda

A trial of spinal cord stimulation for intractable pain is covered when all of the following criteria are met:

- Pain is neuropathic with documented pathology related to pain complaint (i.e., abnormal MRI) for 1 or more of the following:
    - Failed back surgery syndrome
    - Complex regional pain syndrome (also known as reflex sympathetic dystrophy)
    - Inoperable chronic ischemic limb pain secondary to peripheral vascular disease
    - Moderate to severe chronic neuropathic pain, including but not limited to, one of the following:
        - Arachnoiditis
        - Radiculopathies
        - Phantom limb/stump pain
        - Peripheral neuropathy
        - Post-herpetic neuralgia
        - Incomplete spinal cord injury
        - Cauda equina injury
- Other more conservative methods of pain management have been tried and failed including one or more of the following:
    - For limb ischemia, failed surgical or endovascular revascularization, or inoperable vascular disease
    - For neuropathic pain, stellate ganglion or lumbar sympathetic block
    - Conservative treatment tried and failed for 3 or more months for ALL of the following:

    - Pharmacological (including NSAIDs, tricyclic antidepressants, and anticonvulsants unless contraindicated or unable to tolerate)
    - Physical therapy
    - Psychological or cognitive behavioral therapies
- Patient is not a candidate for further surgical intervention
- Psychiatric and substance abuse disorders have been ruled out
- Patient is capable of operating stimulating device and willing to comply with the treatment plan
- No coagulopathy, severe thrombocytopenia, or anticoagulant or antiplatelet therapy
- No current or chronic infection
- Patient has had a face to face evaluation by a psychologist or psychiatrist and cleared for a trial of spinal cord stimulation

Permanent placement of a spinal cord stimulator is covered when all of the following criteria are met:

- Patient has experienced significant pain reduction of 50% or more with a temporary trial of 3 to 7 days.
- Patient has met criteria for trial placement of a spinal cord stimulator
- Patient is capable of operating stimulating device and willing to comply with treatment plan

Regence

Spinal cord stimulation should be initiated with a trial period of spinal cord stimulation with a temporarily implanted lead and may be followed by permanent implantation.

Spinal cord stimulation (standard or high frequency) may be considered medically necessary when all of the following criteria are met:

- Presence of severe and chronic refractory pain of the trunk or limbs, other than critical limb ischemia
- The treatment is used only as a last resort; other treatment modalities (pharmacological, surgical, psychological, or physical, if applicable) have been tried and failed or are judged to be unsuitable or contraindicated
- Trunk and limb pain is neuropathic in nature (i.e. resulting from actual damage to the peripheral nerves). Common indications include, but are not limited to the following: failed back surgery syndrome, complex regional pain syndrome (i.e., reflex sympathetic dystrophy), arachnoiditis, radiculopathies, phantom limb/stump pain, and peripheral neuropathy
- No serious untreated drug habituation exists
- Patient has been carefully screened, evaluated, and diagnosed by appropriate consultants of different specialties, who document agreement with application of these therapies or, at a minimum, do not object to application of these therapies

This policy only applies to the initial (temporary and permanent) placement of the device and does not apply to revision(s) or replacement(s) after the device has been placed.

Dorsal root ganglion stimulation is considered investigational for all indications.

Spinal Cord Stimulators

HERC staff summary

The evidence supporting the efficacy of spinal cord stimulation for back conditions is poor, making it difficult to draw firm conclusions. The rate of complications of SCS is high. Private insurers cover the procedure, but with restrictions. There are currently no explicit restrictions on SCS placement on the Prioritized List.

Generally, the HERC does not remove services from the Prioritized List unless there is evidence of ineffectiveness or of harms that outweigh benefits. HERC staff reading of the literature is that the evidence is insufficient to determine the ratio of benefits to harms. However, a new guideline restricting the procedure to the most symptomatic group of patients would be appropriate given the high cost and risks of the procedure, and the lack of good evidence of effectiveness, as well as the availability of alternative therapies.

The CCO medical director guideline test group have reviewed the proposed new guideline and agree with its wording and feel that it would be valuable to add to the Prioritized List.

HERC staff recommendations:

1) Remove all spinal cord stimulator CPT and HCPCS codes from line 361 SCOLIOSIS as this is not an appropriate diagnosis for this therapy
    a. CPT 63650, 63655, 63685
    b. HCPCS C1767, C1778, C1816, C1820, C1822, C1823, C1897
2) Add the new guideline below to lines
    a. 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
    b. 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS
    c. 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
3) Delete the coding specification regarding spinal cord stimulators from line 292 as the wording is now incorporated into the new guideline

GUIDELINE NOTE XXX SPINAL CORD STIMULATOR THERAPY
Lines 292, 346, 529

A spinal cord stimulator trial is included on lines 292 and 346 only when a patient meets all of the following criteria:

1) The patient has moderate to severe (>5 on the VAS pain scale) neuropathic pain and objective neurologic impairment with documented pathology related to pain complaint (i.e. abnormal MRI). Neurologic impairment is defined as objective evidence of one or more 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; AND
2) The patient has failed 12 or more months of other treatment modalities (e.g. pharmacological, surgical, physical therapy, cognitive therapy, and activity lifestyle modification); AND
3) The patient has had an evaluation by a mental health provider (e.g., a face-to-face assessment with or without psychological questionnaires and/or psychological testing) which revealed no evidence of an inadequately controlled mental health problem (e.g., alcohol or drug dependence, depression, psychosis) and the patient receives written clearance from the mental health provider for device placement; AND
4) The patient has no contraindications (e.g. no coagulopathy, severe thrombocytopenia, or anticoagulant or antiplatelet therapy, or current or chronic infection).

Implantation of a spinal cord stimulator is included on lines 292 and 346 when the trial criteria above are met and the patient experienced significant pain reduction (50% or more) with a 3 to 7 day trial of percutaneous spinal stimulation.

Spinal cord stimulation (63650-63688) is not included on line 292 when paired with ICD-10-CM category G90.5 Complex regional pain syndrome/reflex sympathetic dystrophy.

Otherwise, spinal cord stimulation therapy is included on line 529.

REVIEW ARTICLE

Spinal Cord Stimulation 50 Years Later

Clinical Outcomes of Spinal Cord Stimulation Based on Randomized Clinical Trials—A Systematic Review

Nagy Mekhail, MD, PhD, Ogi Visnjevac, MD, Gerges Azer, MD, Diana Sue Mehanny, MD, Priya Agrawal, DO, and Victor Foorsov, MD

Abstract: To assess the efficacy of spinal cord stimulation (SCS) for each indication, one must critically assess each specific clinical outcome to identify outcomes that benefit from SCS therapy. To date, a comprehensive review of clinically relevant outcome-specific evidence regarding SCS has not been published. We aimed to assess all randomized controlled trials from the world literature for the purpose of evaluating the clinical outcome-specific efficacy of SCS for the following outcomes: perceived pain relief or change pain score, quality of life, functional status, psychological impact, analgesic medication utilization, patient satisfaction, and health care cost and utilization. Interventions were SCS, without limitation to the type of controls or the type of SCS in the active arms. For each study analyzed, a quality assessment was performed using a validated scale that assesses reporting, external validity, bias, confounding, and power. Each outcome was assessed specific to its indication, and the primary measure of each abovementioned outcome was a summary of the level of evidence. Twenty-one randomized controlled trials were analyzed (7 for trunk and limb pain, inclusive of failed back surgery syndrome; 8 for refractory angina pectoris; 1 for cardiac X syndrome; 3 for critical limb ischemia; 2 for complex regional pain syndrome; and 2 for painful diabetic neuropathy). Evidence assessments for each outcome for each indication were depicted in tabular format. Outcome-specific evidence scores were established for each of the abovementioned indications, providing both physicians and patients with a summary of evidence to assist in choosing the optimal evidence-based intervention. The evidence presented herein has broad applicability as it encompasses a breadth of patient populations, variations of SCS therapy, and comparable controls that, together, reflect comprehensive clinical decision making.

(*Reg Anesth Pain Med* 2018;43: 391–406)

The International Association for the Study of Pain defines chronic pain as continuing or intermittent pain that remains longer than the normal course of acute disease or injury, or more than 3 months, and lacks the acute warning function of physiological nociception.[1] Chronic pain is a major source of US health care expenditure (estimated to be $560 billion to $635 billion annually), with 116 million adults suffering from common chronic pain conditions, indicating a profound disease burden.[2] While much of this disease burden has been relegated to medical management and other interventional procedures, spinal cord stimulation (SCS) has been used increasingly in recent years for the treatment of a variety of chronic pain indications.[3,4]

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Fifty years ago, Norman Shealy[5] implanted the first SCS device in a patient with cancer-related chest and abdominal pain. Shealy's original single monopolar electrode has evolved into a complex multi-independent contact percutaneous and paddle leads. More recently introduced is the closed-loop SCS system, which is capable of recording the evoked compound action potential of the dorsal column neurons and adjusting the subsequent wave of stimulation to produce the same action potential. Therefore, electric stimulation remains consistently within the therapeutic range. Furthermore, a wide variety of stimulation parameters, waveforms, and frequencies have developed. In addition, other neuronal targets have been stimulated to produce specific therapeutic effects, of which the dorsal root ganglion (DRG) stimulation is proved to be very effective and widely adopted. In addition, it is important to note the multitude of technological advancements within the implantable pulse generators and battery systems themselves.[6–8] Concurrently, patient factors relating to success or failure of SCS therapy have been identified and, together, have contributed to international guidelines.[9,10] Nearly all recommendations conclude that an appropriate patient is one who demonstrates reasonable therapeutic expectations, is free of significant psychiatric barriers or secondary gain, and has a pain generator that is not reasonably treatable by an alternative, more conservative, modality.[9–11]

While SCS therapy has been used to treat a wide variety of conditions, the most common indications are combined trunk and limb pain (TLP), inclusive of failed back surgery syndrome (FBSS),[12] complex regional pain syndrome (CRPS),[13–15] neuropathic pain including painful diabetic neuropathy (PDN),[16] critical limb ischemia (CLI),[17] and refractory angina pectoris (RAP).[18] As the cost and efficacy of SCS therapy continue to be called into question by public health administrators, payers, and policy makers, there is an increasing demand for high-level evidence for efficacy and cost-effectiveness. When considering the evidence for SCS, however, it is of utmost importance to recognize that this is a diverse therapeutic modality with a multitude of platforms and dynamic parameters implanted for the treatment of a variety of generally difficult-to-treat pain-related indications, most of which exhibit variable phenotypes in and of themselves. Thus, the measurement of SCS outcomes cannot be relegated to a dichotomous yes or no (1 or 0) regarding efficacy.

Unfortunately, to date, a comprehensive review of clinically relevant outcome-specific evidence regarding SCS has not been published. To thoroughly assess the efficacy of SCS for each indication, one must critically assess each specific clinical outcome to identify which outcomes are amenable to SCS therapy and which are not. Hence, the primary objectives of this systematic review were to assess all randomized controlled trials (RCTs), highest-level evidence only, from the world literature for the purpose of evaluating the clinical outcome-specific efficacy of SCS when used for any pain-related indication, without limitation to the type of control comparisons used in each RCT, that is, both placebo-controlled and active comparator were used in this review.

Research Paper

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Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial

Philippe Rigoard[a,b,c,*], Surajit Basu[d], Mehul Desai[e,f], Rod Taylor[g], Lieven Annemans[h], Ye Tan[i], Mary Jo Johnson[i], Carine Van den Abeele[j], PROMISE Study Group, Richard North[k,l]

Abstract

Despite optimal medical management (OMM), low back pain (LBP) can be disabling, particularly after spinal surgery. Spinal cord stimulation (SCS) is effective in reducing neuropathic leg pain; however, evidence is limited for LBP. This prospective, open-label, parallel-group trial randomized (1:1) failed back surgery syndrome (FBSS) patients with predominant LBP to SCS plus OMM (SCS group) or OMM alone (OMM group) at 28 sites in Europe and the Americas. If trial stimulation was successful, a multicolumn SCS system was implanted. Outcomes were assessed at baseline (before randomization) and at 1, 3, 6, and 12 months after randomization. Patients could change treatment groups at 6 months. The primary outcome was the proportion of patients with ≥50% reduction in LBP (responder) at 6 months. Secondary outcomes included change in pain intensity, functional disability, and health-related quality of life (HRQoL). The results are posted at ClinicalTrials.gov under registration number NCT01697358. In the intent-to-treat analysis, there were more responders in the SCS group than in the OMM group (13.6%, 15/110 vs 4.6%, 5/108, difference 9% with 95% confidence interval 0.6%-17.5%, $P = 0.036$) at 6 months. The SCS group improved in all secondary outcomes compared with the OMM group. The OMM group only improved in HRQoL. In the SCS group, 17.6% (18/102) experienced SCS-related adverse events through 6 months, with 11.8% (12/102) requiring surgical reintervention. Adding multicolumn SCS to OMM improved pain relief, HRQoL, and function in a traditionally difficult-to-treat population of failed back surgery syndrome patients with predominant LBP. Improvements were sustained at 12 and 24 months.

Keywords: Spinal cord stimulation, Surgical leads, Failed back surgery syndrome, Randomized controlled trial, Chronic low back pain, Predominant back pain

1. Introduction

Spinal pathologies and low back pain (LBP) represent a major public health issue and impose a considerable financial burden on the society.[2] Low back pain affects 60% to 80% of the population at some point in life,[13,15] and pharmacological treatments can be suboptimal.[4,11]

A substantial fraction of patients who undergo spinal surgery develop new or persistent back and/or leg pain postoperatively.[4,19,20,23] This chronic condition is described as failed back surgery syndrome (FBSS) or postlaminectomy syndrome and remains difficult to treat with conventional medical management alone.[8]

Spinal cord stimulation (SCS) for pain control has been available for 50 years. It is delivered through electrodes placed in the dorsal epidural space to produce paresthesia in the painful area. Several systematic reviews of the impact of SCS in chronic back and leg pain and FBSS have been published.[16,31–33] The systematic review by Taylor et al. in 2014 identified 74 included SCS studies (in 3025 patients) of which only 4 studies (in 104 patients) were in the population with predominant LBP; the remainder were in predominant leg pain (9 studies), mixed back and leg pain (22 studies), or unclassifiable (39 studies). There was evidence of a higher level of pain relief pooled across studies in individuals with predominant back pain after SCS (mean 86% pain relief, 95% confidence interval [CI]: 75%-96%) compared with studies in those with predominant leg pain (mean 53% pain relief, 95% CI: 39%-68%), but the number of studies analyzed was small, and there was no significant association ($P = 0.49$) between the level of pain relief and the location of pain in univariable meta-regression. Furthermore, these 4 studies in predominant LBP were all case series and therefore low in the hierarchy of evidence. The authors recommended randomized controlled trials (RCTs) to confirm the effectiveness and cost-effectiveness of SCS in the population with predominant LBP that included important measurements beyond pain relief including level of physical disability and health-related quality of life (HRQoL). Although SCS is an established and effective treatment in FBSS for predominant radicular pain,[18,24,31] LBP has been difficult to treat with traditional SCS. Initial reports on the use of SCS with a multicolumn lead (electrode array) have shown promising results.[27]

PROMISE was designed to address this gap in LBP evidence. It is an international RCT of SCS in a population of exclusively predominant LBP FBSS patients to compare the clinical effectiveness of SCS with a multicolumn lead combined with optimal medical management (OMM) to OMM alone.

2. Methods

The PROMISE trial was conducted and reported in accordance with the Consolidated Standards of Reporting Trials guidelines.[22] The study design, previously published,[28] is summarized below.

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A Retrospective Database Review of the Indications, Complications, and Incidence of Subsequent Spine Surgery in 12,297 Spinal Cord Stimulator Patients

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Study Design: Retrospective review.

Objective: To analyze the indications, incidence of minor and major complications, and rate of subsequent spinal surgery or revision after spinal cord stimulator (SCS) placement for degenerative spine disease.

Summary of Background Data: Despite the application of SCS in various chronic pain conditions, there remains a growing debate on the efficacy and necessity of SCS in degenerative spine disease.

Methods: A nationally representative sample of Medicare patients who had an open (via laminectomy) SCS placement for degenerative spine disease between 2005 and 2014 were studied. Indications, complications, and the rate of subsequent spinal surgery within 90 days, one year, two years, and three years postoperatively were studied using Current Procedural Terminology (CPT) and International Classification of Diseases (ICD) codes.

Results: We included 12,297 SCS patients in our study cohort. The most common indications for SCS placement were post-laminectomy syndrome (25.2%) and chronic pain syndrome (20.2%). There was a 4.2 and 17.2% incidence of postoperative back or spine emergency department (ED) visits, and a 0.3 and 3.4% incidence of SCS electrode removal or reimplantation within 90 days and 1 year, respectively. Other reported surgical complications were wound infection (4.3%), hematoma (0.5%), and seroma (0.4%) at one year postoperatively. Within 90 days after SCS implantation, the rate of subsequent spine surgery or revision was 0.9%. This incidence was 7.1, 11.7, and 15.5% at one, two, and three years, respectively.

Conclusions: In our retrospective analysis of Medicare patients, the most common indication for SCS implantation was post-laminectomy syndrome. Common postoperative complications included wound infection, and removal of SCS electrodes at one year postoperatively. About 17% patients had an ED visit for spine-related symptoms within one year of device implantation, and 15.5% underwent subsequent spinal decompression and/or fusion within 3 years after primary SCS placement.

Keywords: Chronic pain syndrome, degenerative spine disease, post-laminectomy syndrome, SCS, spinal cord stimulation, spine surgery, surgical indication

Conflict of Interest: The authors report no conflicts of interest relevant to this study.

INTRODUCTION

There remains a growing interest in finding alternative ways of treating chronic pain, especially with the ongoing opioid epidemic. Spinal cord stimulators (SCS) continue to gain acceptance amongst spine surgeons for managing chronic back and/or leg pain after previous spine surgery conditions such as postlaminectomy syndrome or failed back surgery syndrome (FBSS). SCS provides the benefit of alleviating chronic pain in conditions where reoperations or conservative medical management (CMM) have traditionally been the treatment option (1).

