Mental Health Clinical Advisory Group

February 1, 2024 | 8:00 – 8:50 AM | Microsoft Teams

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OHA welcomes all participants. If you have any questions about accommodations or need any assistance to participate, please call or email: Andrew Gibler at: 503-878-1395 or andrew.n.gibler@oha.oregon.gov (voice/text). All relay calls are accepted.

Public comment requires the completion of a public comment form. This form is available on the MHCAG website. The form should be signed and returned to Andrew Gibler at: andrew.n.gibler@oha.oregon.gov. Each speaker is allotted 3 minutes. Time cannot be gifted toanother speaker.

Officers: Nick Kashey, MD (Chair); Kaja Wagner, PharmD (Vice-Chair).

Appointed Members: John Bischof, MD; Chris Bouneff; Donald Dravis, MD; Tyler Duffield, PhD; Samantha DuPont; Neil Falk, MD; Naomi Fishman, MD; Bennett Garner, MD; Maggie Bennington-Davis, MD; Bob Joondeph, JD; Lori Martin, MSN, PMHNP; Katie Peters-Daniel, PharmD; Kaja Wagner, PharmD; Leah Werner, MD.

Agenda subject to change

AGENDA	PAGE	TIME	FACILITATOR
Call to order Approval of January 4, 2024 meeting minutes OHA announcements	1-5	8:00 – 8:05	Kaja Wagner
Public comment (includes OHA staff) about any topic on today's agenda	----------	8:05 – 8:10	Kaja Wagner
OHP FFS proposed SPRAVATO (esketamine) PA changes	6-25	8:10 – 8:20	OSU DURM
Antipsychotic in Children OHP FFS Policy	26-50	8:20 – 8:30	OSU DURM
Movement Disorders Guidance Draft	51-54	8:30 – 8:45	Andrew Gibler
Research Questions for Sleep Disorders		8:45 – 8:50	Andrew Gibler

Next Meeting: Thursday, March 7, 2024; 8:00-8:50 AM

All 2024 Meetings: First Thursdays of each month **(except** December) at 8:00am. No meeting in December.

Attendees: A quorum was present for voting purposes.

Mental Health Clinical Advisory Group Committee: Chris Bouneff; Nick Kashey; Maggie Bennington-Davis; Don Dravis; Neil Falk; Bennett Garner; Davíd Nagarkatti-Gude; Naomi Fishman; Lori Martin; John Bischof; Samantha DuPont

OHA Staff: Meg Cary; Jennifer Bowen; Sarah Servid (OSU DURM); Roger Citron (OSU DURM); Sarah Fletcher (OSU DURM); Chris DeMars; Amanda Parish; Andrew Gibler

Public: Uche Mordi (affiliation unknown), DeAnn Carr (affiliation unknown)

Voting did occur during this meeting.

Call to order, rollcall: The meeting was called to order by Nick Kashey at 8:03 AM.

Review of previous minutes: Minutes from the November 2, 2023, meeting were reviewed. A motion was made by Maggie Bennington-Davis and seconded by Neil Falk. None opposed, and the motion passed.

Brief OHA announcement: Amanda Parish announced that OHA will have a new Director, Dr. Sejal Hathi, beginning mid-January. Amanda also announced her resignation from OHA. Andrew Gibler will coordinate the MHCAG after her departure.

Public comment on any of today's agenda topics: None.

Schizophrenia narrative for revised schizophrenia medication algorithms. The group reviewed the narrative as written, with the additional language added about using a patient-centered, recovery-oriented, and trauma-informed approach when discussing long-acting injectable medications. The motion was made Niel Falk. None opposed, and the motion passed.

MEMBER	PRESENT **Y/N**	VOTE **S**= Full Support **R**=Support w/reservations **N**=No support and articulates alternative with supporting materials to discuss
Kaja Wagner	N	----------
Naomi Fishman	Y	S
Maggie Bennington-Davis	Y	S
Chris Bouneff	Y	S
John Bischoff	y	S
Bennett Garner	Y	S
Samantha DuPont	Y	S
Don Dravis	Y	S
Neil Falk	Y	S
Nick Kashey	Y	S
Lori Martin	Y	S
Tyler Duffield	N	----------
David Nagarkatti-Gude	Y	S
Leah Werner	N	----------

MHCAG Chair and Co-Chair Elections: Nick Kashey elected as Chair and Kaja Wagner elected as Vice-Chair. The motion for Nick's election was made by Maggie Bennington-Davis. None opposed, and the motion passed. The motion for Kaja's election was made by David Nagarkatti-Gude. None opposed, and the motion passed.

MEMBER	PRESENT **Y/N**	VOTE **S**= Full Support **R**=Support w/reservations **N**=No support and articulates alternative with supporting materials to discuss
Kaja Wagner	N	----------
Naomi Fishman	Y	S,S
Maggie Bennington-Davis	Y	S,S
Chris Bouneff	Y	S,S
John Bischoff	y	S,S
Bennett Garner	Y	S,S
Samantha DuPont	Y	S,S
Don Dravis	Y	S,S
Neil Falk	Y	S,S
Nick Kashey	Y	Abstain,S
Lori Martin	Y	S,S
Tyler Duffield	N	----------
David Nagarkatti-Gude	Y	S,S
Leah Werner	N	----------

MHCAG Bylaws: MHCAG bylaws were reviewed by members before the meeting. The motion to approve the bylaws as written was made by Bennett Garner and seconded by David Nagarkatti-Gude. None opposed, and the motion passed.