Studies have shown SCS to be more effective in the treatment of chronic pain in spine patients compared to CMM and reoperation (2–4). The PROCESS (Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation) trial demonstrated that the combination of SCS with conventional medical management (CMM) was superior to CMM alone in the management of FBSS (5). In another randomized, controlled trial of 50 patients with FBSS who underwent either a SCS implantation or reoperation, North et al. reported that SCS was more effective in treatment of

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Spinal Cord Stimulation Infection Rate and Risk Factors: Results From a United States Payer Database

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Objective: Surgical site infections can cause negative clinical and economic outcomes. A recent international survey on Spinal Cord Stimulation (SCS) infection control practices demonstrated low compliance with evidence-based guidelines. This study defines infection rate for SCS implants and identifies infection risk factors.

Materials and Methods: A retrospective analysis of the MarketScan® Databases identified patients with SCS implant (2009–2014) and continuous health plan enrollment for ≥12-months (12 m) preimplant. For logistic regression analysis, patients were enrolled for 12 m postimplant. Kaplan–Meier and Cox Proportional Hazard survival analyses assessed time to infection, with infection rate reported at 12 m postimplant. Logistic regression characterized risk factors based on demographics, comorbidities, and clinical characteristics.

Results: In the logistic regression (n = 6615), 12 m device-related infection rate was 3.11%. Infection risk factors included peripheral vascular disease (OR, 1.784; 95% CI: 1.011–3.149; p = 0.0457) and infection in 12 m before implant (OR, 1.518; 95% CI: 1.022–2.254; p = 0.0386). The odds of patients experiencing an infection decreased by 3.2% with each additional year of age (OR, 0.968; 95% CI: 0.952–0.984; p < 0.0001). Survival analysis (n = 13,214) identified prior infection (HR, 1.770; 95% CI: 1.342–2.336; p < 0.0001) as a risk factor. Infection was less likely in older patients (HR, 0.974; 95% CI: 0.962–0.986; p < 0.0001). Expected risk factors including obesity, diabetes, and smoking were not identified as risk factors in this analysis. There was no significant difference between infection rate for initial and replacement implants.

Conclusions: The 3.11% SCS-related infection rate within 12 m of implant emphasizes the need for improved infection control practices. Research is needed to limit SCS infections in younger patients and those with infection history.

Keywords: Complication, healthcare utilization, infection, spinal cord stimulation

Conflict of Interest: Steven Falowski serves as a consultant for Abbott, Medtronic, and Nevro Corp. He has received research support from Abbott and Medtronic. David Provenzano has served as a consultant for Abbott, Biotronik, Bioness, Boston Scientific, Halyard, Medtronic, Nevro, and Sollis. He has received research support from Abbott and Medtronic. A.H. Doth and Y. Xia are employed by and minor shareholders of Medtronic.

INTRODUCTION

Significant interest has been placed on surgical site infections (SSIs) associated with implantable pain therapies including spinal cord stimulation (SCS). SSIs are associated with significant humanistic, economic, and clinical consequences. Recent publications have highlighted the consequences of SSIs for implantable pain therapies and the low levels of compliance with evidence-based guidelines (1–3). An analysis of the United States Closed Claims Project data base on implantable pain therapies indicated that infection was the most common damaging event (i.e., 23% of all claims) for surgical device-related claims (4).

To date, published SSI rates for SCS have ranged from 1 to 10% (1,5–11). SSI incidence rates for implantable pain therapies have been gathered from data from retrospective and prospective studies, randomized controlled trials, and systematic reviews. Two systematic reviews have reported SCS SSI rates of 3.4–4.6% (5,11). The number of patients in the primary studies are limited, ranging from 24 to 2737 patients (1,7,8).

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[Correction added on 31 August 2018 after first online publication: the affiliations of Steven M. Falowski and David A. Provenzano have been corrected to "St. Luke's University Health Network, Bethlehem, PA, USA" and "Pain Diagnostics and Interventional Care, Sewickley, PA, USA", respectively.].

Yoga and Acupuncture for Treatment of PTSD and Anxiety Disorders

Question: Should yoga and acupuncture CPT codes be paired with post traumatic stress disorder (PTSD) and/or anxiety?

Question source: OHA leadership

Issue: Due to issues with access to psychiatric services in Oregon, OHA leadership has developed several recommendations to try to expand access and treatment types for conditions including PTSD and anxiety. Specifically, the HERC has been asked to look at the effectiveness of yoga and acupuncture for treatment of PTSD and anxiety disorders.

From Pat Allen, Director of OHA

> Consider pairing alternative treatments (such as acupuncture and yoga) with PTSD and other anxiety-related diagnoses that are a result of trauma to decrease demand for psychiatric medication management. OHA believes it would be appropriate for Oregon's Health Evidence Review Commission (HERC) to consider this recommendation. HERC staff will review the literature on alternative therapies, including acupuncture and yoga, for the treatment of PTSD and anxiety. If the literature shows that these treatments are effective, then we will ask the HERC to consider pairing these treatments with anxiety-related conditions on the Prioritized List of Health Services.

Current Prioritized List status

1) Acupuncture (CPT 97810-97814) appears on multiple lines, including the lines for substance abuse and substance-induced anxiety and delirium
2) HCPCS S9451 (Exercise classes, non-physician provider, per session) appears on line 401 CONDITIONS OF THE BACK AND SPINE, with a guideline specifying that it be used for the provision of yoga classes.

This topic was discussed with the Behavioral Health Advisory Panel at their October 2019 meeting.

Laura Ocker, LAc testified that she has treated many patients with these conditions and finds acupuncture to be beneficial for a variety of anxiety conditions. Ocker noted that acupuncture is hard to study, as acupuncture services involve a variety of treatments, such as lifestyle advice and motivational interviewing, as well as acupuncture needle placement.

Lindsey noted that Medicare does not cover acupuncture or yoga for mental health issues. She expressed concern with coverage of yoga for these conditions, given the lack of licensure and oversight for yoga providers. Savicki commented that yoga and/or acupuncture might help divert patients from psychiatric services and need for psychiatric medication. She noted that the evidence that medication helps PTSD is poor. Savicki also felt that adding these services would add tools for OHP patients dealing with these conditions.

The BHAP felt that they did not have the expertise to fully analyze the evidence for acupuncture and yoga for PTSD/anxiety and deferred further discussion to the VbBS

Evidence review

Acupuncture for treatment of PTSD

1) **Grant 2017,** systematic review and meta-analysis of acupuncture for PTSD
    a. N=7 RCTs (709 patients)
        i. Acupuncture sessions ranged from 30 to 60 minutes per session, 2 to 4 sessions per week, and 3 to 12 weeks total in duration
        ii. Included Hollifield 2007, Zhang 2010 and Zhang 2011 as in Young-Dae below
    a. We identified very low quality body of evidence indicating significant differences favoring acupuncture (versus any comparator) at post-intervention on PTSD symptoms (standardized mean difference [SMD] = −0.80, 95% confidence interval [CI] [−1.59, −0.01], 6 RCTs), and low quality body of evidence at longer follow-up on PTSD (SMD = −0.46, 95% CI [−0.85, −0.06], 4 RCTs)
    b. Safety data (7 RCTs) suggest little risk of serious adverse events, though some participants experienced minor/moderate pain, superficial bleeding, and hematoma at needle insertion sites.
    c. Conclusions: Results from meta-analyses of published RCTs indicate positive effects of acupuncture but warrant caution regarding claims that acupuncture is an evidence-based treatment for patients with PTSD based on the best available evidence for key clinical outcomes. To increase confidence in findings, sufficiently powered replication trials are needed that measure all relevant clinical outcomes and dedicate study resources to minimizing participant attrition.
2) **Young-Dae 2013,** systematic review of acupuncture for PTSD
    a. N= 4 RCTs (N=543 patients) and 2 uncontrolled clinical trials
        i. Compared acupuncture to waitlist, sham acupuncture, conventional therapy or no controls
    b. One high-quality RCT (Hollifield 2007) reported that acupuncture was superior to waitlist control. No statistical difference was found between acupuncture and CBT.
    a. One RCT (Zhang 2010) showed no statistical difference between acupuncture and selective serotonin reuptake inhibitors (SSRIs).
    b. One RCT (Zhang 2011) reported a favorable effect of acupoint stimulation plus CBT against CBT alone.
    c. A meta-analysis of acupuncture plus moxibustion versus SSRI favored acupuncture plus moxibustion in three outcomes.
    d. No serious adverse events were reported.
    e. Conclusion: Our main finding of this review is that acupuncture is effective for PTSD based on one high-quality RCT and a meta-analysis. This systematic review and meta-analysis suggest that the evidence of effectiveness of acupuncture for PTSD is encouraging but not cogent. Further qualified trials are needed to confirm whether acupuncture is effective for PTSD.

Acupuncture for treatment of anxiety

1) **Grant 2017,** systematic review and meta-analysis of acupuncture for PTSD
    a. N=7 RCTs (709 patients)
    b. No significant differences were observed between acupuncture and comparators at post-intervention for anxiety symptoms (SMD = −0.82, 95% CI [−2.16, 0.53], 4 RCTs, very low quality of evidence)
2) **Goyata 2016,** review of acupuncture of treatment of anxiety
    a. N=19 studies

   i. 6 RCTs (5 of reasonable quality)
   ii. 11 (57.9%) had a strong level of evidence; four of them (21.0%) had a moderate level; and four (21.0%) had a weak level of evidence
  b. Conclusion: acupuncture seems to be a promising treatment for anxiety; however, there is a need for improving the methodological quality of the research on this field.
3) **Li 2019,** Systematic review of acupuncture for treatment of anxiety
  a. N=10 reviews (included Amorim 2018 below)
    i. The assessment results of AMSTAR-2 showed that the methodological quality of all included studies was critically low.
    ii. A total of four MAs reported pooled results of acupuncture therapy (AT) versus sham acupuncture. Their results showed that the effect of acupuncture on anxiety is controversial. A meta-analysis (6 RCTs) compared acupuncture to placebo/sham acupuncture using the (80-point) State-Trait Anxiety Inventory (STAI) score, they found a clinically irrelevant and non-significant reduction (mean differences (MD)=−1.54, 95% CI−4.73 to 1.64). However, Doreen et al combined results of the five trials showed a greater overall reduction in anxiety in the acupuncture group than in the sham controls (standardized mean differences (SMD)=−1.11; 95% CI−1.61 to −0.61). The other two reviews concluded that acupuncture seems to be an effective approach in relieving anxiety, and placebo effects may partially contribute to the benefits. All of them mentioned that there is currently insufficient research evidence for firm conclusions to be drawn.
    iii. One review focused on AT versus non treatment. Results showed that acupuncture interventions led to greater reductions in preoperative anxiety relative non treatment (STAI score, MD=5.63, p < 0.00001, 95%CI 4.14-–7.11, 14 RCTs).
    iv. Three reviews compared electroacupuncture (EA) with conventional treatment or drug treatment on the effectiveness on anxiety. All showed higher overall efficacy in the EA group, Luo et al pooled OR=1. 98, 95%CI (1. 10, 3. 55), p=0.02, I2=0, 5 RCTs).
    v. Conclusion: Although most of the included reviews indicated that acupuncture group was more effective than control group in the treatment of anxiety, more importantly, the methodological quality of the included reviews and the quality of evidence were low. More high-quality evidence is needed to determine whether acupuncture is more effective than other treatments.
4) **Amorim 2018**, systematic review of acupuncture for treatment of anxiety
  a. N=13 trials
    i. Interventions ranged from 1 session to 36 sessions
    ii. Outcomes measured varied widely between studies
  b. All 13 studies reported an anxiety decrease for their treatment group relative to the control groups
  c. Conclusions: Acupuncture seems to be an adequate, safe and effective alternative for the treatment of anxiety. More research studies in this area are however required with more robust methodologies to ensure acupuncture efficacy on the treatment of anxiety disorders.
5) **Bae 2014,** systematic review and meta-analysis of acupuncture for treatment of pre-operative anxiety
  a. N=14 studies (1034 patients)

   b. Six publications, using the State-Trait Anxiety Inventory-State (STAI-S), reported that acupuncture interventions led to greater reductions in preoperative anxiety relative to sham acupuncture (mean difference = 5.63, *P* < .00001, 95% CI [4.14, 7.11]).
   c. Further eight publications, employing visual analogue scales (VAS), also indicated significant differences in preoperative anxiety amelioration between acupuncture and sham acupuncture (mean difference = 19.23, *P* < .00001, 95%CI [16.34, 22.12]).
   d. *Conclusions*. Acupuncture therapy aiming at reducing preoperative anxiety has a statistically significant effect relative to placebo or nontreatment conditions. Well-designed and rigorous studies that employ large sample sizes are necessary to corroborate this finding

Yoga for treatment of PTSD

1) **Cramer 2018**, systematic review and meta-analysis for yoga in the treatment of PTSD
   a. N=7 RCTs (N = 284 patients)
   b. Meta-analysis revealed evidence for statistically significant effects of yoga on PTSD symptoms compared to no treatment (SMD = − 1.10, 95% CI [− 1.72, − 0.47], p < .001), with significant heterogeneity (I2 = 72%, p = .007). The mean difference (MD = − 13.11, 95% CI [− 17.95, − 827]) was above the defined threshold of 10 points indicating clinical relevance, while the confidence interval also included values below the threshold for clinical relevance. The quality of evidence was downgraded to low due to high likelihood of bias, imprecision of results and the unclear risk of publication bias.
   c. Only three RCTs reported any safety-related data; no adverse events were reported
   d. Conclusions: There is low quality evidence that yoga interventions including physical postures could be an effective, acceptable and safe intervention for PTSD. According to the GRADE guidelines, only a weak recommendation for the use of yoga as an adjunctive intervention for PTSD can be made because the true effect may be substantially different from the effect estimated in this analysis. Therefore, more high-quality studies are needed to confirm or disconfirm these findings.
2) **Gallegos 2017**, meta-analysis of RCTs for meditation and yoga for treatment of PTSD
   a. N=4 RCTs for yoga (3 included in the Cramer review above)
   b. Effect size (ES = −.71, p < .055, 95% CI = [−1.44, .02]) which was only marginally significant
   c. These findings suggest that meditation and yoga are promising complementary approaches in the treatment of PTSD among adults and warrant further study.
3) **Sciarrino 2017**, systematic review of yoga for PTSD
   a. N=7 RCTs (5 included in Carter 2018 above)
   b. Results: Cohen's d for each study ranged (in absolute value) from a low of -0.06 to a high of 1.42 (average weighted d across studies was 0.48; 95% CI: 0.26, 0.69).
   c. Conclusions: the weighted average effect of studies is in the moderate range, which indicates that these results are promising and warrant additional empirical inquiry.
4) **Institute of Medicine 2014**, report of Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder
   https://www.ncbi.nlm.nih.gov/books/NBK224878/pdf/Bookshelf_NBK224878.pdf
   a. Acupuncture used in several VA programs. Report notes lack of evidence to support use.

Yoga for treatment of anxiety

1) **Cramer 2017**, systematic review and meta-analysis of yoga for anxiety

   a. N=8 RCTs with 319 participants
   b. Meta-analyses revealed evidence for small short-term effects of yoga on anxiety compared to no treatment (standardized mean difference [SMD]=−0.43; 95% confidence interval [CI]=−0.74, −0.11; *P* = .008), and large effects compared to active comparators (SMD=−0.86; 95% CI=−1.56, −0.15; *P* = .02).
   c. Effects were robust against potential methodological bias.
   d. No effects were found for patients with anxiety disorders diagnosed by Diagnostic and Statistical Manual criteria, only for patients diagnosed by other methods, and for individuals with elevated levels of anxiety without a formal diagnosis.
   e. Only three RCTs reported safety-related data but these indicated that yoga was not associated with increased injuries.
   f. In conclusion, yoga might be an effective and safe intervention for individuals with elevated levels of anxiety. There was inconclusive evidence for effects of yoga in anxiety disorders. More high-quality studies are needed and are warranted given these preliminary findings and plausible mechanisms of action.
2) **Weaver 2016**, systematic review of yoga for treatment of anxiety in children and adolescents
   a. N=16 studies (6 RCTs,9 pre-post studies, 1 case study)
   b. CONCLUSION. Nearly all studies indicated reduced anxiety after a yoga intervention. However, because of the wide variety of study populations, limitations in some study designs, and variable outcome measures, further research is needed to enhance the ability to generalize and apply yoga to reduce anxiety

Disposition of other submitted articles:

1) Hollifield 2007: study included in included systematic reviews
2) Errington-Evans 2011: article appeared to be a study protocol
3) Herman 2012: 2 articles listed as examining acupuncture treatment for mental health disorders, but no details of these articles given
4) Spackman 2014: study examined acupuncture for treatment of depression

Other payer coverage:

1) No private payers surveyed covered acupuncture for either PTSD or anxiety treatment. No policies on yoga coverage were found.

Comparisons to evidence for back conditions:

AHRQ 2018 https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/nonpharma-chronic-pain-cer-209.pdf

Short term reduction of pain from chronic back conditions

Yoga (SOE moderate).

Acupuncture (SOE low)

Intermediate/long term reduction of pain from chronic back conditions

Yoga (SOE low).

Acupuncture (no effectiveness for intermediate, SOE low for long term)

HERC staff summary: Yoga and acupuncture appear to be promising treatments for PTSD and anxiety. However, acupuncture has not been adequately studied for either condition to allow determination of effectiveness. Yoga has a low level of evidence that it is effective for treatment of PTSD with considerable uncertainty to the level of evidence; yoga has inconclusive evidence for the treatment of anxiety disorders.

BHAP members and experts who testified at BHAP felt that both yoga and acupuncture might be valuable additions to the treatment options for PTSD and anxiety and reduce the need for psychiatric medications and other psychiatric services for these conditions. Experts noted that medications for PTSD also have low level of evidence to support their use. Yoga and acupuncture both have a good safety profile, and may be preferred by some patients. Compared to evidence for back conditions, yoga and acupuncture have a lower level of evidence for PTSD and anxiety disorders (yoga: low for anxiety/PTSD vs moderate for back pain; acupuncture: inconclusive for anxiety/PSTD vs low for back pain).

The CCO medical directors had concerns regarding inclusion of yoga for PTSD due to difficulty in managing such a benefit.

HERC staff recommendations:

1) Discuss adding HCPCS S9451 (Exercise classes, non-physician provider, per session) to line 173 POSTTRAUMATIC STRESS DISORDER with the following coding specification:
    a. "HCPCS S9451 appears on this line for provision of yoga classes."
2) Discuss adding acupuncture to lines 173 POSTTRAUMATIC STRESS DISORDER and 414 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED
    a. CPT 97810-97814
    b. Modify GN92 ACUPUNCTURE as shown below
        i. 12 visit limit is consistent with other conditions

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,5,173,202,361,401,409,414,461,538

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 12 sessions of acupressure/acupuncture per pregnancy.

Breech presentation

ICD-10-CM: O32.1

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 6 session per pregnancy.

Back and pelvic pain of pregnancy

ICD-10-CM: O99.89

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions per pregnancy.

Line 5 TOBACCO DEPENDENCE

Acupuncture is included on this line for a maximum of 12 sessions per quit attempt up to two quit attempts per year; additional sessions may be authorized if medically appropriate.

Line 173 POSTTRAUMATIC STRESS DISORDER

Acupuncture is included on this line for up to 12 sessions per year.

Line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions per year, with documentation of meaningful improvement; patients may have additional visits authorized beyond these limits if medically appropriate.

Line 361 SCOLIOSIS

Acupuncture is included on this line with visit limitations as in Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

Line 401 CONDITIONS OF THE BACK AND SPINE

Acupuncture is included on this line with visit limitations as in Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

Line 409 MIGRAINE HEADACHES

Acupuncture pairs on Line 409 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions per year.

Line 414 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED

Acupuncture is included on this line for up to 12 sessions per year.

Line 461 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 461 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions per year.

*Line 538 TENSION HEADACHES

Acupuncture is included on Line 538 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions per year.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

*Below the current funding line

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Acupuncture for the Treatment of Adults with Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis

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ABSTRACT

Acupuncture has been suggested as a treatment for posttraumatic stress disorder (PTSD), yet its clinical effects are unclear. This review aims to estimate effects of acupuncture on PTSD symptoms, depressive symptoms, anxiety symptoms, and sleep quality for adults with PTSD. We searched 10 databases in January 2016 to identify eligible randomized controlled trials (RCTs). We performed random effects meta-analyses and examined quality of the body of evidence (QoE) using the GRADE approach to rate confidence in meta-analytic effect estimates. Seven RCTs with 709 participants met inclusion criteria. We identified very low QoE indicating significant differences favoring acupuncture (versus any comparator) at post-intervention on PTSD symptoms (standardized mean difference [SMD] = −0.80, 95% confidence interval [CI] [−1.59, −0.01], 6 RCTs), and low QoE at longer follow-up on PTSD (SMD = −0.46, 95% CI [−0.85, −0.06], 4 RCTs) and depressive symptoms (SMD = −0.56; 95% CI [−0.88, −0.23], 4 RCTs). No significant differences were observed between acupuncture and comparators at post-intervention for depressive symptoms (SMD = −0.58, 95% CI [−1.18, 0.01], 6 RCTs, very low QoE), anxiety symptoms (SMD = −0.82, 95% CI [−2.16, 0.53], 4 RCTs, very low QoE), and sleep quality (SMD = −0.46, 95% CI [−3.95, 3.03], 2 RCTs, low QoE). Safety data (7 RCTs) suggest little risk of serious adverse events, though some participants experienced minor/moderate pain, superficial bleeding, and hematoma at needle insertion sites. To increase confidence in findings, sufficiently powered replication trials are needed that measure all relevant clinical outcomes and dedicate study resources to minimizing participant attrition.

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Posttraumatic stress disorder (PTSD) is a mental health condition that can develop after a person witnesses or experiences a traumatic event (American Psychiatric Association, 2013; Breslau, 2009; Kessler et al., 2005). Characteristic indicators include re-experiencing or intrusive symptoms, avoiding reminders of the event, negative thoughts and feelings, and hyper-

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Review Article

Acupuncture for Posttraumatic Stress Disorder: A Systematic Review of Randomized Controlled Trials and Prospective Clinical Trials

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To evaluate the current evidence for effectiveness of acupuncture for posttraumatic stress disorder (PTSD) in the form of a systematic review, a systematic literature search was conducted in 23 electronic databases. Grey literature was also searched. The key search terms were "*acupuncture*" and "*PTSD.*" No language restrictions were imposed. We included all randomized or prospective clinical trials that evaluated acupuncture and its variants against a waitlist, sham acupuncture, conventional therapy control for PTSD, or without control. Four randomized controlled trials (RCTs) and 2 uncontrolled clinical trials (UCTs) out of 136 articles in total were systematically reviewed. One high-quality RCT reported that acupuncture was superior to waitlist control and therapeutic effects of acupuncture and cognitive-behavioral therapy (CBT) were similar based on the effect sizes. One RCT showed no statistical difference between acupuncture and selective serotonin reuptake inhibitors (SSRIs). One RCT reported a favorable effect of acupoint stimulation plus CBT against CBT alone. A meta-analysis of acupuncture plus moxibustion versus SSRI favored acupuncture plus moxibustion in three outcomes. This systematic review and meta-analysis suggest that the evidence of effectiveness of acupuncture for PTSD is encouraging but not cogent. Further qualified trials are needed to confirm whether acupuncture is effective for PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) develops following a stressful event or situation of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress [1]. PTSD is classified as an anxiety disorder and is typically defined by the coexistence of 3 clusters of symptoms, namely, *reexperiencing*, *marked avoidance*, and *hyperarousal* [2]. The prevalence rates of PTSD have been reported as 6–25% [3], and approximately 25–30% of people experiencing a traumatic event may go on to develop PTSD [4].

Current first-line PTSD therapies include trauma-focused cognitive behavioral therapy (CBT), stress inoculation training, and pharmacotherapies [5]. Complementary and alternative medicine (CAM) interventions include a range of therapies that are not considered standard to the practice of medicine in the USA. CAM therapies are widely used by mental health consumers, including veterans, and numerous stakeholders have expressed strong interest in fostering the evidence base for these approaches in PTSD [6]. In addition, approximately 21% of CAM users met diagnostic criteria for at least one problematic mental disorder, according to one study [7].

Acupuncture is commonly recognized worldwide as a mainstream CAM therapy. Acupuncture is the practice of inserting a needle or needles into certain points in the

body, known as meridian acupuncture points, for therapeutic or preventive purposes [8]. Numerous studies have shown that acupuncture is well tolerated by patients, safe, and cost effective compared to routine care [9].

Additionally, acupuncture is widely used in mental disorders such as anxiety disorders [10], dementia [11], eating disorders [12], schizophrenia [13], sleep disorders [14], and substance-related disorders [15, 16]. Electroacupuncture is effective in rat models of stress and thus might be a useful adjunct therapy in stress-related anxiety disorders [17]. Acupuncture has positive effects in PTSD patients, although the evidence is still lacking as to its true efficacy for this condition [18].

There have been two reviews published on acupuncture or its variants for PTSD [19, 20]. David Feinstein reviewed 2 randomized controlled trials (RCTs) and 6 outcome studies which tested whether brief psychological exposure with acupoint tapping was effective for PTSD or not and its conclusion was not confirmative [19]. Also Michael Hollifield reviewed acupuncture for PTSD referring one published and one unpublished clinical trial and suggested further definitive research is needed because of lack of well-conducted RCTs [20]. However, there has been no systematic review published to date fully summarizing the current total evidence about the quality and effectiveness of acupuncture for PTSD. For this reason, we conducted a systematic review of RCTs and prospective clinical trials to assess critically whether acupuncture improves the symptoms of PTSD and to make recommendations for future research based on gap areas identified in this review.

2. Methods

2.1. Data Sources and Search Strategy. Following the COSI model [21], we searched the following electronic databases over time periods from their inception to July 2012: Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE through PubMed, EMBASE, Allied and Complementary Medicine Database (AMED), CINAHL, Pilots, Google, Korean databases (which include DBpia, Korea Institute of Science and Technology Information (KISTI), KoreaMed, Korean traditional knowledge portal, OASIS, RISS, the National Assembly Library, and The National Library of Korea), Chinese databases (which include China Academic Journal, http://www.cqvip.com and WANFANG DATA), and a Japanese database (Japan Science and Technology Information Aggregator Electronic). We also searched the grey literature; unpublished trials were searched via the Register of the Controlled Trials databases (http://www.controlled-trials.com and http://www.clinicaltrials.gov), and we communicated with identified experts in the field of acupuncture and PTSD, searched our departmental files, and pearled the references of all included articles for other relevant articles perhaps not picked up through other methods of searching.

The key search terms were "(acupuncture OR acup*) AND (stress disorders, post-Traumatic OR posttraumatic stress disorder OR posttraumatic stress disorder OR PTSD)." MeSH strategy was applied to ensure the most powerful search where applicable. Search strategies were adjusted for each of the databases. Personal contacts were made with the original authors of the searched studies to identify any potential missing data from the publications.

2.2. Study Selection. Two psychiatrists (J. H. Lim and H. W. Kang) actively participated in the study selection process based on clinical expertise, and two experienced researchers (B. C. Shin, C. Cindy) monitored the whole process of systematic review. All reviewers were fully trained in the systematic review process executed.

2.2.1. Types of Studies. The review was not restricted by study design, however, study should be prospective clinical trials. We included RCTs and nonrandomized controlled trials that compared acupuncture or its variants with a control or control groups. We also included uncontrolled clinical trials (UCTs) of acupuncture for PTSD to give our research question a more solid ground or to make recommendations for future research. However, we separately analyzed RCTs and others, and interpreted more weighted on RCTs because of research quality following the validity of evidence. No restrictions were imposed on studies with regard to blinding, languages, or year published.

2.2.2. Types of Participants. We selected all studies including patients with PTSD diagnosed by any set of criteria, DSM-IV or ICD-10, regardless of gender, age, nationality, or outpatient therapy or inpatient therapy.

2.2.3. Types of Interventions/Controls. Clinical trials investigating any type of needling acupuncture, specifically classical acupuncture, electroacupuncture, auricular acupuncture were included. We also included trials that included acupuncture as a more complex intervention, that is, acupuncture plus another intervention if the comparison group was that other intervention. We included trials using control groups with no treatment, sham/placebo acupuncture, and conventional treatments for PTSD patients. We excluded laser acupuncture and acupoint stimulation such as acupressure, moxibustion, tapping, and so forth because of the lack of needling. We excluded trials with controls that acted as "healthy participants."

2.2.4. Types of Outcome Measures. The most recent guideline for treatment of PTSD [5] includes the following major outcomes: 1st: "reduction in severity of PTSD symptoms"; 2nd: "prevention/reduction of trauma-related comorbid conditions"; 3rd: "patient adherence to treatment plan"; 4th:"response to treatment"; 5th: "social, occupational, adaptive, and interpersonal functioning"; 6th: "quality of life" and 7th: "rate of relapse." The main outcome measures were any relevant PTSD scales as clinician-administered PTSD scale (CAPS), depression scale, and anxiety scale. Other scales as related to impairment, proportion of patients recovered were extracted following predefined protocol.

2.3. Screening, Data Extraction, and Quality Assessment. After screening titles and abstracts retrieved through our search, we excluded all articles that did not match our inclusion/exclusion criteria according to the predefined eligibility criteria mentioned above. Then, expected inclusions were carefully read in full text, and final inclusion was decided by two independent reviewers (Y. D. Kim, I. Heo) by matching method. If studies were written in languages incomprehensible for the reviewers, all articles not written in native language were translated by colleagues. Then we first classified these by the eligibility criteria. If there was a need for full text review, we evaluated these after translation. Data were extracted independently based on predefined characteristics to describe each study (refer to Table 1) by the two reviewers. All disagreements were resolved by discussion and consensus, or by the first author. The Cochrane risk of bias for assessing the quality of included RCTs [22], the CONSORT 2010 checklist for reporting quality of RCTs [23] and the revised standards for reporting interventions in clinical trials of acupuncture (STRICTA) guideline for reporting quality of acupuncture trials [24] were used to evaluate the methodological quality of the included publications. All reviewers were fully trained in the quality assessment and data extraction methodology.

2.4. Data Synthesis and Statistics. Two authors (Y. D. Kim, B. C. Shin) calculated effect estimates (effect size: ES) to summarize the effects of acupuncture on each outcome by recalculation for mean and standard deviation (SD) because all original data were continuous ones. The standardized mean difference (SMD) and 95% confidence interval (CI) on each outcome measurement were calculated using Cochrane Collaboration software (Review Manager (RevMan) Version 5.1.7 for Windows. Copenhagen: The Nordic Cochrane Centre). For meta-analysis, we pooled data across studies using weighted mean difference (WMD) because same measurement was used. Random effect model was used because clinical heterogeneities were expected across the studies. To assess the heterogeneity among the trials, Chi-square test and the Higgins I^2 test were used.

3. Results

3.1. Study Description. The searches retrieved 136 potentially relevant articles. After screening the titles and abstracts, we excluded 120 studies (Figure 1). 16 articles were read in full and evaluated. Subsequently, 5 studies were excluded because 1 was a controlled trial but the control group members were healthy subjects [30], 1 was active status not recruiting [31], 1 was recruiting status [32], and 2 were completed but with the results not published [33, 34]. Finally 9 RCTs and 2 UCTs were identified. Of 9 RCTs published, Zhang et al. RCT [25] was split or duplicated published with same data [25, 35–39]. So we included only 1 RCT with full data [25] from the 6 RCTs [25, 35–39]. Consequently, 4 RCTs [18, 25–27] and 2 UCTs [28, 29] met our inclusion criteria. Figure 1 sums up the search results based on a four-phase flow diagram in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement format [40]. The key data are summarized in Table 1. One RCT originated from the USA [18], while all the others were from China [25–29]. All RCTs adopted a parallel-group design. Two of them were two-parallel-arm group designs [26, 27], one was a three-parallel-arm group design [18], and one was a four-parallel-arm group design [25]. Two RCTs [18, 25] were based on a sample size calculation, whereas the other two RCTs [26, 27] did not report this.

The four RCTs evaluated 543 PTSD patients (mean sample size per arm: 49). The duration of treatment was 1 to 12 weeks. A table showing baseline clinical characteristics for each group was reported in only one RCT [18].

3.2. Interventions. One RCT compared needle acupuncture to cognitive-behavioral therapy (CBT) and a waitlist control [18], and another used electroacupuncture only or with moxibustion or with auricular acupuncture versus oral selective serotonin reuptake inhibitors (SSRIs) [25]. One RCT tested electroacupuncture plus moxibustion versus oral SSRI [26], and one RCT compared acupoint stimulation plus CBT to CBT alone [27]. One UCT [29] used just acupuncture, the other UCT [28] used electroacupuncture plus auricular acupuncture and moxibustion. 1 RCT [18] and 1 UCT [29] used manual stimulation without electrical stimulation, and the other 3 RCTs [25–27] and 1 UCT [28] used electrical stimulation.

3.3. Outcomes

3.3.1. Acupuncture versus CBT/Acupuncture versus Waitlist Control/CBT versus Waitlist Control. One high-quality RCT evaluated the effect of acupuncture against CBT and a waitlist control [18]. No statistical difference was found between acupuncture and CBT. But, acupuncture treatment was statistically superior to waitlist control on four outcome measures; posttraumatic symptom scale-self report (PSS-SR) (ES, −0.98; $P = 0.001$), Depression: self-rated Hopkins symptom checklist-25 (HSCL-25) (ES, −0.68; $P = 0.02$), Anxiety: HSCL-25 (ES, −0.91; $P = 0.003$), and Impairment: Sheehan Disability Inventory (SDI) (ES, −0.64; $P = 0.03$, Table 1). The CBT was also statistically superior to waitlist control on four outcome measures; PSS-SR (ES, −0.85; $P = 0.004$), Depression: HSCL-25 (ES, −0.80; $P = 0.008$), Anxiety: HSCL-25 (ES, −0.79; $P = 0.008$), Impairment (ES, −0.64; $P = 0.03$). The therapeutic effects of acupuncture and CBT were similar on the ESs [41] (Table 1).

3.3.2. Acupuncture versus Oral SSRI. One RCT evaluated the effect of electroacupuncture versus oral SSRI [25]. No statistical difference was found between two groups.

3.3.3. Acupuncture Plus CBT versus CBT Alone. One RCT assessed the effect of acupoint stimulation plus CBT in comparison to CBT alone [27]. Recalculation of the mean difference (MD) revealed a favorable effect of acupoint stimulation plus CBT in terms of IES-R (ES, −1.56; $P < 0.00001$) and the self-compiled questionnaire (ES, −0.59; $P = 0.01$) (Table 1).

Table 1: Summary of randomized controlled trials and prospective clinical trials of acupuncture for posttraumatic stress disorder.