MEMBER	PRESENT **Y/N**	VOTE **S**= Full Support **R**=Support w/reservations **N**=No support and articulates alternative with supporting materials to discuss
Kaja Wagner	N	----------
Naomi Fishman	Y	S
Maggie Bennington-Davis	Y	S
Chris Bouneff	Y	S
John Bischoff	y	S
Bennett Garner	Y	S
Samantha DuPont	Y	S
Don Dravis	Y	S
Neil Falk	Y	S
Nick Kashey	Y	S
Lori Martin	Y	S
Tyler Duffield	N	----------
David Nagarkatti-Gude	Y	S
Leah Werner	N	----------

Policy Evaluation: OHP Antipsychotic Use in Children. The group provided no comments on the proposed recommendation and recommend reviewing policy again at February meeting**.**

Esketamine
PA Update

February 2024

Background/Policy Rationale

- Esketamine is indicated for people with major depressive disorder (MDD) and acute suicidal ideation or behavior.
  - Evidence is limited to the hospital setting.

- Current PA criteria allows for continuation after a hospitalization, but some hospitals do not offer esketamine.

- Goal: Evaluate a medically appropriate pathway for outpatient initiation of esketamine in people with MDD and acute suicidal ideation or behavior.

VA/DoD Guidelines (2019)

- cognitive behavioral therapy (strong recommendation)
- a crisis response plan (weak recommendation)
- dialectical behavior therapy (weak recommendation)
- problem-solving based psychotherapy for suicide prevention (weak recommendations).

- Short-term use of intravenous ketamine for people with major depressive disorder
- lithium for people with bipolar disorder or unipolar depression
- clozapine for people with schizophrenia or schizoaffective disorder
- Note: evidence for esketamine was published after the literature search was completed for this guideline

Randomized Controlled Trials (RCTs)

- Esketamine: mean change of 16.4 (SD 11.95) and 15.7 (SD 11.56) points in each study
- Placebo: mean change of 12.8 (SD 10.73) and 12.4 (SD 10.43) points in each study.
- mean difference from placebo was -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for each study.
  - Note: minimum clinically important difference (MCID) is 2 points
- Similar changes were observed at 4 weeks

- Median 1 point improvement in each group
- Difference from placebo: none

- Limited long-term data
- Imbalances in baseline study characteristics
- Low rate of suicide attempts during and after the studies
- Use in people with comorbid conditions

Recommendations

Update the safety edit for esketamine to include outpatient initiation of esketamine for people with suicidal ideation who have optimized alternative treatments for depression.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	**Yes:** Go to #10	**No:** Go to #8~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.~~

Approval Criteria		
8. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
9. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~ 10. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction ~~requested doses~~ (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

Randomized Controlled Trials (RCTs)

- MDD without psychotic features, MADRS score > 28 (moderate depression), suicidal ideation within 24 hours, AND need for hospitalization due to imminent suicide risk.
- Excluded patients with multiple comorbidities

- In conjunction with optimized oral antidepressant and hospitalization (mean length-of-stay of 19-22 days)

Prior Authorization Update: Esketamine

Date of Review: February 2024
Generic Name: esketamine
PDL Class: Antidepressants

Date of Last Review: December 2023
Brand Name (Manufacturer): Spravato (Janssen Pharmaceuticals, Inc.)

See **Appendix 1** for Prescribing Information Highlights

Purpose for Class Update:
Evaluate evidence for the effectiveness and safety of esketamine in people with suicidal ideation or behavior to establish a policy for outpatient initiation of therapy in people with depression and acute risk for suicide. This document provides a summary of previous reviews and recent guidelines from the Veterans Administration.

Plain Language Summary:
- Suicide is a common cause of death in the United States. Guidelines recommend risk evaluation for people who have suicidal thoughts or behavior.
- Studies show that some types of talk therapy (like cognitive behavior therapy, dialectical behavior therapy, and/or problem-solving based psychotherapy) decrease risk of suicide. Some medicines also may decrease risk of suicidal thoughts for some groups of people. Medicines with some benefit include:
    - Ketamine infusion for people with depression,
    - Lithium for people with bipolar disorder or depression, and
    - Clozapine for people with psychosis.
- Esketamine is a medicine that the Food and Drug Administration approved for depression in people at risk for suicide. Studies show that esketamine improves depression symptoms but may not change suicide risk compared to placebo (e.g., sugar pill).
- We recommend the Oregon Health Authority pay for esketamine for people with suicidal thoughts and depression when:
    - they have been referred to psychotherapy and
    - the doctor has re-evaluated the medicine they take by mouth for depression.

Research Questions:
1. What is the evidence for esketamine in improving symptoms, function, or quality of life in patients with depression and suicidal ideation?
2. What is the evidence for safety of esketamine in people with depression and suicidal ideation or behavior?
3. Are there specific subpopulations for which esketamine may be specifically indicated, more effective, or associated with less harm?

Conclusions:

- Guidelines updated in 2019 from the Veterans Administration/Department of Defense (VA/DOD) recommend several treatments with evidence for reduction in suicidal ideation and behavior.[1] Non-pharmacologic treatment includes cognitive behavioral therapy (strong recommendation), a crisis response plan, dialectical behavior therapy, and/or problem-solving based psychotherapy for suicide prevention (weak recommendations).[1] Short-term use of intravenous ketamine was suggested for people with major depressive disorder, lithium was suggested for people with bipolar disorder or unipolar depression, and clozapine was suggested for people with schizophrenia or schizoaffective disorder (weak recommendation for all therapies).[1] Esketamine was approved by the Food and Drug Administration (FDA) after the literature search was completed for this guideline.
- The VA/DOD also recommends management of co-occurring conditions for all people with suicidal ideation or behavior.[1] Evidence shows that patients with psychiatric conditions (e.g., substance use disorder, mood disorders), and psychiatric symptoms (e.g., hopelessness, insomnia, agitation) have increased risk for suicide.[1]
- Two randomized controlled trials (RCTs) evaluated use of esketamine in patients with major depressive disorder (MDD) at high risk for suicide.[2,3] Over 60% of people in these RCTs had a prior suicide attempt, 45-61% were prescribed an oral antidepressant plus oral augmentation therapy, and 67-75% were prescribed a benzodiazepine.[2,3] There is low quality evidence that esketamine does not decrease suicidality, but has a slight improvement in depression symptoms compared to placebo with a mean difference [MD] in the Montgomery-Asberg Depression Rating Scale (MADRS) of -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for each study.[2,3] A 2 point improvement on MADRS may be associated with a clinically significant improvement.[4]
- There is insufficient evidence for other outcomes including suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

Recommendations:

- Update the safety edit for esketamine to include outpatient initiation of esketamine for people with suicidal ideation who have optimized alternative treatments for depression.

Summary of Prior Reviews and Current Policy:

- Esketamine was approved by the Food and Drug Administration (FDA) for people with major depressive disorder and acute suicidal ideation or behavior in 2020. Evidence supporting approval for this indication was reviewed by the Pharmacy and Therapeutics Committee in 2021. Esketamine is also FDA-approved as adjunct therapy for treatment-resistant depression.
- The current safety edit for esketamine allows continuation of therapy when esketamine is initiated in a hospital setting for acute suicidal ideation or behavior because studies evaluated for FDA approval were conducted in the inpatient setting.
- Esketamine is carved-out of CCO plans and is paid for by FFS when billed as a pharmacy claims. Medical claims for esketamine are not carved-out and can be covered by CCOs for their members.

Background:

In the United States in 2017, suicide was the 10th leading cause of death (with a death rate of 14 deaths per 100,000 individuals).[5] Epidemiologic studies show that suicidal ideation is higher in women than men, but completed suicides are more common in men.[5] In the United States, the most common means of suicide include use of firearms (for men) and poisoning (for women).[1] Age-adjusted death rates from 2013 to 2015 also indicate that suicide is highest in rural areas and increases with age.[5] Risk factors for suicide include prior suicide attempts, current suicidal ideation, current psychosocial stressors, availability of firearms, prior

psychiatric hospitalization, psychiatric conditions (e.g., substance use disorder, mood disorders), and psychiatric symptoms (e.g., hopelessness, insomnia, agitation).[1]

Recent guidelines from the VA/DOD suggest against the use of a single instrument or method to evaluate suicide risk.[1] Instead, they recommend a comprehensive risk assessment to evaluate risk for suicide based on individual patient factors and circumstances.[1] While risk stratification is routinely done in clinical practice, authors found insufficient information to recommend for or against the use of risk stratification to evaluate the level of suicide risk.[1] Risk stratification usually includes assessment for risk based on intent, preparatory behaviors or a current suicidal plan and the ability of the person to independently maintain their safety with coping skills and social supports.[1,5]

Treatment is generally recommended in the least restrictive setting that is likely to be safe and effective.[5] For people with high acute risk, recommended treatment typically includes psychiatric hospitalization.[1] For people with intermediate acute risk, 2019 VA/DOD guidelines recommend hospitalization if related factors driving risk are responsive to inpatient treatment or intensive outpatient management including frequent contact, regular re-assessment of risk, and a well-articulated safety plan.[1] For people with low acute risk, primary care management is reasonable with outpatient mental health treatment for co-occurring conditions. For all categories of risk, treatment should include management of co-occurring conditions.[1] For people with high chronic risk of suicide, routine mental health follow-up is recommended. These people are considered to be at chronic risk for becoming acutely suicidal, particularly in the context of unpredictable psychosocial changes (e.g., job or relationship loss, relapse on drugs). Routine care should include a well-articulated safety plan, lethal means safety (e.g., no access to guns, limited medication supply), routine suicide risk screening, building coping skills, and management of co-occurring conditions.[1] Similar recommendations are made for people at intermediate chronic risk including routine mental health care, a well-articulated safety plan including lethal means safety, and management of co-occurring conditions.[1] For people at low chronic risk, primary care management or mental health care when needed for successful treatment is usually reasonable.[1]

Goals for people with suicidal ideation or suicide risk include reduction of immediate risk and prevention of recurrent symptoms for people with chronic suicide risk. Goals of treatment for depression typically focus on improvement in symptoms, function, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. Some of the most commonly used rating-scales and thresholds include the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[4] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52). [4] Values associated with remission and minimum clinically important differences for each of these scales vary. A 2 point improvement on MADRS may be associated with a clinical improvement and HAM-D scores of 3 to 7 points may be clinically significant.[4] Typically, a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[4]