First author [ref] (year) country	Population	Study design	Sample size/N, analyzed	Intervention/control group (regime)	Treatment session	Main outcomes	Intergroup difference	Comments
RCT ($n = 4$)								
Hollifield [18] (2007) U.S.A.	28 out of 84 identified childhood abuse/ Others, unknown trauma	3 arm parallel, open	84/73	(A) AT + AAT ($n = 29$)/ (B) CBT ($n = 28$) (C) WLC ($n = 27$)	24 sessions	(1) PTSD scale (PSS-SR) (2) Depression (HSCL-25) (3) Anxiety (HSCL-25) (4) Impairment (SDI)	(1) A versus B: $P = 0.36$, MD, −0.26 [−0.83, 0.30] A versus C: $P = 0.001$, MD, −0.98 [−1.58, −0.38] B versus C: $P = 0.004$, MD, −0.85 [−1.44, −0.27] (2) A versus B: $P = 0.92$ MD, 0.03 [−0.53, 0.59] A versus C: $P = 0.02$, MD, −0.68 [−1.27, −0.10] B versus C: $P = 0.008$, MD, −0.80 [−1.38, −0.21] (3) A versus B: $P = 0.39$, MD, −0.25 [−0.81, 0.31] A versus C: $P = 0.003$, MD, −0.91 [−1.51, −0.32] B versus C: $P = 0.008$, MD, −0.79 [−1.37, −0.21] (4) A versus B: $P = 0.98$, MD, −0.01 [−0.57, 0.55] A versus C: $P = 0.03$, MD, −0.64 [−1.22, −0.06] B versus C: $P = 0.03$, MD, −0.64 [−1.22, −0.07]	The AT group had significantly better improvements in PTSD symptoms than the WLC group. But, there was no statistically significant difference between the AT group and the CBT group.
Zhang [25] (2010) China	Earthquake	4 arm parallel, open	276/256	(A) EA ($n = 69$) (B) EA + moxa ($n = 69$) (C) EA + AAT ($n = 69$)/ (D) Oral SSRI ($n = 69$)	36 sessions	(1) PTSD scale (CAPS) (2) Depression (HAMD) (3) Anxiety (HAMA)	(1) A versus D: $P = 0.43$, MD, −0.13 [−0.47, 0.20] B versus D: $P = 0.88$, MD, −0.03 [−0.36, 0.31] C versus D: $P = 0.55$, MD, −0.10 [−0.44, 0.23] (2) A versus D: $P = 0.14$, MD, −0.25 [−0.59, 0.08] B versus D: $P = 0.34$, MD, −0.16 [−0.50, 0.17] C versus D: $P = 0.23$, MD, −0.21 [−0.54, 0.13] (3) A versus D: $P = 0.34$, MD, −0.16 [−0.50, 0.17] B versus D: $P = 0.64$, MD, −0.08 [−0.41, 0.25] C versus D: $P = 0.54$, MD, 0.11 [−0.23, 0.44]	The therapeutic effect of EA was not better than that of oral SSRI.
Zhang [26] (2010) China	Earthquake	2 arm parallel open	92/81	(A) EA + moxa ($n = 46$)/ (B) Oral SSRI ($n = 46$)	36 sessions	(1) PTSD scale (CAPS) (2) Depression (HAMD) (3) Anxiety (HAMA)	(1) A versus B: $P < 0.00001$, MD, −1.77 [−2.26, −1.29] (2) A versus B: $P < 0.00001$, MD, −1.96 [−2.46, −1.46] (3) A versus B: $P < 0.00001$, MD, −1.53 [−2.00, −1.07]	EA plus moxa was more effective than oral SSRI therapy.
Zhang [27] (2011) China	Earthquake	2 arm parallel open	91/90	(A) Acupoint Stimulation + CBT ($n = 67$)/ (B) CBT ($n = 24$)	3~4 sessions*	(1) PTSD scale (IES-R) (2) PTSD scale (self compiled questionnaire)	(1) A versus B: $P < 0.00001$, MD, −1.56 [−2.08, −1.04] (2) A versus B: $P = 0.01$, MD, −0.59 [−1.07, −0.12]	The acupoint stimulation plus CBT showed better efficacy than CBT therapy alone.
UCT ($n = 2$)								
Wang [28] (2009) China	Earthquake	UCT	69	EA + AAT + moxa	36 sessions	(1) The number of cured/improved/non-improved	Not applicable	Treatment was effective in 65 out of 69 (94.2%).

Table 1: Continued.

First author [ref] (year) country	Population	Study design	Sample size/N, analyzed	Intervention/control group (regime)	Treatment session	Main outcomes	Intergroup difference	Comments
UCT ($n = 2$)								
Yuan [29] (2009) China	Earthquake	UCT	34	AT	20 sessions	(1) The number of cured/improved/non-improved	Not applicable	AT was effective in 31 out of 34 (91.2%).

Abbreviations: RCT: randomized controlled trial; UCT: uncontrolled clinical trial; AT: classical acupuncture; EA: electro-acupuncture; moxa, moxibustion; AAT: auricular acupuncture; CBT: cognitive behavioral therapy; WLC: waitlist control; SSRI: selective serotonin reuptake inhibitors; PSS-SR: posttraumatic symptom scale-self report; HSCL-25: self-rated Hopkins symptom checklist-25; SDI: Sheehan Disability Inventory; MD: mean difference; CAPS: clinician-administered PTSD scale; HAMD: Hamilton depression rating scale; HAMA: Hamilton anxiety rating scale; IES-R: Chinese version of the incident effect scale revised; * treated a time every other day for 1 week.

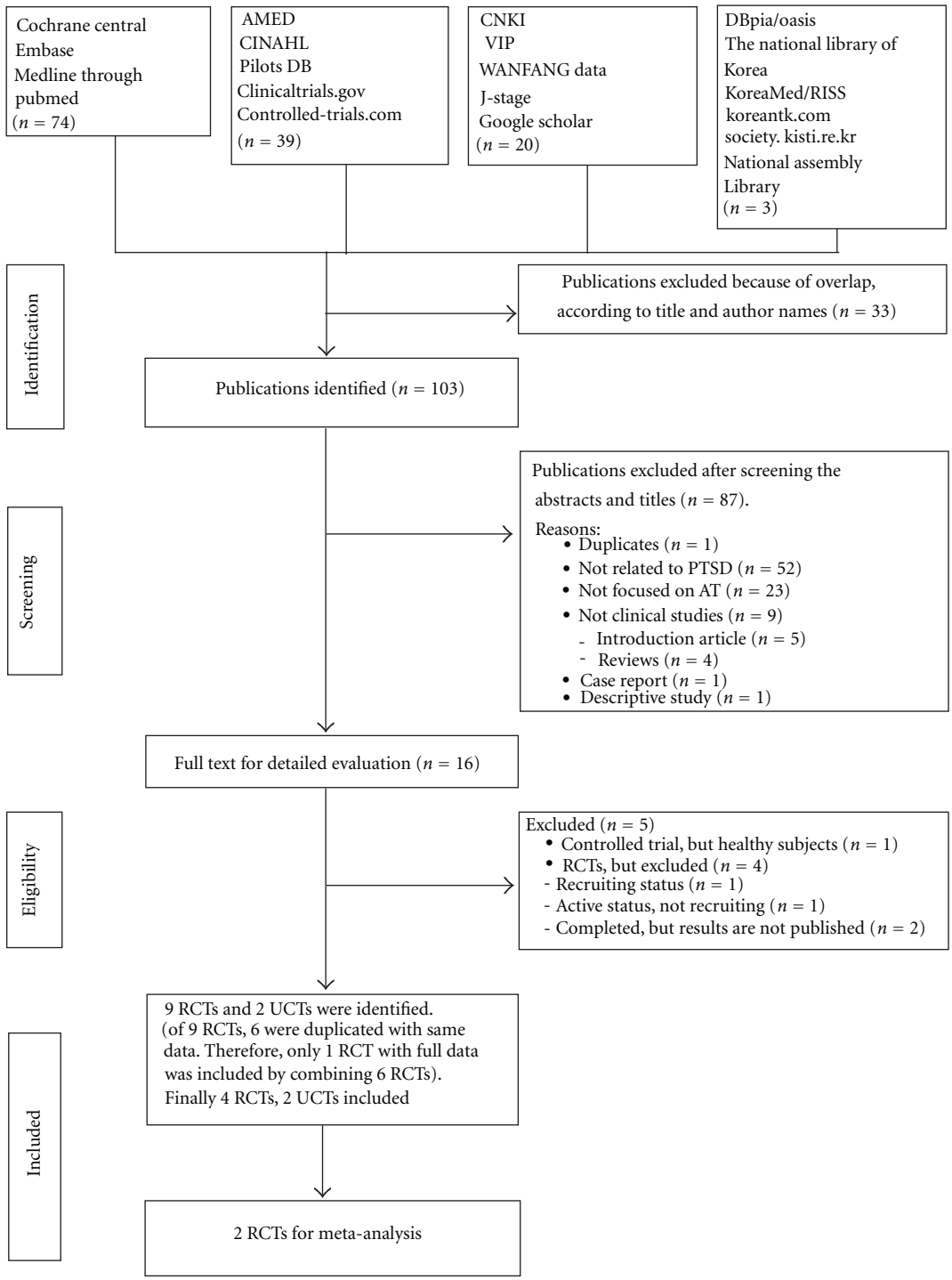


Figure 1: Flow chart of the trial selection process. PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; UCT: uncontrolled clinical trial; AT: acupuncture.

3.3.4. Acupuncture Plus Moxibustion versus Oral SSRI. Two RCTs assessed the effects of electroacupuncture plus moxibustion against oral SSRI [25, 26]. One RCT reported no statistical difference between the two groups [25]. However, the other RCT showed that electroacupuncture plus moxibustion was statistically superior to oral SSRI on outcome clinician-administered PTSD scale (CAPS) (ES, −1.77; $P < 0.00001$), depression (ES, −1.96; $P < 0.00001$), and anxiety (ES, −1.53; $P < 0.00001$) [26] (Table 1).

The meta-analysis of electroacupuncture plus moxibustion versus oral SSRI showed a significant favorable effect of electroacupuncture plus moxibustion on outcome CAPS (2 studies, $n = 115$, ES, −3.19; 95% CI: −3.93 to −2.46, $P < 0.00001$, heterogeneity: $\chi^2 = 0.50$, $P = 0.48$, $I^2 = 0\%$),

Table 2: Cochrane risk of bias of included randomized controlled trials.

First author [ref] (Year)	Hollifield [18] (2007)	Zhang [25] (2010)	Zhang [26] (2010)	Zhang [27] (2011)
(1) Random sequence generation (selection bias)	L (computerized randomization)	L (computerized randomization)	U	U
(2) Allocation concealment (selection bias)	L (central allocation)	L (sequentially numbered, opaque sealed envelopes)	U	U
(3) Blinding of participants (performance bias)	H	H	H	H
(4) Blinding of outcome assessment (detection bias)	L (mentioned)	L (mentioned)	U	U
(5) Incomplete outcome data (attrition bias)	L (mentioned)	U	U	U
(6) Selective reporting (reporting bias)	U	U	U	U
(7) Other sources of bias (other bias)	U	U	U	U

L: low risk of bias; H: high risk of bias; U: unclear.

depression (2 studies, $n = 115$, ES, −1.76; 95% CI: −2.21 to −1.31, $P < 0.00001$, heterogeneity: $\chi^2 = 1.04$, $P = 0.31$, $I^2 = 4\%$), and anxiety (2 studies, $n = 115$, ES, −1.14; 95% CI: −1.44 to −0.84, $P < 0.00001$, heterogeneity: $\chi^2 = 0.62$, $P = 0.43$, $I^2 = 0\%$) (Table 4).

3.3.5. Acupuncture Treatment in 2 UCTs. Two UCTs evaluated acupuncture treatment for total 103 earthquake-caused PTSD patients and showed effectiveness of 94.2% [28] and 91.2% [29], respectively (Table 1).

3.3.6. Adverse Events. Of all 6 studies, 2 RCTs described adverse events related to needle acupuncture [18, 25]. One study noted that some patients (original paper did not report the exact number) mentioned roughness of operational practices, fear of needles, bleeding, hematoma, pain, and fainting [25]. Another study reported just one perceived adverse effect (kidney pain) as a reason for withdrawal from acupuncture treatment [18]. No serious adverse events were reported.

3.4. Risk of Bias and Reporting Quality

3.4.1. Risk of Bias in Included RCTs Based on Cochrane Criteria. The risk of bias was low in one RCT [18], whereas one trial [25] had a moderate risk of bias and two trials [26, 27] had a high risk of bias in most categories (Table 2). Two RCTs employed adequate sequence generation methods and allocation concealment [18, 25], whereas the other two [26, 27] failed to report those categories. Assessor blinding was reported in the former two RCTs [18, 25]. The risk of bias for incomplete outcome data was low in only one RCT [18]. In all, the four included RCTs had an unclear risk of bias in terms of selective reporting and other sources of bias.

3.4.2. Reporting Quality of 4 Included RCTs Based on CONSORT 2010 Checklist. Many leading medical journals and major international editorial groups have endorsed the CONSORT statement, and the statement facilitates critical appraisal and interpretation of RCTs [23]. For this reason, the current review assessed the reporting quality of included RCTs based on the CONSORT 2010 guideline. The 4 included RCTs described 22 items (59.5%) [18] among 37 items, 15 items (40.5%) [25], 9 items (24.3%) [26], and 8 items (21.6%) [27] according to the CONSORT 2010 checklist [23].

3.4.3. Reporting Quality of 4 Included RCTs Based on Revised STRICTA. The STRICTA reporting guideline is an extension of CONSORT was designed to improve the completeness and transparency of reporting of interventions in controlled trials of acupuncture [24], so that such trials may be more accurately interpreted and readily replicated [24]. The reporting quality of acupuncture was high for two of the included RCTs [18, 25], medium in one [26], and low in remaining RCT [27]. The 4 included RCTs reported 16 of 17 items (94.1%) [18], 15 items (88.2%) [25], 13 items (76.5%) [26], and 8 items (47.1%) [27] according to the revised STRICTA guideline. The two high-quality trials [18, 25] presented almost all items transparently except one or two items, whereas the low-quality trial [27] did not describe clearly even the reported 8 items (Table 3).

4. Discussion

This is the first systematic review and meta-analysis of prospective clinical trials on the effectiveness of acupuncture for treatment of PTSD. Only 4 RCTs and 2 UCTs met the inclusion criteria for this review. Our main finding of this review is that acupuncture is effective for PTSD based on one high-quality RCT [18] and a meta-analysis.

The high-quality RCT showed that acupuncture had statistically significant effects compared to a waitlist control, although no statistical difference was found between

Table 3: Reporting quality of 4 included RCTs based on revised STRICTA.

Checklist item	Hollifield et al. [18] (2007)	Zhang et al. [25] (2010)	Zhang et al. [26] (2010)	Zhang et al. [27] (2011)
(1) Acupuncture rationale				
(1a) Style of acupuncture	TCM	TCM	TCM	n.r.
(1b) Reasoning for treatment provided	A paper by Napadow et al., 2005 [42]	A paper by Hollifield et al., 2007 [18]	A paper by Hollifield et al., 2007 [18]	n.r.
(1c) Extent to which treatment was varied	2 types of AT (1) AT: 25 fixed needles plus up to 3 flexible needles within 15 points (2) AAT: ≥6 vaccaria seeds	Fixed interventions (A) EA only (B) EA + moxa (C) EA + AAT	Fixed interventions EA + moxa	Fixed intervention
(2) Details of needling				
(2a) Number of needle insertions per subject per session	(1) AT: 25 plus up to 3 needles (2) AAT: ≥6 vaccaria seeds	(1) EA: 8 needles (2) AAT: 6 vaccaria seeds	EA: 8 needles	unclear.
(2b) Names of points used	(1) AT: bilateral at LR3, PC6, HT7, ST36, SP6, GB20, BL14, 15, 18, 20, 21 and 23/unilateral at Yintang (2) AAT: unilateral at Shenmen, Sympathetic, Liver, Kidney, Lung points	(1) EA: bilateral at GB20/unilateral at GV24, EX-HN1, GV20 (2) AAT: unilateral at Subcortex, Shenmen, Sympathetic, Heart, Liver, Kidney (3) moxa: bilateral at BL23, BL52/unilateral at GV4	(1) EA: bilateral at GB20/unilateral at GV24, EX-HN1, GV20 (2) moxa: bilateral at BL23, BL52/unilateral at GV4	Unilateral at left PC8
(2c) Depth of insertion	(1) AT: 1/4 to 1/2 inch (2) AAT: not inserted	(1) EA: 0.5 to 1.2 cun (2) AAT: not inserted	EA: 0.5 to 1.2 cun	n.r.
(2d) Responses sought	(1) AT: n.r. (2) AAT: not applicable	(1) EA: de-qi (2) AAT: not applicable.	EA: de-qi	n.r.
(2e) Needle stimulation	(1) AT: manipulation (2) AAT: self-massage on the seeds for 15 min/d	(1) EA: electrical stimulation, 100 Hz (2) AAT: 1-2 min pressure	EA: electrical stimulation, 5~8.3 Hz	A Japanese stimulator with 50 Hz was used
(2f) Needle retention time	(1) AT: 25–40 min (2) AAT: unclear	(A) 30 min (B) 30 min (C) 30 min	30 min	Unclear, but the left PC8 was stimulated for 30 min
(2g) Needle type	(1) AT: Viva needles, 34 g (2) AAT: vaccaria seeds	(1) EA: 0.30 mm × 40 mm (2) AAT: vaccaria seeds	n.r.	n.r.
(3) Treatment regimen				
(3a) Number of treatment sessions	24 sessions	36 sessions	(1) EA: 18 sessions (2) moxa: 36 sessions	3~4 sessions*
(3b) Frequency and duration of treatment sessions	Twice a week, 1 hour per session, 12 weeks	Three times a week, 12 weeks	(1) EA: three times a week, 6 weeks (2) moxa: three times a week, 12 weeks	A time every other day for 1 week
(4) Other components of treatment				
(4a) Details of other interventions administered to the acupuncture group	Patients were taught how to use vaccaria seeds for symptom management	(3) moxa: 30 g and 20 min/session, wooden moxibustion box 20 mm × 15 mm × 12 mm	(2) moxa: 20 min/session	CBT
(4b) Setting and context of treatment	n.r.	n.r.	n.r.	n.r.

Table 3: Continued.