Methods:
A Medline literature search for new randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for recent high quality systematic reviews.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Guidelines:
In 2019, the Veterans Administration/Department of Defense updated guidelines for the assessment and management of people at risk for suicide.[1] Recommendations were based on a systematic literature search through April 2018.[1] Literature for esketamine, which was approved by the Food and Drug Administration (FDA) in 2019, was not included. An update of this guideline is currently in progress. Guideline authors used "suggest" to describe recommendations based on weak evidence and "recommend" to describe recommendations with strong evidence. Recommendations were divided into the following categories:

- **Screening**: A validated screening tool, such as the Patient Health questionnaire-9 (PHQ-9), was suggested to identify suicide-related behavior and risk (weak recommendation).[1]
- **Evaluation**: Include an assessment of risk factors as part of a comprehensive evaluation for suicide risk (strong recommendation).[1] They suggest against the use of a single instrument or method to evaluate suicide risk (weak recommendation). While risk stratification is routinely done in clinical practice, authors found insufficient information to recommend for or against the use of risk stratification to evaluate the level of suicide risk.[1]
- **Non-pharmacologic therapy**: Cognitive behavioral therapy for suicide prevention was recommended for people with a recent history of self-directed violence to reduce risk of suicide (strong recommendation).[1] Completion of a crisis response plan is suggested for all patients with suicidal ideation (weak recommendation). Dialectical behavioral therapy was suggested for people with borderline personality disorder or recent self-directed violence (weak recommendation).[1] They suggest offering problem-solving based psychotherapies for people with a history of more than one prior incident of self-directed violence, people with a recent history of self-directed violence, or people with hopelessness and a history of moderate to severe traumatic brain injury (weak recommendation).[1]
- **Pharmacotherapy**: For all patients at risk of suicide, treatment should include management of co-occurring conditions. For people with comorbid major depressive disorder, ketamine infusion was suggested for short-term reduction in suicidal ideation (weak recommendation).[1] Lithium was suggested to reduce the risk of death by suicide as monotherapy in people with bipolar disorder or add-on therapy for people with unipolar depression or bipolar disorder (weak recommendation).[1] For people with comorbid schizophrenia or schizoaffective disorder, clozapine was suggested to reduce risk of death (weak recommendation).[1]
- **Post-acute care:** In addition to usual care after a psychiatric hospitalization, there were weak recommendations to support sending periodic caring communications (e.g., postcards) for 12-24 months, offering home visits to support reengagement for people not presenting for outpatient visits, and offering the World Health Organization brief intervention and contact treatment modality following an ER visit.[1]
- **Technology-based treatments:** There was insufficient evidence to recommend for or against self-directed or provider-driven technology-based, virtual interventions.[1]
- **Population/community-based interventions:** They suggest reducing access to lethal means to decrease suicide rates at a population level (weak recommendation). There was insufficient data to recommend for or against other community-based interventions.[1]

Recommendations for pharmacotherapy were based on the following evidence:

- **Ketamine:** Evidence for this recommendation was based on a meta-analysis of trials evaluating intravenous ketamine infusion which report that 55% of patients at 24 hours post-infusion and 66% of patients at 7 days post-infusion reported no suicidal ideation (moderate quality evidence).[1] Trials were primarily based in the inpatient hospital setting, and there is limited long-term evidence following discharge.[1] Repeated administration is not recommended because of the potential risk of addiction and known dissociative effects which may exacerbate psychotic symptoms.[1] Authors found no data to support ketamine's effect on suicide attempts or deaths.[1]

- **Lithium:** Recommendations for lithium were based on several cohort studies and systematic reviews which demonstrated reduced suicidal behavior and deaths associated with lithium in patients with bipolar depression.[1] Despite these benefits, discontinuations due to adverse events contributed to large variation in adherence across studies.[1] Adverse events related to discontinuations included gastrointestinal effects, polyuria, polydipsia, weight gain, hypothyroidism, and leukocytosis. Lithium has a low therapeutic index and caution is recommended in elderly people and people with comorbidities (e.g, seizure disorders and chronic kidney disease).[1]
- **Clozapine:** Evidence from systemic reviews and meta-analyses show that clozapine can lower death by suicide, suicide attempts, and suicidal behaviors with long-term treatment.[1] While evidence is most favorable for clozapine, evidence suggests that any antipsychotic may protect against suicide risk.[1] Clozapine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program which mandates frequent follow-up visits to monitor for adverse events.[1]

New Indications:

In July 2020, esketamine nasal spray received an expanded indication for depressive symptoms in adults (18-64 years of age) with MDD and acute suicidal ideation or behavior. Esketamine was previously approved for treatment-resistant depression. Approval was based on 2 identical, double-blind, 4-week, multicenter RCTs in adults (ASPIRE I and II).[3] These trials enrolled a total of 456 patients (n=226 in ASPIRE I and n=230 in ASPIRE II) from the United States, Europe, Asia, South Africa, South America, and Canada.[2,3] Participants had a diagnosis of MDD without psychotic features, suicidal ideation within the 24 hours prior to randomization with need for hospitalization due to imminent suicide risk, and a MADRS score greater than 28 indicating at least moderate depression.[2,3] Imminent suicide risk was defined based on affirmative answers to the Mini-International Neuropsychiatric Interview questions B3 ("Did you think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") upon screening in the emergency department or on inpatient psychiatric admission.[2] Patients received comprehensive standard of care treatment including an initial 5 to 14 day hospitalization in a psychiatric unit.[2,3] Esketamine, administered twice weekly, was initiated upon enrollment with standard antidepressant optimization during the first 2 weeks of each trial.[2,3] Pharmacotherapy standards of care could include either antidepressant monotherapy or an antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic or mood stabilizer).[2] Patients with clinically significant comorbidities were excluded from the studies (e.g., bipolar disorder, obsessive compulsive disorder [OCD], personality disorder, moderate to severe substance use disorder, psychotic disorder, renal or liver insufficiency, uncontrolled hypertension, history of malignancy, or clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic or metabolic disease).[2,3] The primary endpoint was change in depressive symptom severity evaluated with the MADRS score from baseline to 24 hours.[2,3] The key secondary outcome was symptom severity using the Clinical Global Impression of Severity of Suicidality - Revised scale (CGI-SS-r; range 0 to 6) which is a one-item, clinician-rated assessment of suicide severity.[2,3]

Overall, 78-89% of patients receiving esketamine and 82-83 % of patients receiving placebo completed 4 weeks of treatment, and about 72% of patients in each study completed the 90 day follow-up.[2,3] Baseline mean MADRS score was 40-41 indicating severe depressive symptoms, clinician-rated suicidality based on CGI-SS-r was moderate to extremely suicidal for 90-91% of patients.[2,3] Over 60% of patients in each study had a prior suicide attempt. In ASPIRE I, 28% had a recent attempt in the past month.[2] Common therapy included venlafaxine, escitalopram, duloxetine, quetiapine (as adjunct therapy), mirtazapine, and sertraline.[2,3] On average, an antidepressant plus oral augmentation therapy was prescribed to 45% and 61% of people in ASPIRE I and II, respectively. About 67-75% of patients received concomitant benzodiazepines, though use was not permitted within 8 hours of esketamine dosing.[2,3] Most baseline characteristics were balanced between groups. However, in ASPIRE I, more males were randomized to esketamine compared to placebo (42% vs. 34%) and a slightly higher proportion of patients randomized to esketamine were prescribed antidepressant plus oral augmentation therapy compared to placebo (47% vs. 42%).[2] In ASPRE II, the proportion of patients with a recent suicide attempt within the past 28 days at baseline differed between groups with more patients in the esketamine group

with a recent suicide (31.6%) compared to placebo (21.2%).[3] A prior suicide attempt is a known risk factor for subsequent attempts which may indicate that patients randomized to treatment had more severe suicidality than those given placebo.

There was a substantial difference in MADRS from baseline to 24 hours for both esketamine and placebo groups. Patients given esketamine had mean improvements in MADRS of 16.4 (SD 11.95) and 15.7 (SD 11.56) points while patients randomized to placebo improved by 12.8 (SD 10.73) and 12.4 (SD 10.43) points in each study.[2,3] The mean difference from placebo at 24 hours was -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for ASPIRE I and II, respectively. A 2-point change in MADRS may correspond with clinically meaningful improvements in symptoms. The difference from placebo was maintained at 4 weeks. Both placebo and esketamine groups had a decrease in acute suicidality (median 1 point improvement on CGI-SS-r from baseline to 24 hours), and there was no statistical difference compared to placebo indicating that hospitalization and standard therapy had a greater impact on acute suicidality than esketamine.[2,3] In general, subgroup analyses for the primary outcome based on baseline MADRS score, prior suicide attempts, oral antidepressant therapy, sex and age showed similar treatment effects.[2,3]

The overall rate of suicide attempts during and after the study was low compared to current epidemiological data which authors attribute to the comprehensive clinical care and frequent follow-up required as part of the study. The mean length of hospital stay in ASPIRE II was 21.6 days (SD 20.6) for patients receiving esketamine and 19.1 days (SD 19.6) for placebo indicating that the majority of the trial occurred during an inpatient stay.[3] Hospital duration was not reported in ASPIRE I. Psychotherapy was permitted, but less than 5% of patients received psychotherapy during the 4-week treatment phase.[3]

Nineteen percent (n=21) and 11% (n=13) of patients had a dose reduction due to intolerance in ASPIRE I and II, respectively.[2,3] In total, suicide-related adverse events (including suicidal ideation) occurred in 12 patients in the 4-week treatment period and were generally balanced between groups.[2,3] Eight suicide attempts occurred during therapy (4 in each group) on treatment.[2,3] During the 90 day follow-up period while on standard therapy, 10 patients had suicide attempts (7 with prior esketamine and 3 with prior placebo) during the follow-up period.[2,3] One patient, previously randomized to esketamine, completed suicide.[2] In most cases, patients with a suicide attempt after enrollment also had an attempt prior to enrollment.[2,3]

In these studies, depression symptoms (evaluated with MADRS score) were improved with esketamine compared to placebo. However, there is no evidence to suggest that esketamine decreases suicidal thoughts, suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide. These studies evaluated inpatient initiation of esketamine, and there is limited applicability to outpatient treatment. Both groups had a decrease in acute suicidality with no difference from placebo indicating that standard therapy, including hospitalization and greater clinical follow-up, likely continues to be the most effective treatment for suicidal symptoms.