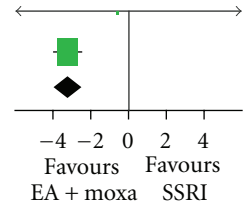
Checklist item	Hollifield et al. [18] (2007)	Zhang et al. [25] (2010)	Zhang et al. [26] (2010)	Zhang et al. [27] (2011)
(5) Practitioner background				
(5) Description of participating Acupuncturists	Doctor of Oriental Medicine in New Mexico with 4 years postgraduate TCM clinical experience	n.r.	n.r.	n.r.
(6) Control or comparator interventions				
(6a) Rationale for the control or comparator	(B) A review by Bisson and Andrew, 2005 [43] (C) not applicable	Approval of FDA	n.r.	n.r.
(6b) Precise description of the control or comparator	(B) CBT (C) WLC	(D) Oral SSRI (Paroxetine 20 mg, once/day, 12 weeks)	Oral SSRI (Paroxetine 20 mg, once/day, 12 weeks)	(B) CBT

Abbreviations: RCT: randomized controlled trial; TCM: traditional Chinese medicine; n.r: not reported; AT: classical acupuncture; EA: electro-acupuncture; moxa, moxibustion; AAT: auricular acupuncture; CBT: cognitive behavioral therapy; WLC: waitlist control; SSRI: selective serotonin reuptake inhibitors.
*treated a time every other day for 1 week.

Table 4: Meta-analysis of acupuncture for posttraumatic stress disorder. PTSD: posttraumatic stress disorder; CAPS, clinician-administered PTSD scale; HAMD, Hamilton depression rating scale; HAMA, Hamilton anxiety rating scale; EA, electro-acupuncture; moxa, moxibustion; SSRI, selective serotonin reuptake inhibitors;

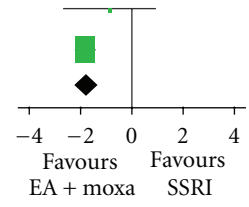
(a) PTSD scale (CAPS).

Study or subgroup	EA + Moxa			SSRI				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Zhang et al., 2010 [25]	−36.15	21.72	69	−35.58	22.12	69	1.0%	−0.57 [−7.88, 6.74]	
Zhang et al., 2010 [26]	−17.17	1.84	46	−13.95	1.76	46	99.0%	−3.22 [−3.96, −2.48]	
Total (95% CI)			**115**			**115**	**100.0%**	**−3.19 [−3.93, −2.46]**	
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.50$, df = 1 ($P = 0.48$); $I^2 = 0\%$									
Test for overall effect: $Z = 8.55$ ($P < 0.00001$)									



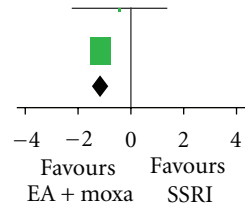
(b) Depression (HAMD).

Study or subgroup	EA + Moxa			SSRI				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Zhang et al., 2010 [25]	−7.42	5.58	69	−6.55	5.1	69	6.2%	−0.87 [−2.65, 0.91]	
Zhang et al., 2010 [26]	−7.27	0.93	46	−5.45	0.91	46	93.8%	−1.82 [−2.20, −1.44]	
Total (95% CI)			**115**			**115**	**100.0%**	**−1.76 [−2.21, −1.31]**	
Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 1.04$, df = 1 ($P = 0.31$); $I^2 = 4\%$									
Test for overall effect: $Z = 7.72$ ($P < 0.00001$)									



(c) Anxiety (HAMA).

Study or subgroup	EA + Moxa			SSRI				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Zhang et al., 2010 [25]	−6.51	5.26	69	−6.08	5.43	69	2.9%	−0.43 [−2.21, 1.35]	
Zhang et al., 2010 [26]	−5.48	0.75	46	−4.32	0.75	46	97.1%	−1.16 [−1.47, −0.85]	
Total (95% CI)			**115**			**115**	**100.0%**	**−1.14 [−1.44, −0.84]**	
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.62$, df = 1 ($P = 0.43$); $I^2 = 0\%$									
Test for overall effect: $Z = 7.39$ ($P < 0.00001$)									



acupuncture and CBT. Also the therapeutic effect of acupuncture was similar with CBT therapy based on the trial. Additionally, the clinical improvement related to acupuncture or CBT lasted for at least 3 months after the end of treatment in the high-quality RCT.

The meta-analysis showed that acupuncture plus moxibustion was superior to oral SSRI for PTSD. But, we should interpret these results with caution because the meta-analysis was based on one medium-quality RCT [25] and one low-quality RCT [26].

One RCT [27] showed that acupoint stimulation plus CBT was more effective than CBT alone in reducing PTSD symptoms. However, acupuncture treatment was not described transparently. Therefore, this result had doubtful reliability.

We found a similar pattern of reporting quality when comparing the Cochrane risk of bias [22] with the CONSORT 2010 checklist [23]. Two of the included studies [18, 25] had a high reporting quality in terms of acupuncture based on the revised STRICTA guideline [24]. All the studies failed to describe in detail adverse effects related to acupuncture.

We would like to emphasize the clinical importance of acupuncture for PTSD. Acupuncture might be useful in emergency medicine [44]. A recent case series study suggested possible effectiveness of acupuncture in emergency conditions involving PTSD and emotional trauma [45]. In addition, acupuncture is a conveniently portable medical device for taking emergency measures, and it is very cheap, safe, and easy to handle for trained practitioners.

According to a study [46], during long-term SSRI therapy, the most troubling adverse effects were sexual dysfunction, weight gain, and sleep disturbance. The incidence rate of sexual dysfunction was reported as 2% to 7% [47]. Mean weight gain of 10.8 kg (24 lbs) was found after 6 to 12 months of paroxetine therapy [48]. On the other hand, for acupuncture, "mild" adverse events of such as bleeding, bruising, pain on needling occurred in rate of 6.8% (2,178 out of 31,822 sessions) [49]. And no serious adverse events were reported in total 66,229 treatment sessions according to two studies [49, 50]. Therefore acupuncture may be a relatively safe alternative for PTSD in contrast to SSRI, if long-term therapy is needed for treatment.

This systematic review has several limitations. First, although we made strong efforts to retrieve all RCTs on the subject, the evidence reviewed is potentially incomplete because only one rigorous study was included. Second, because there was no RCT on PTSD with a sham acupuncture control, we could not evaluate the effects of acupuncture compared to an inert placebo control [51]. Third, study design was quite different across the four included RCTs. Two RCTs [18, 25] compared acupuncture with different controls (CBT and oral SSRI), and the other two RCTs [26, 27] employed acupuncture as a cointervention of moxibustion and CBT. These very different designs across studies prevented us from abstracting a firm conclusion. Furthermore, the paucity of included trials and the suboptimal methodological quality of the primary data overall, except for one high-quality trial, are also important vulnerabilities of this review.

In total, from these drawbacks we could suggest several important recommendations for future research in this area. One is a need for appropriate controls such as sham/placebo control or other relevant active controls for testing the efficacy or effectiveness of acupuncture for PTSD in the design of parallel RCT or comparative effectiveness research. The second is outcomes should be used by validated one as primary one is PTSD scale and the secondary one is depression or anxiety with safety reporting. The third is high methodological quality is strongly required, as adequate randomization with allocation concealment, blinding of participants and assessors, or sample size estimation for power of trial, with following guideline of CONSORT and STRICTA.

5. Conclusions

The results of this systematic review and meta-analysis suggest that evidence of the effectiveness of acupuncture for PTSD is encouraging but not cogent, because only two RCTs were included in meta-analysis, and it is too small to verify the efficacy of acupuncture. For the future researches, sham-controlled RCTs [52] or comparative effectiveness researches [53] are required to test efficacy and effectiveness of acupuncture for PTSD. To prevent performance bias and detection bias, blinding of participants and outcome assessment should be kept in future trials, too.

Disclosure

The authors report no financial relationship or other relevant to the subject of this paper.

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REVIEW

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Effects from acupuncture in treating anxiety: integrative review

Efeitos da acupuntura no tratamento da ansiedade: revisão integrativa

Efectos de la acupuntura en el tratamiento de la ansiedad: revisión integradora

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ABSTRACT

Objective: to evaluate the scientific evidence that is available in the literature on the effects of acupuncture for treating anxiety and on the quality of such studies. **Method:** the study is an integrative review of CINAHL, LILACS, PUBMED-PICO, SciELO, and The Cochrane Library between 2001 and 2014. Keywords *anxiety*, *acupuncture therapy*, *acupuncture*, and *anxiety disorders* were combined among themselves to ensure a wide search of primary studies. **Results:** among 514 articles, 67 were selected to be fully read and 19 were included. Among these, 11 were found to have strong evidence levels. Among the six articles about randomized clinical studies, five were found to be of reasonable quality. Two studies used acupuncturist nurses to perform their interventions. Its results showed positive and statistically significant effects from using acupuncture for treating subjects with anxiety. **Conclusion:** acupuncture seems to be a promising treatment for anxiety; however, there is a need for improving the methodological quality of the research on this field.

Descriptors: Acupuncture; Anxiety; Acupuncture Therapy; Evidence-Based Medicine; Comprehensive Health Care.

RESUMO

Objetivo: avaliar as evidências científicas disponíveis na literatura sobre os efeitos da acupuntura no tratamento da ansiedade e a qualidade desses estudos. **Método:** revisão integrativa, realizada nas bases/bancos de dados CINAHL, LILACS, PUBMED-PICO, SciELO, *The Cochrane Library*, no período entre 2001 a 2014. Os descritores *anxiety*, *acupuncture therapy*, *acupuncture* e *anxiety disorders* foram combinados entre si para garantir a ampla busca de estudos primários. **Resultados:** dos 514 artigos, 67 foram selecionados para leitura na íntegra e 19 incluídos. Desses, 11 apresentaram forte nível de evidência. Dos seis artigos de estudos clínicos randomizados, cinco apresentaram qualidade classificada como razoável. Dois estudos utilizaram acupunturistas enfermeiros para a aplicação da intervenção. Os resultados mostram efeitos positivos e estatisticamente significativos do uso da acupuntura para tratamento de indivíduos com ansiedade. **Conclusão:** a acupuntura parece ser um tratamento promissor para a ansiedade, no entanto, há necessidade de melhorar a qualidade metodológica das pesquisas nessa temática.

Descritores: Acupuntura; Ansiedade; Terapia por Acupuntura; Medicina Baseada em Evidências; Assistência Integral à Saúde.

RESUMEN

Objetivo: evaluar las evidencias científicas disponibles en la literatura sobre los efectos de la acupuntura en el tratamiento de la ansiedad, y la calidad de dichas investigaciones. **Método:** revisión integradora, llevada a cabo en las bases y bancos de datos CINAHL, LILACS, PubMed PICO, SciELO, The Cochrane Library, en el periodo entre el año 2001 hasta el 2014. Se combinaron entre sí mismas las palabras clave "*anxiety*", "*acupuncture therapy*", "*acupuncture*" y "*anxiety disorders*" con el fin de garantizar

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Acupuncture for treatment of anxiety, an overview of systematic reviews

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ABSTRACT

Purpose: To evaluate the methodological quality and summarize evidence of important outcomes of systematic reviews (SRs)/Meta analyses (MAs) of acupuncture for anxiety.

Methods: We conducted a comprehensive literature search for SRs/MAs in PubMed, EMBASE, Cochrane library, Chinese Biomedical Databases (CBM), Wanfang database and China National Knowledge Infrastructure (CNKI) until November 30, 2018. Three reviewers independently extracted data and assessed the methodological quality of the reviews according to the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to rate the quality of evidence. In the pre-experiment, we used the intra-class correlation coefficient (ICC) to assess reviewer agreement, the ICC value for overall score was 0.978.

Results: Ten reviews were included. The assessment results of AMSTAR-2 showed that the methodological quality of all included studies was critically low. The lowest score were item "provide a list of excluded studies and justify the exclusions" and item "report sources of funding for the included studies", none of studies provided information about the above two items, followed by the "providing a priori design" item with only two (20%) studies conforming to this item. For GRADE, of the 7 outcomes, high quality evidence was provided in only 1 (14.3%), moderate in 2 (28.6.7%), and low in 4 (57.1%).

Conclusion: Although most of the included reviews indicated that acupuncture group was more effective than control group in the treatment of anxiety, more importantly, the methodological quality of the included reviews and the quality of evidence were low. More high-quality evidence is needed to determine whether acupuncture is more effective than other treatments.

1. Introduction

Anxiety ranks in the top ten causes of disability worldwide and is the most prevalent psychiatric condition in the European Union with over 60 million people being affected by this condition [1] it has been reported to contribute substantially to the Global Burden of Disease as stated in the 2015 report (GBD 2015).[2]

Pharmacotherapy and psychotherapy are conventional treatments for anxiety, and pharmacotherapy has always been considered the standard treatment [3] Nonetheless, pharmacotherapy is not free from concern since they can lead to habituation (especially in long-term treatments), and present side effects and drug interactions, among other problems [4,5] Therefore, there is a need for more effective, safer interventions for anxiety. This has led to an increase in the attention

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Acupuncture and electroacupuncture for anxiety disorders: A systematic review of the clinical research

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ABSTRACT

Anxiety disorders are one of the most common mental health concerns with a major contribution to the global burden of disease. When not treated, anxiety can be aggravated to more serious and complicated health problems. Pharmacology and psychotherapy stand for the conventional treatment for anxiety disorders but these present limited efficacy, especially in the case of chronic anxiety, with high relapse rates and often causing adverse side effects. Clinical research studies render acupuncture as a valid treatment therapy for anxiety disorders without significant adverse effects.

The objective of this paper is to review the literature on the effectiveness of acupuncture and electroacupuncture for the treatment of patients with anxiety disorders in order to find strong scientific evidence for its regular practice in Western culture.

The systematic review of the clinical research was focused on published clinical trials (controlled, randomized and non-randomized) regarding the treatment of anxiety with acupuncture. Only clinical trials where anxiety was treated as the therapeutic target, and not as a secondary measurement or being associated with other health condition or disease, were considered. Two authors extracted the data independently and exclusion and inclusion criteria were set. The search rendered 1135 papers addressing anxiety as a primary therapeutic target. After review, 13 papers were identified to match exclusion and inclusion criteria and were selected for this analysis. Methodology, design, and quality of the research were highly variable and are discussed and compared.

Overall, there is good scientific evidence encouraging acupuncture therapy to treat anxiety disorders as it yields effective outcomes, with fewer side effects than conventional treatment. More research in this area is however needed.

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Review Article

Efficacy of Acupuncture in Reducing Preoperative Anxiety: A Meta-Analysis

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Background. Acupuncture has been shown to reduce preoperative anxiety in several previous randomized controlled trials (RCTs). In order to assess the preoperative anxiolytic efficacy of acupuncture therapy, this study conducted a meta-analysis of an array of appropriate studies. *Methods*. Four electronic databases (MEDLINE, EMBASE, CENTRAL, and CINAHL) were searched up to February 2014. In the meta-analysis data were included from RCT studies in which groups receiving preoperative acupuncture treatment were compared with control groups receiving a placebo for anxiety. *Results*. Fourteen publications (N = 1,034) were included. Six publications, using the State-Trait Anxiety Inventory-State (STAI-S), reported that acupuncture interventions led to greater reductions in preoperative anxiety relative to sham acupuncture (mean difference = 5.63, $P < .00001$, 95% CI [4.14, 7.11]). Further eight publications, employing visual analogue scales (VAS), also indicated significant differences in preoperative anxiety amelioration between acupuncture and sham acupuncture (mean difference = 19.23, $P < .00001$, 95% CI [16.34, 22.12]). *Conclusions*. Acupuncture therapy aiming at reducing preoperative anxiety has a statistically significant effect relative to placebo or nontreatment conditions. Well-designed and rigorous studies that employ large sample sizes are necessary to corroborate this finding.

1. Introduction

Anxiety prior to undergoing surgery is experienced by approximately 60–70% of adult patients [1]. The effects of reducing preoperative anxiety can be observed by estimating heart rate (HR), blood pressure (BP), and neuroendocrinological changes [2]. These effects can also be determined during or after surgery through the examination of analgesic requirements, behavioral recovery, time taken to awaken, pain, and whether such outcomes also engender additional financial costs to patients [3, 4]. Pharmacological (e.g., opioids and sedatives used as anxiolytics) and psychological interventions (e.g., music and preparatory education regarding the operation) are commonly used to reduce preoperative anxiety [5, 6]. However, conventional medical treatments are only moderately effective and often produce problematic side effects, including bradycardia, hypotension, drowsiness, respiratory depression, pruritus, laryngeal rigidity, postoperative nausea and vomiting (PONV), delayed emergence, and tolerance and dependence, thereby prolonging patient recovery and treatment duration [7, 8]. Therefore, there is a clear need for more effective, safer interventions. This has led to an increase in the attention received by complementary and alternative interventions such as acupuncture, which is

the most widely used of such approaches [9]. Patients benefit from the lack of side effects and relatively low cost involved in acupuncture [10].

Acupuncture is gaining popularity in western medical culture as a tool for pain relief [11, 12], and evidence is emerging concerning its potential mechanisms of action. For example, electroacupuncture blocks pain by activating a variety of bioactive chemicals via peripheral, spinal, and supraspinal mechanisms [13].

Recently, several studies have evaluated the "extra 1" acupuncture or acupressure point with respect to relieving preoperative and general anxiety [8, 14–18]. However, to date, there have been no meta-analyses performed regarding this topic; therefore, we sought to summarize and critically assess evidence from randomized controlled trials (RCTs). The aim of this meta-analysis was to evaluate the efficacy of various types of acupuncture therapy with respect to reducing preoperative anxiety.

2. Methods

A meta-analysis of the literature was conducted according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement pertaining to reporting systematic reviews and meta-analyses of studies that evaluate preoperative care interventions.

2.1. Literature Search. Electronic searches were performed independently by two authors on MEDLINE (1950 to February 2014), Embase (1980 to February 2014), CENTRAL (the Cochrane Library 2014, Issue 1), and CINAHL (1982 to February 2014). As all of these databases employ their own subject headings, each was searched independently. We did not restrict our search on the basis of language, publication type, or year. Article bibliographies were checked for current relevant publications and experts in the field contacted. We also searched for additional relevant journals that may have been overlooked in the initial electronic search and available proceedings of conferences for information on additional trials. In an effort to identify other published, unpublished, and ongoing relevant researches, we also searched the reference sections of pertinent studies.