References:

1. VA/DOD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. May 2019. Available at: https://www.healthquality.va.gov/guidelines/MH/srb/VADoDSuicideRiskFullCPGFinal5088212019.pdf. Accessed December 29, 2023.
2. Fu D-J, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *The Journal of clinical psychiatry*. 2020;81(3).
3. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol.* 2020.
4. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Nov. APPENDIX 5, VALIDITY OF OUTCOME MEASURES. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409740/ Accessed December 2, 2020.
5. DynaMed. Suicidal Ideation and Behavior. EBSCO Information Services. Accessed January 2, 2024. https://www-dynamed-com.liboff.ohsu.edu/condition/suicidal-ideation-and-behavior.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRAVATO® safely and effectively. See full prescribing information for SPRAVATO®.

SPRAVATO® (esketamine) nasal spray, CIII
Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)**
- **Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)**
- **SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	07/2020
Dosage and Administration (2.3, 2.6)	07/2020
Warnings and Precautions (5.1, 5.2, 5.4, 5.6)	07/2020

----------INDICATIONS AND USAGE----------

SPRAVATO® is a non-competitive *N*-methyl *D*-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults. (1)
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. (1)

Limitations of Use:

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO. (1)
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)
- Assess blood pressure prior to and after administration. (2.1)
- *TRD:* Evidence of therapeutic benefit should be evaluated at the end of the 4-week induction phase to determine need for continued treatment. (2.2)
- *Depressive symptoms in MDD with acute suicidal ideation or behavior*: Evidence of therapeutic benefit should be evaluated after 4 weeks to determine need for continued treatment. Treatment beyond 4 weeks has not been systematically evaluated. (2.3)
- See Full Prescribing Information for recommended dosage. (2.2, 2.3)
- See Full Prescribing Information for important administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

----------CONTRAINDICATIONS----------

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Increases in Blood Pressure:* Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment:* SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery:* Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity:* May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant):

- TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)
- Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2020

Appendix 2: Key Inclusion Criteria

Population	People with major depressive disorder and suicidal ideation or behavior
Intervention	Esketamine
Comparator	Placebo, another antidepressant, or standard of care
Outcomes	Symptoms of depression or suicidal ideation, function or quality of life, hospitalizations or urgent care visits, attempted or completed suicides, all-cause mortality
Setting	Outpatient treatment

Appendix 3: Prior Authorization Criteria

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression or suicidal ideation.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	**Yes:** Go to #10	**No:** Go to #8~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.~~
8. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
9. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~10. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction ~~requested doses~~ (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19
Implementation:1/1/22; 3/1/21; 8/19/19

Antipsychotic Prescribing in Children

January 2024

Background/Policy Rationale

- In October 2022, the Oregon Health Plan (OHP) implemented prospective safety edits for antipsychotics in children.

- Population: patients ≤ 5 years of age prescribed an antipsychotic for > 30 days

- Requirements:
  - Screening for diabetes in the past year OR clinical rationale for lack of monitoring
  - Engagement in, referral for, or inability to access non-pharmacological treatments
  - Prescription by or in consultation with a child psychiatrist or developmental pediatrician OR detailed documentation regarding risk/benefit assessment and the decision to prescribe antipsychotics

- This analysis evaluates:
  1) How that policy is working, and
  2) Utilization trends in antipsychotic prescribing for older members (6 to 17 years of age)

Utilization in ≤ 5 years of age

- Very small number of members prescribed antipsychotics (31 before, 33 after)
- Risperidone and aripiprazole were most common
- Common diagnoses included autism (42%), ADHD (42%), other developmental disorders (33%), and challenging behavior (42%)
- Glucose monitoring remained low (39%) after implementation of the policy
- More members had initial denied claims (n=17, 52%), but most providers submitted a PA request.
- Short-term PAs (up to 90 days) were often approved in order to allow providers time to submit additional information

Recommended Policy Changes

Update the safety edit in **Appendix 1** to:

- include assessment of rapid weight gain for members without glucose monitoring,
- allow longer initial therapy (up to 90 days) before PA is required to minimize administrative burden, and
- include members 6 years of age in the policy to provide monitoring for members who are turning 6 years old.

Continue to improve provider educational initiatives to notify providers about the policy before members have a denied claim.

Questions for MHCAG

PA Outcomes and Duration of Approvals

- No PA required for 24% of members (n=7) because they turned 6 years of age or had <30 days supply
- No PA submitted for 3% of members (n=1)
- PA requests submitted for 73% of members (n=24).
  - PA denied 3% (n=1) – submitted diagnosis of ADHD
  - PA denied after short-term approval 6% (n=2); one member switched to alternative drug therapy
  - PA approved for long-term treatment 52% (n=17)
  - Short-term PA approved 12% (n=4) with subsequent glucose monitoring