Keywords used to search for the RCTs were (anxiety OR anxioly∗ OR sedat∗ OR distress OR fear OR panic OR stress, psychological OR stress, physiological) AND (acupressure OR acupoint OR auriculotherapy OR meridians OR electroacupuncture OR acupuncture) AND (surgical OR procedure∗ OR preoperative care OR surgery) AND (randomized controlled trial [PT] OR randomized [AB] OR controlled clinical trial [PT] OR placebo [AB] OR clinical trial as topic [SH] OR randomly [AB] OR trial [TI]) in MEDLINE. Each database used its own subheadings and was searched individually.

The exclusion and inclusion criteria were applied separately by the two authors, who scanned the titles and abstracts of each record retrieved from the search. If information in the abstract clearly indicated that the trial did not meet our requirements, it was rejected. When a title or abstract could not be rejected with certainty, the authors inspected the full text independently and applied an inclusion criterion form to definitively assess its eligibility. Where disagreements occurred, the authors discussed the issue until a consensus was reached. If an article was excluded, a record was of the reason for exclusion. The final step was to exclude double publications.

2.2. Study Types. The meta-analysis included studies on inpatients and outpatients and nonemergency, emergency, and transported patients, who were scheduled to undergo both major and minor surgical or endoscopic procedures. Dental surgery procedures were also included. No restrictions were placed on age, sex, or ethnicity, but patients were excluded if they had a history of psychiatric or neurological problems or serious medical conditions, such as abuse of or addiction to drugs or alcohol, or used analgesics within the week preceding the procedure.

Included studies were restricted to RCTs that compared all forms of acupuncture-treated (delivered using classical sterile single-use needles, plastic balls, or occlusive press needles) and control groups, which included nontreatment or placebo treatment (sham acupuncture unrelated to known acupoints for treatment, using a superficial depth of acupuncture, or without electronic stimulation), with the aim of reducing preoperative anxiety. Quasirandomized trials were not included. No restrictions were imposed with respect to publication type or language.

We did not include studies in which treatments were administered on days other than the day of surgery. The primary outcome was the degree of reduction in preoperative anxiety produced by acupuncture in controlled trials involving a group to whom acupuncture was administered and a control group. Measures of anxiety included the State Anxiety Subscale (STAI-S) of the State-Trait Anxiety Inventory (STAI), which asks respondents how they feel "right now" on 20 items measuring subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. Anxiety scores in the STAI-S range from 1 (*not at all*) to 4 (*very much so*) for each item [26]. The mean difference (MD) in changes in continuous scale scores for preoperative anxiety represented a degree of reduction in STAI and visual analogue scale (VAS) scores. VAS simply indicated levels of anxiety according to a 100 mm scale line, where 0 represents a complete absence of anxiety and 100 the greatest possible level of anxiety. Where scales were scored between 0 and 10, values and standard deviations were multiplied by a factor of 10 [27]. Secondary outcomes included physiological variables, heart rate (HR), bispectral index (BIS), and blood pressure (BP), patient satisfaction, and adverse events.

2.2.1. Quality Assessment. The two authors assessed all included studies for risk of bias and were blinded to each other's assessments. Continuous data were preferred to binary data because most of the eligible studies reported continuous outcomes. Further information was requested from the authors where articles contained inadequate information

to make a decision about eligibility. Quality assessment for all studies was undertaken according to the Cochrane Handbook for Systematic Reviews of Interventions [28]. Studies were assessed by reviewers drawn from six domains. If articles contained inadequate information to allow for a decision made about their eligibility, then further information was requested from the authors. No studies were excluded from the analysis as a result of the quality assessment procedure.

2.2.2. Data Synthesis and Statistical Analyses. Continuous data were summarized as mean differences (MD) between pre- and posttreatment STAI-S or VAS scores. The degree of reduction in preoperative anxiety, with 95% confidence intervals (CIs), was calculated using Review Manager (RevMan) software (version 5.2 for Windows, The Nordic Cochrane Centre, Copenhagen, Denmark). If the 95% CI included a value of 0, then no significant difference existed between acupuncture-treated and control groups.

We subtracted final values from baseline mean values, even if these were not presented explicitly, such that a positive MD of the changes in scores indicated effective reduction of preoperative anxiety. If either of the standard deviations (at baseline or final) was unavailable, then one was substituted for the other if it was reasonable to assume that the intervention did not alter the variability of the outcome measure [28]:

$$\mathrm{SD} = \sqrt{\left(\mathrm{SD}_1{}^2 + \mathrm{SD}_2{}^2 - 2R_{\mathrm{corr}}\,\mathrm{SD}_1\mathrm{SD}_2\right)}\,. \quad (1)$$

We considered a 30% greater reduction in STAI and VAS scores following acupuncture treatment, relative control conditions, to be clinically relevant [29, 30]. Our meta-analysis employed a random-effects model, which assumes that effects estimated across different studies are not identical. If there was significant heterogeneity, however, then a fixed-effects model was applied. Concerning statistically significant differences in side effects, "number needed to harm" (NNH) values were calculated. Forest plots were used to graphically represent and evaluate treatment effects. Funnel plots of effects estimates against standard error were generated if a sufficient number of studies for each treatment regimen was available [31].

A sensitivity analysis was performed in order to identify sources of heterogeneity and ensure the stability of results. We excluded studies with two or more unclear biases or a high risk of bias for any of the risks in key bias domains. An additional sensitivity analysis was performed where sample sizes exceeded 100.

Studies were combined in instances where statistical heterogeneity was not evident. Heterogeneity was examined via the I^2-test, where I^2 values of 50% or more were indicative of significant heterogeneity.

3. Results

3.1. Study Description. An initial search identified 206 potentially relevant articles, of which 14 (N = 1,034) met our inclusion criteria and were thus added to the final analysis. The agreement rate, as measured using Cohen's kappa, was 0.9 [32]. Acupuncture treatments were administered to 439 patients; the other 595 participants served as controls. One author requested additional data from the authors of four studies; however, the data from one study were not obtained (Figure 1).

Studies offered acupuncture sessions lasting between 10 and 30 min; sessions were conducted in operating waiting rooms on the day of surgery. Two studies offered sessions during ambulance transfer [15, 22]. Participants were inpatients in one study and outpatients in two studies; the status of the participants in the remaining studies was unclear. Administration of acupuncture was examined during transportation and emergency cases in two studies and in nonemergency cases in eight studies; the environment in which acupuncture was administered was unclear in the remaining studies. Eight studies used acupuncture needles [10, 14, 15, 19–22, 24]; the other six used acupressure balls or beads [8, 16–18, 23, 25]. Five studies applied auricular acupoints, five others applied body acupoints, and four applied both. According to "Standards for Reporting Interventions in Clinical Trials of Acupuncture" (STRICTA), eight of the included studies reported the types of needles used, including the diameter and length as well as the manufacturer and/or the material, and the others reported only the types of needles. All of the studies were based on acupuncture point selection in traditional acupuncture theory. Various acupoints were used for decreasing preoperative anxiety in the included RCTs; the third eye (Yin-Tang), located between the two eyebrows, was commonly used in six trials, and the relaxation auricular point, located in the superior lateral wall of the triangular fossa, was also used in six trials. Needle stimulation was administered manually in four RCTs and electronically (2 Hz 25 V) in one RCT. Two studies reported "de qi" sensations, where reportage of such was recommended. These data are reported in the STRICTA recommendations [33]. Characteristics of all included studies are provided in Table 1.

The 14 included studies exhibited various degrees of bias susceptibility (Figures 2 and 3). The agreement rate, as measured using Cohen's kappa, was 0.8 [32]. Only six studies reported concealed allocation; the other six described a method of adequate randomization, although the word "randomization" appeared in all of the articles. Thirteen studies prevented blinding of the participants. Participants in these studies had no previous experience of acupuncture. According to STRICTA, two studies enquired after patients' beliefs as a group: there were no significant differences [20, 24].

3.2. STAI-S. A meta-analysis of six studies using the STAI-S to examine state anxiety in 378 participants revealed significantly lower state anxiety levels in participants who received real versus sham acupuncture interventions (MD = 5.63, $P <$ .00001, 95% CI [4.14, 7.11], Figure 4(a)). This was expressed in mean group differences in pre- and postintervention STAI-S scores. A random-effects model was used in the analysis, and statistical heterogeneity was not observed across the studies (I^2 = 0%). Regarding studies distinguishing between

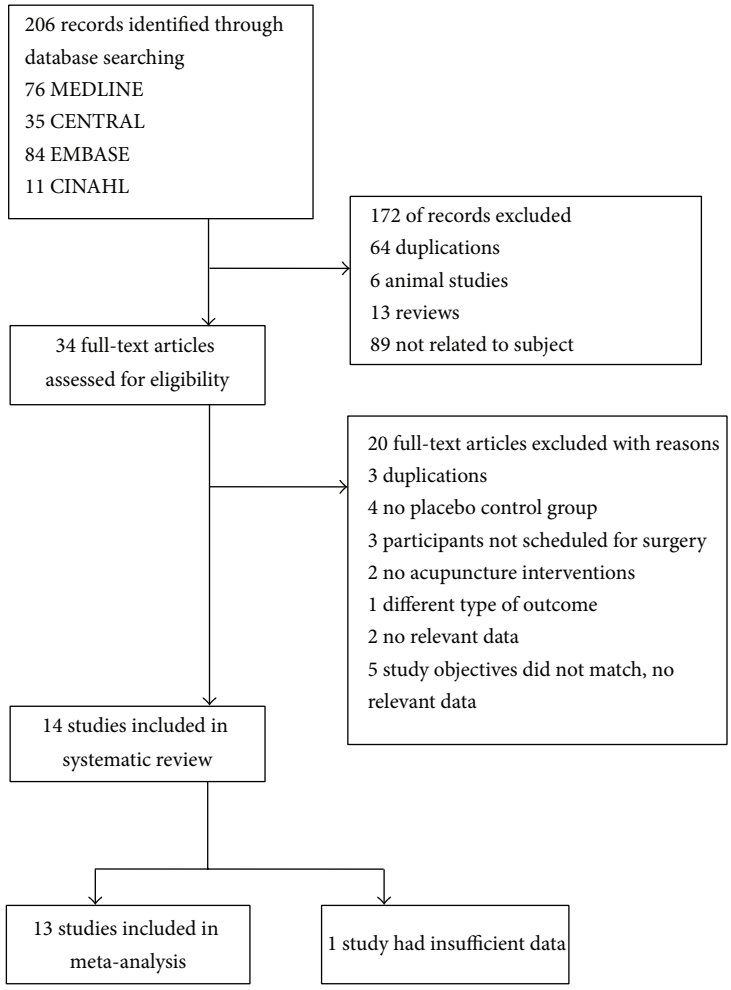


Figure 1: Flow chart for included studies.

adults and children, a significant reduction in scores was observed in five studies that measured STAI-S scores in adults (MD = 5.93, $P < .00001$, 95% CI [4.31, 7.54]). Similarly, a significant reduction was found in one study measuring STAI-S scores in children (STAI-C, MD = 3.94, $P = .04$, 95% CI [0.13, 7.75]). The width of the CI and the P value suggested that these data were statistically sufficient to allow for a conclusion; however, the reduction in the mean change in STAI-S scores did not reach clinical significance [34, 35].

When restricting the analysis to studies with 100 or more participants, acupuncture treatment was still associated with significantly decreased preoperative anxiety [24] (MD = 5.2, $P = .006$, 95% CI [1.51, 8.89]). A sensitivity analysis, which removes studies with lower-quality methodologies, was not performed for any of the included studies.

3.3. VAS. We identified eight studies ($n = 495$) that employed VAS measurements. The pooled analysis demonstrated that acupuncture interventions led to greater reductions in VAS anxiety relative to sham acupuncture (MD = 19.23, $P < .00001$, 95% CI [16.34, 22.12], Figure 4(b)). A fixed-effects model was used owing to the heterogeneity of the results ($I^2 = 86\%$). Two studies reported significant decreases in preoperative anxiety following acupuncture treatment versus nontreatment (MD = 27.34, $P < .00001$, 95% CI [18.07, 36.61]). These data were statistically significant, based on the P value and the width of the CI, and the mean difference was closer to clinical significance in the acupuncture-treated group relative to the control group; however, the sample size was small ($n = 88$). A sensitivity analysis was performed for two of the included studies [23, 25] in order to investigate the source of their heterogeneity. Acupuncture's association with reduced preoperative anxiety, in comparison to sham acupuncture, remained in place (MD = 34.59, $P < .00001$, 95% CI [26.68, 42.51]) following the exclusion of studies with lower-quality methodologies, where this exclusion also improved the homogeneity of results ($I^2 = 0\%$). Although the MD was based on more than 30 VAS change scores, it should not be considered conclusive in light of the small sample size ($n = 136$).

3.4. Subgroup Analysis. For both types of acupuncture instrument (needles and beads), acupoint location (body versus ear) had no impact on the primary outcome measure of

Table 1: Characteristics of included studies.

Author (year, location)	Subject age (years)	Number of participants (Acu[a]/Sham[b]/Con[c]1/Con2)	Surgery	Type of design	Type of intervention (duration, side, and type of stimulation)	Treated acupoints	Type of control group	Outcome measure reported (*P*value)	Adverse events reported (*n*)
Wang et al. (2001, USA) [19]	19–66	91 (31/32/27)	Elective ambulatory surgery (orthopedic, gynecologic, genitourinary, otolaryngologic, plastic, general ophthalmologic)	RCT[d]	Auricular acupressure needle (30 min, nondominant hand side)	Relaxation Tranquilizer Mmaster cerebral	(1) Traditional Chinese medicine group (2) Sham acupuncture	STAI[e] (.01)	NR[f]
Wang et al. (2007, USA) [20]	18–65	56 (29/27)	Elective lithotripsy procedure	RCT	Auricular acupressure needle (dominant, 30 min) Bilateral body acupuncture with 2 Hz, 25 V electrical stimulation	Relaxation valium, master cerebral, [k]LI4, [l]LV3	(1) Sham auricular acupressure, no electrical stimulation, superficial insertion in the same locations	STAI (.029)	PONV[g]-acu (4%) con (15%) $P = .412$
Wang et al. (2008, USA) [18]	8–17	52 (26/26)	General anesthesia for GI endoscopy (upper endoscopy and colonoscopy)	RCT	Acupressure beads (30 min)	Yin Tang	(1) Sham acupressure	STAIC (.012)	PONV-acu (5) con (8)
Paraskeva et al. (2004, Greece) [15]	NR	49 (25/24)	Minor or moderate surgery	RCT	Acupuncture (15 min)	Yin Tang	(1) Sham acupuncture	VSS[h] (NS)	NR
Gioia et al. (2006, Italy) [21]	71.3 (mean age)	75 (25/25/25)	Cataract surgery under topical anesthesia	RCT	Body acupuncture (20 min, dominant) Auricular (manually rotated De Qi) acupuncture	LI4, LV3 [m]PC6, [n]HT7 [o]TE5 Shenmen	(1) Nontreatment (2) Sham acupuncture	VAS[i] (.037)	NR
Cabrini et al. (2006, Italy) [22]	18+	48 (16/16/16)	Elective diagnostic fiberoptic bronchoscopy	RCT	Bilateral body acupuncture and auricular (20 min, manually rotated De Qi) acupuncture	[p]LU7, PC6 LI4, HT7 Shenmen	(1) Nontreatment (2) Sham acupuncture	VAS (.002)	None
Karst et al. (2007, German) [10]	18–65	67 (19/19/19/10)	Dental extractions	RCT	Acupuncture (nondominant, 25 min)	Relaxation Tranquilizer Master cerebral	(1) Placebo auricular acupuncture (2) Intranasal midazolam (3) Nontreatment	STAI (<.001) VAS (.012)	Nasal burning (7) None in the other groups
Mora et al. (2007, German) [23]	65–90	100 (50/50)	Transported by ambulance before receiving ESWL	RCT	Bilateral auricular acupressure (NR, 1 mm plastic ball)	Relaxation	(1) Sham acupressure	VAS (.001)	NR
Michalek-Sauberer et al. (2012, Austria) [24]	18+	182 (61/60/61)	Dental treatment	RCT	Auricular acupuncture (20 min, dominant)	Relaxation Tranquilizer Master cerebral	(1) Sham acupuncture (2) Nontreatment	STAI (.008)	Acupuncture (14), Sham (12)
Acar et al. (2013, Turkey) [14]	18–65	52 (26/26)	General/regional anesthesia	RCT	Auricular acupuncture (20 min, ear-press needle)	Yin Tang	(1) Sham acupressure	STAI (<.05)	NR

Table 1: Continued.

Author (year, location)	Subject age (years)	Number of participants (Acu[a]/Sham[b]/Con[c]1/Con2)	Surgery	Type of design	Type of intervention (duration, side, and type of stimulation)	Treated acupoints	Type of control group	Outcome measure reported (*P*value)	Adverse events reported (*n*)
Kober et al. (2003, Austria) [25]	23–89	36 (17/19)	Transported by ambulance for gastrointestinal illness	RCT	Bilateral auricular acupressure (NR)	Relaxation	(1) Sham acupressure	VAS (.002)	NR
Agarwal et al. (2005, India) [8]	18–50	76 (36/36)	Elective surgical procedure	RCT	Acupressure (10 min, 20–25 cyc/min manually rotated)	Yin Tang	(1) Sham acupressure	VSS (<.001)	NR
Borimnejad et al. (2012, China) [16]	9–12	80 (40/40)	Elective surgery	RCT	Acupressure (30 min, 1.3 psi acupressure bead)	Yin Tang	(1) Sham acupressure	STAIC (NS[j])	NR
Valiee et al. (2012, Iran) [17]	44.04 ± 11.25 (mean age)	70 (35/35)	Abdominal surgery (cholecystectomy, hysterectomy, herniorrhaphy, laparoscopy)	RCT	Acupressure (10 min, nondominant, 20–25 cyc/min, acupressure bead) Auricular acupressure	Shenmen Yin Tang	(1) Sham acupressure	VAS (<.001)	NR

[a]Acu: acupuncture; [b]Sham: sham acupuncture; [c]Con: control group; [d]RCT: randomized controlled trials; [e]STAI: the State-Trait Anxiety Inventory; [f]NR: not reported; [g]PONV: postoperative nausea and vomiting; [h]VSS: verbal-scale score; [i]VAS: visual analogue scale; [j]NS: not significant; [k]LI: large intestine; [l]LV: liver; [m]PC: pericardium; [n]HT: heart; [o]TE: triple energizer; [p]LU: lung.

Figure 2: Risk of bias. Each risk of bias item presented as percentages across all included studies.

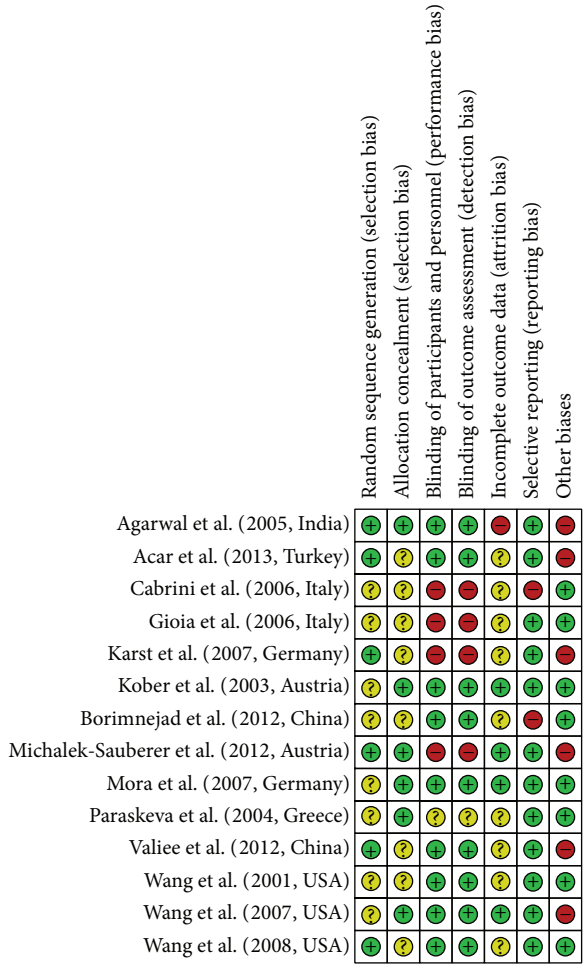


Figure 3: Methodological quality summary. Methodological quality indices for all included studies. "+" = low risk of bias, "−" = high risk of bias, and "?" = unclear risk of bias.

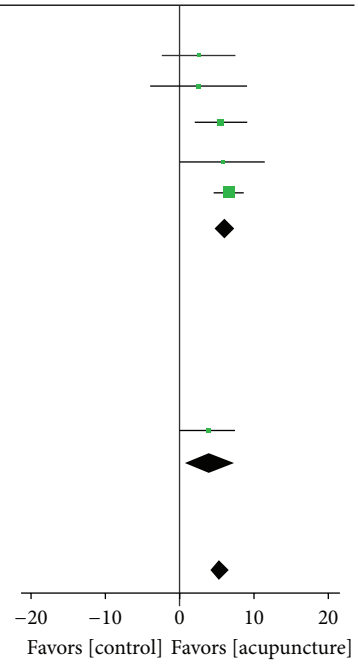
preoperative anxiety. Publication bias was reported via Begg's funnel plot (Figure 5), where asymmetry of the plots may have arisen through publication bias and the relationship between trial size and effect size.

3.5. Secondary Outcomes. For exploratory purposes, additional analyses of secondary outcomes were performed for physiological variables (HR, BIS, and BP). Six studies measured heart rate before and after intervention; none of these reported a significant difference between the acupuncture and sham groups [10, 21–23, 25, 36]. Two studies also reported no significant difference in blood pressure [17, 23]. No significant changes in BIS scores were observed between groups in four studies [8, 14, 15, 18]; one of these also reported that BIS values did not differ between the groups before, during, or after acupuncture, but, during acupuncture, BIS scores were significantly lower in the group receiving acupuncture but not in the placebo group [15]. In contrast to the significant reductions seen for the primary outcome measure of anxiety, no significant difference in physiological measurements was identified.

3.6. Side Effects. Among studies reporting adverse events, two found no adverse events in either the acupuncture or sham acupuncture groups, relative to the control group, for which a burning sensation in response to intranasal medication was reported in 32.6% of the participants (NNH = 7) [10, 22]. Two RCTs reported PONV in both the intervention and control groups, but with no significant differences in rate of occurrence (OR = 0.42, $P = 0.13$, 95% CI [0.14, 1.29]) [18, 20]. Ear warmth and peculiar sensations and dizziness were reported in only one study, but there was no significant difference in occurrence rates between groups (Figure 4(c)) [24].

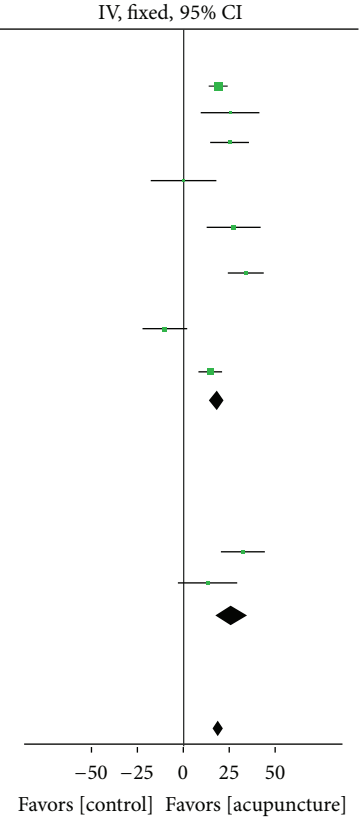
3.7. Patient Satisfaction. Two of the included studies investigated patient satisfaction via VAS scales (0–10 points) [20] and discontinuous numeric scales (from 1 to 5) [10]; no

Study or subgroup	Real acupuncture Mean	SD	Total	Sham acupuncture Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
3.1.1 STAI								
Acar et al. (2013, Turkey)	3.49	9.588217	26	0.88	9.219431	26	8.5%	2.61 [−2.50, 7.72]
Karst et al. (2007, Germany)	6.94	9.463472	19	4.11	12.37298	19	4.5%	2.83 [−4.17, 9.83]
Michalek-Sauberer et al. (2012, Austria)	8.7	10.60566	61	3.5	10.10149	60	16.2%	5.20 [1.51, 8.89]
Wang et al. (2001, USA)	11	10.58301	32	5	13.52775	27	5.6%	6.00 [−0.28, 12.28]
Wang et al. (2007, USA)	5	3.605551	29	−2	4.358899	27	49.9%	7.00 [4.90, 9.10]
Subtotal (95% CI)			**167**			**159**	**84.7%**	**5.93 [4.31, 7.54]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.52$; df = 4 ($P = 0.48$); $I^2 = 0\%$								
Test for overall effect: $Z = 7.20$ ($P < 0.00001$)								
3.1.2 STAIC								
Borimnejad et al. (2012, China)	0	8.54	40	2.32	8.797744	40		Not estimable
Wang et al. (2008, USA)	3.24	7	26	−0.7	7	26	15.3%	3.94 [0.13, 7.75]
Subtotal (95% CI)			**26**			**26**	**15.3%**	**3.94 [0.13, 7.75]**
Heterogeneity: not applicable								
Test for overall effect: $Z = 2.03$ ($P = 0.04$)								
Total (95% CI)			**193**			**185**	**100.0%**	**5.63 [4.14, 7.11]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.41$; df = 5 ($P = 0.49$); $I^2 = 0\%$								
Test for overall effect: $Z = 7.42$ ($P < 0.00001$)								
Test for subgroup differences: $\chi^2 = 0.89$; df = 1 ($P = 0.35$); $I^2 = 0\%$								



(a)

Study or subgroup	Real acupuncture Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, fixed, 95% CI
3.2.1 acupuncture versus sham acupuncture								
Agarwal et al. (2005, India)	30	10	38	10	10	38	37.6%	20.00 [15.50, 24.50]
Cabrini et al. (2006, Italy)	26.7	21.96657	16	−0.4	24.89518	16	2.9%	27.00 [10.83, 43.37]
Gioia et al. (2006, Italy)	30	18.68154	25	3	17.34935	25	7.6%	27.00 [17.01, 36.99]
Karst et al. (2007, Germany)	12.2	26.94958	19	11.5	28.78819	19	2.4%	0.70 [−17.03, 18.43]
Kober et al. (2003, Austria)	25.2	18.01444	17	−4.2	28.11423	19	3.3%	29.40 [14.13, 44.67]
Mora et al. (2007, Germany)	42.2	18.91137	50	5.7	27.5229	50	8.9%	36.50 [27.24, 45.76]
Paraskeva et al. (2004, Greece)	10	20	25	20	20	24	6.1%	−10.00 [−21.20, 1.20]
Valiee et al. (2012, China)	22	12.36487	35	6.1	12.40121	35	22.6%	15.90 [10.10, 21.70]
Subtotal (95% CI)			**225**			**226**	**91.2%**	**19.23 [16.34, 22.12]**
Heterogeneity: $\chi^2 = 50.03$; df = 7 ($P < 0.00001$); $I^2 = 86\%$								
Test for overall effect: $Z = 13.06$ ($P < 0.00001$)								
3.2.1 acupuncture versus nontreatment								
Gioia et al. (2006, Italy)	30	18.68154	25	−4	21.93171	25	6.0%	34.00 [22.71, 45.29]
Karst et al. (2007, Germany)	12.2	26.94958	19	−1.4	24.01041	19	2.9%	13.60 [−2.63, 29.83]
Subtotal (95% CI)			**44**			**44**	**8.8%**	**27.34 [18.07, 36.61]**
Heterogeneity: $\chi^2 = 4.09$; df = 1 ($P = 0.04$); $I^2 = 76\%$								
Test for overall effect: $Z = 5.78$ ($P < 0.00001$)								
Total (95% CI)			**269**			**270**	**100.0%**	**19.95 [17.19, 22.70]**
Heterogeneity: $\chi^2 = 56.80$, df = 9 ($P < 0.00001$); $I^2 = 84\%$								
Test for overall effect: $Z = 14.19$ ($P < 0.00001$)								
Test for subgroup differences: $\chi^2 = 2.68$; df = 1 ($P < 0.10$); $I^2 = 62.7\%$								

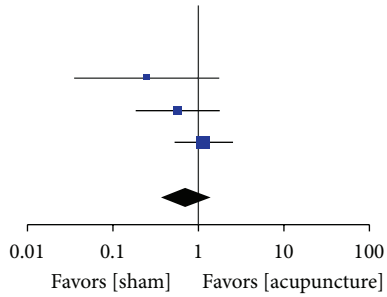


(b)

Figure 4: Continued.

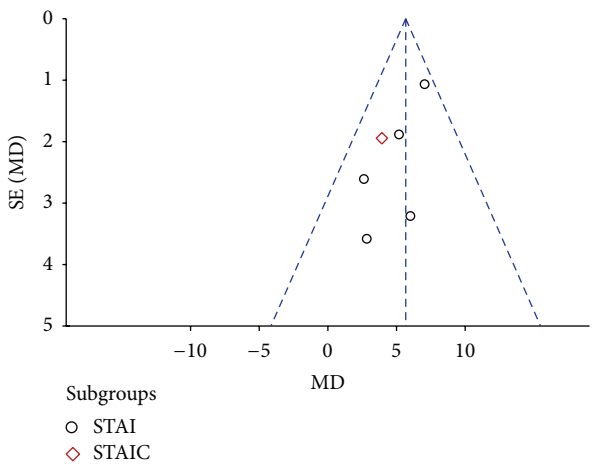
Study or subgroup	Acupuncture Events	Acupuncture Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
Karst et al. (2007, Germany)	0	19	0	19		Not estimable
Cabrini et al. (2006, Italy)	0	16	0	0		Not estimable
Wang et al. (2007, USA)	1	29	4	27	12.5%	0.21 [0.02, 1.97]
Wang et al. (2008, USA)	5	26	8	26	32.5%	0.54 [0.15, 1.93]
Michalek-Sauberer et al. (2012, Austria)	14	61	12	60	55.0%	1.19 [0.50, 2.84]
Total (95% CI)		**151**		**132**	**100.0%**	**0.74 [0.32, 1.71]**
Total events	20		24			

Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 2.58$; df = 2 ($P = 0.27$); $I^2 = 23\%$
Test for overall effect: $Z = 0.71$ ($P = 0.48$)

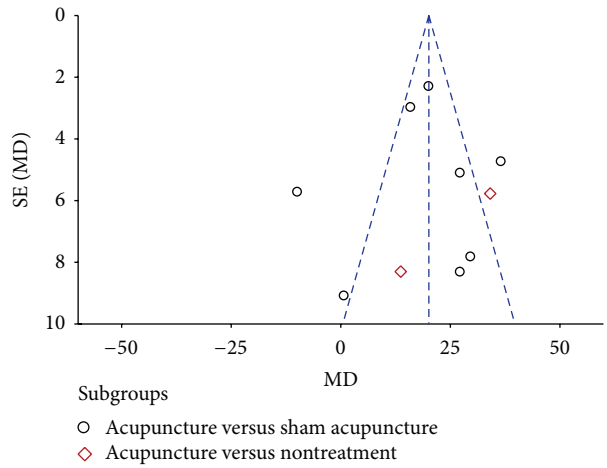


(c)

Figure 4: Forest plot of acupuncture efficacy in reducing preoperative anxiety. (a) STAI acupuncture versus sham acupuncture. (b) VAS acupuncture versus control groups. (c) Side effect acupuncture versus sham acupuncture. The term "STAIC" in part (a) indicates the State Anxiety Subscale of the State-Trait Anxiety Inventory in children. The term "events" in part (c) indicates the number of patients who reported adverse events including PONV. "Weight" refers to the contribution of each study to the side effects total.



(a)



(b)

Figure 5: Funnel plot of the mean difference (MD) in anxiety ratings between acupuncture treatment and control groups, versus standard error (SE).

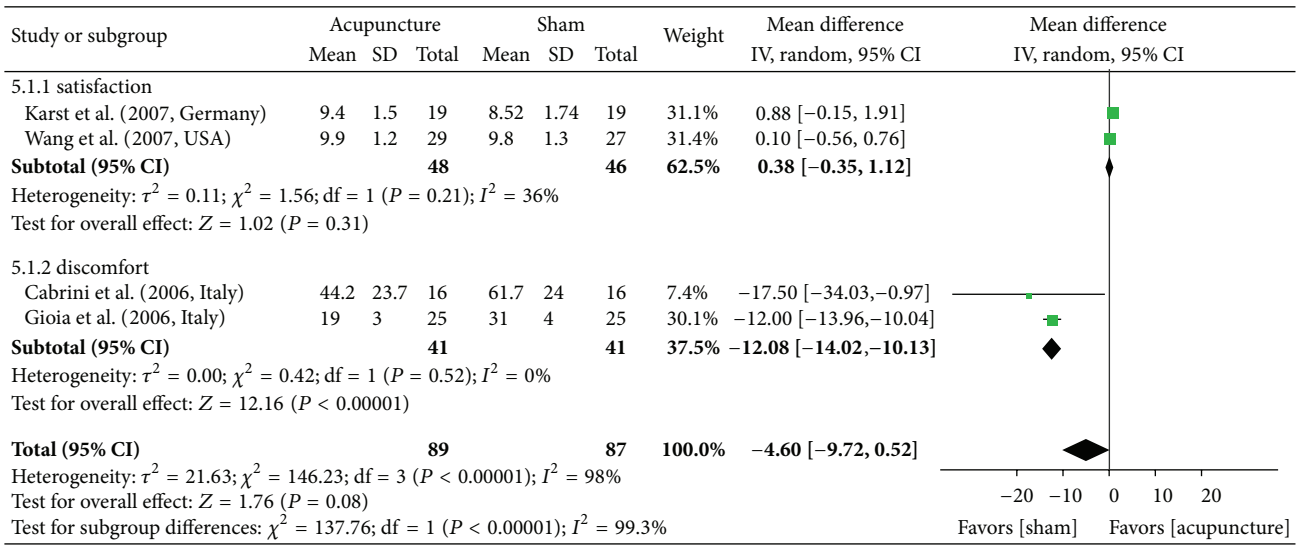
significant group differences were observed (MD = 0.38, P = .31, 95% CI [−0.35, 1.12]).

Another study investigated the comfort level associated with acupuncture treatment according to a dichotomous scale comprising "good" or "other" ratings; again, there were no significant differences (OR = 0.88, P = .81, 95% CI [0.30, 2.59]) [24]. Two other studies investigated discomfort according to VAS scale ratings (0–100 points) and reported that discomfort was higher in control groups (MD = −12.08, P < .00001, 95% CI [−14.2, −10.13], Figure 6) [21, 22].