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for use of olanzapine as an antiemetic associated with cancer or chemotherapy?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Has the patient been screened for diabetes (blood glucose or A1C) within the last 12 months?	**Yes:** Go to #5	**No:** Go to #4
4. Is there documented clinical rationale for lack of metabolic monitoring (e.g. combative behaviors requiring sedation) OR documentation of patient weight before and after initiation of treatment? Note: Caregivers failing to take patients to the laboratory is not a clinical rationale for lack of monitoring.	**Yes:** Document rationale. Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Annual metabolic screening or consistent evaluation for rapid weight gain is required for chronic use of antipsychotics. Refer denied requests to the OHA for follow-up. ~~A single 90 day continuation of therapy may be granted upon request to allow for laboratory testing.~~
5. Is the patient engaged in, been referred for, or have documented inability to access evidence based first-line non-pharmacological therapy (e.g., applied behavior analysis therapy for autism, parent behavioral therapy, or parent child interaction therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. ~~A single 90 day continuation of therapy may be granted upon request to allow time for engagement.~~

Approval Criteria		
6. Is the drug prescribed by or in consultation with a child psychiatrist or developmental pediatrician?	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Go to #7
7. Is there detailed documentation regarding risk/benefit assessment and the decision to prescribe antipsychotic therapy? A thorough assessment should include ALL the following: a. Multidisciplinary review including a mental health specialist b. Mental health assessment including documentation of diagnoses, symptoms, and disease severity c. Discussion and consideration of first-line non-pharmacological therapies d. Assessment of antipsychotic risks and monitoring strategies e. Specific therapeutic goals of antipsychotic therapy, and for ongoing therapy, discussion of progress toward or achievement of therapeutic goals (or reasons for lack of progress and remediation strategies) f. Anticipated duration of therapy g. Detailed follow-up plan	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. ~~A single 90 day continuation of therapy may be granted upon request to allow for submission of required documentation.~~

Policy Evaluation: Antipsychotics in Children

Plain Language Summary:

- In children less than 6 years old, providers sometimes prescribe medicines called antipsychotics for serious behavior issues related to developmental disorders.
- Antipsychotics can cause weight gain, movement problems, and changes in hormones. Risk for side effects increases with length of therapy. Providers should regularly monitor for these side effects, and limit use to the shortest duration and lowest dose needed to improve symptoms. Because of these side effects, guidelines suggest people try other behavioral therapy before taking an antipsychotic.
- The Oregon Health Authority requires providers to explain why they are prescribing an antipsychotic to people less than 6 years of age before Oregon Health Plan (OHP) will pay for the medication. We evaluated how this policy is working and found that:
    - Only a small number of people less than 6 years old are prescribed antipsychotics.
    - Antipsychotics were prescribed most often for developmental disorders and challenging behavior.
    - Blood sugar testing occurs for about 40% of young children prescribed an antipsychotic.
    - The policy may decrease the number of people prescribed antipsychotics for longer than 30 days, but more data is needed to confirm these findings.
- We recommend continuing this policy to encourage appropriate antipsychotic use and suggest changes to decrease administrative burden.

Purpose:

The purpose of this policy evaluation is to evaluate administrative burden and changes in antipsychotic prescribing after implementation of a safety edit for children less than 6 years of age.

Research Questions:

1. For members less than 6 years of age prescribed antipsychotics, what diagnoses are present in medical claims that are potential indications for therapy?
2. For members less than 6 years of age, has duration of antipsychotic therapy changed after implementation of the policy?
3. For members less than 6 years of age prescribed antipsychotics, has the proportion of members with metabolic monitoring or with engagement of a mental health specialist changed after implementation of the policy?
4. For members less than 6 years of age prescribed antipsychotics, what proportion of members have denied claims or prior authorization requests?

Conclusions:

- This analysis identified 33 members who were less than 6 years of age and prescribed an antipsychotic in the 6 months after implementation of the policy. In the 6 months before implementation of the safety edit, 31 members were prescribed an antipsychotic. The most common diagnoses for members prescribed antipsychotics included autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and other developmental

disorders. Challenging behavior (e.g., aggressive, combative, explosive, violent or self-harmful behavior) was documented for 42% of members (n=14) during the prior authorization (PA) process.

- The most common antipsychotics prescribed to children less than 6 years of age were risperidone (58%) and aripiprazole (27%). Both risperidone and aripiprazole have an indication for irritability associated with autism for patients at least 5 and 6 years of age, respectively.
- Because of the small number of members and the short follow-up duration, it is difficult to identify whether there were changes in relevant clinical outcomes after implementation of the policy. Preliminary data do not indicate changes in glucose monitoring or the number of prescriptions written by a specialist.
    - In the 6 months before implementation of the policy, 26% of members had antipsychotic prescriptions written by a psychiatrist or neurodevelopmental pediatrician compared to 24% after implementation of the safety edit.
    - In the 6 months before implementation of the policy, 35% of members had claims for glucose monitoring compared to 39% of members in the 6 months after implementation of the safety edit. Profile review identified that 4 members (12%) had glucose monitoring only after the PA requirement.
- This policy was implemented in conjunction with a retrospective provider educational initiative in which providers were faxed information about the new policy when a member had their first paid claim for an antipsychotic. Because automated faxes were successfully sent for only 45% of members, manual efforts were made to call provider offices and send information about the policy.
    - Despite efforts to notify providers about the new policy, about half of members (n=17, 52%) with claims for an antipsychotic had an initial denied claim after implementation of the policy. Some members had subsequent denied claims after short-term approvals or when titrating doses.
- In the 6 months before implementation of the policy, 90% of members had therapy longer than 30 days compared to 73% in the 6 months after implementation of the safety edit.
    - After implementation of the safety edit, PA requests were submitted for 73% of members (n=24). The current policy applies to members less than 6 years of age, and PA was not required for 24% of members because they turned 6 years of age (n=7) before their second antipsychotic claim or had less than 30 days of therapy (n=1). Prior authorization was required, but not submitted for one member (3%).
    - Long-term therapy beyond 90 days was approved for 17 members (52%). For one member (3%) a PA was initially denied. Short-term approvals (up to 90 days) were approved for 6 members (18%). Short-term approvals were intended to avoid interruptions in ongoing care and allow providers additional time to submit information needed to meet PA requirements. Two members had a subsequent denied PA after a short-term approval.