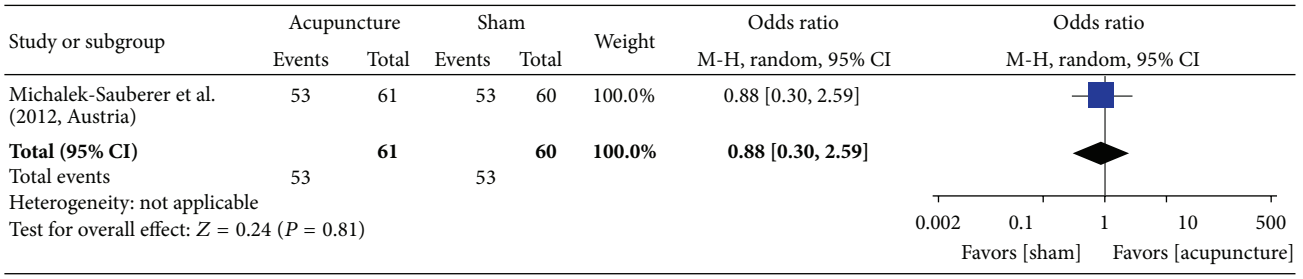
4. Discussion

This meta-analysis demonstrates that acupuncture therapy, administered in isolation, can decrease preoperative anxiety in patients with scheduled surgery. To our knowledge, there have been no other systematic reviews or meta-analyses of RCTs conducted concerning acupuncture's efficacy in reducing preoperative anxiety. Moreover, no restrictions were applied for age or language, and several literature databases were searched via a comprehensive strategy. A previous meta-analysis indicated that acupuncture treatment reduces postoperative pain and is associated with a lower incidence of nausea among PONV cases [37]. However, the sample was restricted to adults and there was wide variability in the type and timing of acupuncture regimens applied and the duration and number of treatment sessions.

Acupuncture was generally associated with greater reductions in anxiety prior to surgery relative to control (nontreatment) and sham treatment conditions. Based on the findings of the current meta-analysis, all varieties of acupuncture therapy, delivered in isolation to patients on the day of surgery, are effective.



(a)



(b)

Figure 6: Forest plot depicting various outcomes for postsurgical patient satisfaction. (a) VAS (satisfaction and discomfort after surgery). (b) Number of patients reporting a "good" level of treatment satisfaction.

Karst et al. [10] compared the effects of pharmaceutical agents and acupuncture for preoperative stress. They concluded that, although the number of studies included was insufficient for meaningful analysis, auricular acupuncture and intranasal midazolam were similarly effective for the treatment of anxiety.

Griffiths et al. [38] assessed the efficacy of interventions (pharmacological and nonpharmacological, including acupressure therapy) aiming to prevent nausea and vomiting in women undergoing regional anesthesia for a caesarean section. Acupressure was only found to be effective for intraoperative nausea and was not effective for postoperative nausea or vomiting. Their review was specifically concerned with pregnancy-related underlying risk factors for nausea and vomiting.

Some reviews have reported on studies involving infants and children. Several studies found no significant statistical or clinical differences in the efficacy of nonpharmacological methods, such as parental acupuncture versus sedative premedications [39–41]. The effects of parental acupuncture on children's anxiety remain unclear and were not evaluated in this study. Assuming that acupuncture reduces preoperative anxiety, the potential mechanisms of action may be similar to those previously documented for acupuncture [42, 43]. In our meta-analysis, two studies included participants under the age of 18, for whom the STAI-C, which was used in both studies, is considered the gold standard in the assessment of anxiety in children older than 6 years of age. This questionnaire is well validated, has been used in more than 1,000 studies [44], is easy to read, and can be administrated verbally. Although there are no data regarding the issue of clinical significance in the pediatric anxiety literature, we found that a minimum difference of 10% in state anxiety levels, as assessed by the adult version of the STAI-S, is considered clinically significant [34, 35]. Borimnejad et al. [16] reported significant differences not for an acupuncture-treated group but for a sham treatment group.

The present review has several limitations. The small number of included trials did not allow for the performance of a metaregression examining all of the possible predictors together, given the suggested threshold of 14 studies required per predictor [28]. The small number of included studies also resulted in wide CIs for the pooled results of many of the reported outcomes, thereby rendering the drawing of definitive conclusions difficult. In addition, we could not combine all of the results of the STAI-S in children owing to insufficient data, where postintervention anxiety scores in acupuncture treatment groups were occasionally not

provided; in some instances, attempts to contact authors were also unsuccessful. Despite a general lack of relevant data, we did not exclude data in an effort to avoid publication bias.

Even when considering the caveats described above, our analyses support the possibility that acupuncture treatment is able to reduce preoperative anxiety better than sham acupuncture. Clinically important differences were observed in the reduction of preoperative anxiety between acupuncture-treated and control (nontreatment) conditions, although the overall sample size was small. The findings of our analyses are clinically important, in which the results support the proposition that acupuncture is beneficial in reducing preoperative anxiety. Based on this assumption, potential mechanisms of action may be similar to those documented in the acupuncture literature [42, 45].

Our study has identified some areas in which further research on acupuncture treatment is warranted. For example, it remains unclear as to whether there is a difference in the efficacy of acupuncture therapy versus conventional premedication treatments. Additional studies are also required in order to establish objective assessment methods and ideal techniques for blinding.

5. Conclusion

In conclusion, this meta-analysis suggests that acupuncture therapy aiming at reducing preoperative anxiety has some beneficial effects as compared to placebo or nontreatment alternatives. Further RCTs should be conducted to gain a better understanding of the role of acupuncture in this context.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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RESEARCH ARTICLE Open Access

Yoga for posttraumatic stress disorder – a systematic review and meta-analysis

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Abstract

Background: Yoga is increasingly used as a therapeutic treatment and seems to improve psychiatric conditions such as anxiety disorders and depression. The aim of this systematic review was to assess the evidence of yoga for reducing symptoms of posttraumatic stress disorder (PTSD).

Methods: The Cochrane Library, Medline/PubMed, PsycINFO, Scopus, and IndMED were searched through July 2017 for randomized controlled trials (RCTs) assessing the effects of yoga on symptoms of PTSD. Mean differences (MD) and standardized mean differences (SMD) with 95% confidence intervals (CI) were computed. The quality of evidence and the strength of recommendation were graded according to the GRADE recommendations.

Results: Seven RCTs ($N = 284$) were included. Meta-analysis revealed low quality evidence for clinically relevant effects of yoga on PTSD symptoms compared to no treatment (SMD = − 1.10, 95% CI [− 1.72, − 0.47], $p < .001$, $I^2 = 72\%$; MD = − 13.11, 95% CI [− 17.95, − 8.27]); and very low evidence for comparable effects of yoga and attention control interventions (SMD = − 0.31, 95%CI = [− 0.84, 0.22], $p = .25$; $I^2 = 43\%$). Very low evidence was found for comparable retention of patients in the trial for yoga and no treatment (OR = 0.68, 95%CI [0.06, 7.72]) or attention control interventions (OR = 0.66, 95%CI [0.10, 4.46]). No serious adverse events were reported.

Limitations: Few RCTs with only limited sample size were available.

Conclusions: Only a weak recommendation for yoga as an adjunctive intervention for PTSD can be made. More high quality research is needed to confirm or disconfirm these findings.

Keywords: Posttraumatic stress disorder, PTSD, Yoga, Meta-analysis

Background

With a lifetime prevalence of up to 6.1% worldwide, posttraumatic stress disorder (PTSD) is a major public health problem [1]. PTSD often results from substantial traumatic experiences and is thus far more common among veterans, survivors of wars or natural disasters, and victims of violence. The syndrome is associated with re-experiencing, avoidance, arousal, cognition, and mood symptoms [2].

A wide range of pharmacological and psychotherapeutic approaches are used in the treatment of PTSD [3]. Recent meta-analyses demonstrated that differences between most pharmacological treatments for PTSD and placebo are small at best [4, 5]. While phenelzine seems to be most effective, the paucity of available studies hindered definite conclusions [5]. The strong placebo effect in pharmacological treatment of PTSD might be a main reason for their perceived efficacy [4]. Psychotherapy, especially trauma-focused psychotherapy, seems to be superior to medication as a first-line treatment [6]. While psychotherapy thus seems to be the most promising first-line treatment for PTSD [3], a recent Cochrane Review rated the quality of evidence to be very low even for trauma-focused psychotherapy; and a considerable number of patients terminated the included psychotherapeutic trials early during the treatment period [7]. The latter might hint to a limited tolerability of these treatment approaches in some patients. In recent years, complementary therapy approaches for individuals with PTSD and other trauma-related disorders have received increasing interest [8]. Specifically mind-body approaches might

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Meditation and Yoga for Posttraumatic Stress Disorder: A Meta-Analytic Review of Randomized Controlled Trials

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Abstract

Posttraumatic stress disorder (PTSD) is a chronic and debilitating disorder that affects the lives of 7-8% of adults in the U.S. Although several interventions demonstrate clinical effectiveness for treating PTSD, many patients continue to have residual symptoms and ask for a variety of treatment options. Complementary health approaches, such as meditation and yoga, hold promise for treating symptoms of PTSD. This meta-analysis evaluates the effect size (*ES*) of yoga and meditation on PTSD outcomes in adult patients. We also examined whether the intervention type, PTSD outcome measure, study population, sample size, or control condition moderated the effects of complementary approaches on PTSD outcomes. The studies included were 19 randomized control trials with data on 1,173 participants. A random effects model yielded a statistically significant *ES* in the small to medium range (*ES* = −.39, $p < .001$, 95% CI [−.57, −.22]). There were no appreciable differences between intervention types, study population, outcome measures, or control condition. There was, however, a marginally significant higher *ES* for sample size ≤ 30 (*ES* = −.78, $k = 5$). These findings suggest that meditation and yoga are promising complementary approaches in the treatment of PTSD among adults and warrant further study.

Keywords

complementary health; yoga; meditation; PTSD; traumatic stress

1. Introduction

Several decades of research reveal chronic and debilitating biological, psychological, and social ramifications for individuals suffering from posttraumatic stress disorder (PTSD). The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., DSM-5; American Psychiatric Association, 2013) classifies the symptoms of PTSD within four symptom clusters of intrusion, persistent avoidance, negative alterations in cognitions and mood, and marked alterations in arousal. Both pharmacological and psychological interventions are

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REVIEWS

Assessing the Effectiveness of Yoga as a Complementary and Alternative Treatment for Post-Traumatic Stress Disorder: A Review and Synthesis

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Abstract

Objectives: Posttraumatic stress disorder (PTSD) is a debilitating condition that affects many who have experienced trauma. In addition to skills-focused treatments, exposure-based treatments, cognitive therapy, combination treatments, and EMDR, a number of alternative treatments for PTSD have emerged in recent years. The search for alternative treatments is justified based on the empirical observation that a large percentage of individuals fail to benefit optimally from existing treatments (e.g., between 30 and 60). Moreover, current studies often utilize stringent inclusion criteria (e.g., absence of comorbid disorders), raising the likelihood that results will not generalize to many individuals currently experiencing PTSD. The primary objective of the current paper was to explore the effects of one type of alternative treatment: yoga.

Design: A comprehensive review of the literature was conducted targeting research examining yoga postures and PTSD. Seven randomized controlled trials (RCTs) were identified and reviewed, and effect sizes were computed for the post-test assessments.

Results: Cohen's *d* for each study ranged (in absolute value) from a low of −0.06 to a high of 1.42 (average weighted *d* across studies was 0.48; 95% CI: 0.26, 0.69).

Conclusions: Putative mechanisms of action for the possible beneficial effects of yoga for PTSD-related symptomatology and clinical implications are discussed.

Keywords: yoga, PTSD, trauma, intervention

Introduction

For many, the response of a traumatic event is characterized by intrusive memories, avoidance of stimuli reminiscent of the trauma, changes in arousal, and alterations in negative cognitions and mood. When considered jointly, these clusters of symptoms denote post-traumatic stress disorder (PTSD).[1]

PTSD prevalence, common comorbidities, and treatment

A large percentage of trauma survivors manifest PTSD-related symptoms following a traumatic event, although this percentage dissipates over time.[2] General population prevalence estimates have varied over the past 20 years from a low of 6.8% to a high of 12.3%,[3,4] with a projected lifetime prevalence rate at 8.7%.[1] These prevalence estimates vary by sex, with women reporting higher prevalence estimates (e.g., 9.7% vs. 3.6%).[3] The occurrence is also higher among military personnel, with prevalence estimates ranging from 10% for Gulf War veterans to 31% in male Vietnam veterans.[3]

Individuals afflicted with PTSD often experience high levels of impairment across multiple domains of functioning (e.g., social, occupational, and interpersonal) and are 80% more likely to have a co-occurring mental health diagnosis[1]

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REVIEW

WILEY ADAA ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA

Yoga for anxiety: A systematic review and meta-analysis of randomized controlled trials

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Yoga has become a popular approach to improve emotional health. The aim of this review was to systematically assess and meta-analyze the effectiveness and safety of yoga for anxiety. Medline/PubMed, Scopus, the Cochrane Library, PsycINFO, and IndMED were searched through October 2016 for randomized controlled trials (RCTs) of yoga for individuals with anxiety disorders or elevated levels of anxiety. The primary outcomes were anxiety and remission rates, and secondary outcomes were depression, quality of life, and safety. Risk of bias was assessed using the Cochrane tool. Eight RCTs with 319 participants (mean age: 30.0–38.5 years) were included. Risk of selection bias was unclear for most RCTs. Meta-analyses revealed evidence for small short-term effects of yoga on anxiety compared to no treatment (standardized mean difference [SMD] = −0.43; 95% confidence interval [CI] = −0.74, −0.11; $P = .008$), and large effects compared to active comparators (SMD = −0.86; 95% CI = −1.56, −0.15; $P = .02$). Small effects on depression were found compared to no treatment (SMD = −0.35; 95% CI = −0.66, −0.04; $P = .03$). Effects were robust against potential methodological bias. No effects were found for patients with anxiety disorders diagnosed by Diagnostic and Statistical Manual criteria, only for patients diagnosed by other methods, and for individuals with elevated levels of anxiety without a formal diagnosis. Only three RCTs reported safety-related data but these indicated that yoga was not associated with increased injuries. In conclusion, yoga might be an effective and safe intervention for individuals with elevated levels of anxiety. There was inconclusive evidence for effects of yoga in anxiety disorders. More high-quality studies are needed and are warranted given these preliminary findings and plausible mechanisms of action.

KEYWORDS
anxiety, anxiety disorders, meta-analysis, yoga

1 | INTRODUCTION

Anxiety is a normal response to specific situations or events. However, excessive fear or anxiety may be indicative of an anxiety disorder (American Psychiatric Association, 2013). In generalized anxiety disorder (GAD), elevated levels of anxiety, which are associated with concerns about health, relationships, work, and financial issues, lead to a wide variety of physical symptoms and behavioral changes. Excessive anxiety also has implications for long-term health, with somatic symptoms of anxiety, such as palpitations and irregular heartbeat, associated with an increased risk of cardiovascular disease in women (Nabi et al., 2010). Anxiety disorders are estimated to range in prevalence from 0.9 to 28.3% worldwide (Baxter, Scott, Vos, & Whiteford, 2013), with factors contributing to this variation including demographic factors of gender, age, financial status, and culture, as well as methodological differences such as definitions of anxiety disorders and measurement or diagnostic tools. In the United States, 12-month and lifetime prevalence of GAD have been reported as 2.1 and 4.1%, respectively (Grant et al., 2005).

Psychological approaches and medication are the mainstays of treatment for anxiety disorders (Katzman et al., 2014). Guidance on the management of GADs and panic attacks recommends low-intensity psychological interventions including psychological therapy (such as cognitive behavioral therapy), medication, and self-help (including support groups and exercise) (National Institute for Health and Care Excellence, 2011). However, many people who experience high levels of anxiety do not seek a medical opinion, or choose not to accept psychological or pharmaceutical interventions,

Systematic Review of Yoga Interventions for Anxiety Reduction Among Children and Adolescents

Lindy L. Weaver, Amy R. Darragh

MeSH TERMS
- adolescent medicine
- anxiety
- anxiety disorders
- outcome and process assessment (health care)
- pediatrics
- yoga

OBJECTIVE. Anxiety disorders are the most prevalent psychological disorders among children and youths. There is growing interest in intervention options for anxiety. Yoga is widely used in clinical, school, and community settings, but consolidated sources outlining its effectiveness in reducing anxiety are limited.

METHOD. This systematic review examined the evidence base (1990–2014) for yoga interventions addressing anxiety among children and adolescents (ages 3–18 yr).

RESULTS. We identified 2,147 references and found 80 articles that were eligible for full-text review. The final analysis included 16: 6 randomized controlled trials, 2 nonrandomized preintervention–postintervention control-group designs, 7 uncontrolled preintervention–postintervention studies, and 1 case study.

CONCLUSION. Nearly all studies indicated reduced anxiety after a yoga intervention. However, because of the wide variety of study populations, limitations in some study designs, and variable outcome measures, further research is needed to enhance the ability to generalize and apply yoga to reduce anxiety.

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An estimated 21% of children and adolescents in the United States have a diagnosable psychiatric disorder resulting in at least minimal impairment, and upward of 4 million youths have a serious psychiatric disorder that causes significant functional impairments across social, familial, and community domains (Merikangas et al., 2010; U.S. Department of Health and Human Services, 1999). Anxiety disorders are the most prevalent of these disorders in children (Alyahri & Goodman, 2008; Cartwright-Hatton, McNicol, & Doubleday, 2006), with 10%–17% of community samples and ≤45% of children in mental health clinics affected (Last, Perrin, Hersen, & Kazdin, 1992; Weiss & Last, 2001). Prevalence data of a representative U.S. sample demonstrated that among adolescents affected by anxiety disorders, 50% had their onset by age 6 (Merikangas et al., 2010). These statistics demonstrate that anxiety disorders occur early and often in children. In addition, anxiety disorders in children are associated with mood and anxiety disorders in adolescence and adulthood, suicide attempts, and psychiatric hospitalization (Storch, 2005). Given the high prevalence and functional impairment associated with childhood anxiety disorders, the need for effective ways to nurture these children's mental health and well-being is imperative.

Yoga has increasingly been used with a variety of child populations. In 2007, upward of 1.5 million children were participating in yoga programs across the United States (Barnes, Bloom, & Nahin, 2009), and this number continues to increase as these programs are implemented in a growing number of community studios, clinical settings, and schools. Yoga, a subset of mindful and contemplative practice, includes structured activities that "require individuals to exercise volitional control" over their physical and mental activity (Davidson et al., 2012, p. 147) through focus on improving attention, enhancing emotional