Recommendations:

- Update the safety edit in **Appendix 1** to:
    - include assessment of rapid weight gain for members without glucose monitoring,
    - allow longer initial therapy (up to 90 days) before PA is required to minimize administrative burden, and
    - include members 6 years of age in the policy to provide monitoring for members who are turning 6 years old.
- Continue to improve provider educational initiatives to notify providers about the policy before members have a denied claim.

Background

Few antipsychotics have been studied in young children, and efficacy and safety has not been established for any antipsychotic in young children less than 5 years of age. Prior reviews evaluated by the Pharmacy & Therapeutics Committee have identified evidence that antipsychotics may improve behavior that challenges in children with autism or disruptive behavior disorders.[1] Both risperidone and aripiprazole have an indication for irritability associated with autism

(including symptoms of aggression towards others, deliberate self-injury, temper tantrums, and quickly changing moods) for patients at least 5 and 6 years of age, respectively.[2,3] These drugs also have the most evidence of benefit for disruptive behavior disorders.[1] Lurasidone has been studied in people with autism spectrum disorder, but did not demonstrate symptom improvement compared to placebo, and there is low quality evidence that quetiapine may have symptomatic and functional improvement in people with disruptive behavior disorder.[1]

Current guidelines recommend non-pharmacological therapy as first-line therapy for children prior to prescription of an antipsychotic.[4-6] Antipsychotics can be associated with significant risk of long-term adverse events. Because antipsychotics increase the risk of metabolic syndrome, laboratory monitoring is recommended before starting treatment and routinely during long-term therapy. In Medicaid, several national quality metrics aim to improve use of psychotropic medications in children. The 2023 core set of children's health care quality measures includes metabolic monitoring and use of first-line psychosocial care in children and adolescents on antipsychotics.[7]

In 2021, the Oregon Pharmacy and Therapeutic Committee recommended implementation of a safety edit to support appropriate use of antipsychotics in children 5 years of age or younger. The proposal targeted children after their first prescription in order to accommodate prescribing for urgent or acute symptoms and to avoid interruptions in therapy during transitions of care for patients newly enrolled in Medicaid. Ongoing therapy requires documentation of clinical rationale, metabolic monitoring, use of first-line non-pharmacologic therapy, and specialist consult. Upon their first claim for an antipsychotic, outreach will be conducted for prescribers of the antipsychotic in order to assess appropriateness of care, provide education on evidence-based use of non-pharmacological therapy, and facilitate access to services for appropriate patients.

The goal of this evaluation is to measure the impact on duration of therapy and metabolic monitoring under this policy.

Methods:
Members were identified for inclusion in the study based on paid or denied fee-for-service (FFS) claims for an antipsychotic medication. Antipsychotics were identified for inclusion based on their Preferred Drug List (PDL) class. The evaluation window for antipsychotic claims was from 10/1/2021 to 3/31/2022 for the control period before policy implementation and from 10/1/22 to 3/31/23 for the study period after policy implementation. The index event (IE) was the defined as the first paid or denied antipsychotic claim in the evaluation window. Denied claims were included based on error codes in **Appendix 1**.

For each patient, the baseline and follow-up periods were based on the IE.
- The baseline period was defined as the 90 days prior to the IE (exclusive of the IE).
- The follow-up period was defined as the 60 days following the IE (inclusive of the IE)

Inclusion Criteria:
1. Medicaid members with a paid or denied FFS claim for an antipsychotic in the evaluation window
2. Members less than or equal to 5 years of age at the time of the IE

Exclusion criteria:
1. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow-up period
2. Non-continuous Medicaid eligibility during the baseline period
3. Non-continuous Medicaid eligibility during the follow-up period

4. Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these patients may be incomplete. Patients were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug
	BMD	Oregon Health Plan with Limited Drug
	MED	Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND	Transplant package
	CWM	Citizenship Waived Emergency Medical
	SMF	Special Low-Income Medicare Beneficiary Only
	SMB	Special Low-Income Medicare Beneficiary Only

Population descriptors included:

1. Members with a diagnosis of autism or self-harm in medical claims during the baseline or follow-up period or submitted with a PA
2. Coordinated Care Organization (CCO) enrollment at the time of the IE
3. Drug prescribed at the time of the IE
4. Current foster care enrollment (historical enrollment is unavailable)
5. Race and age

Outcomes that were planned for this analysis included:

1. Proportion of members with claims for metabolic monitoring (see **Appendix 1** for medical codes)
2. Proportion of members with prescriptions from a psychiatrist or developmental pediatrician (see **Appendix 1** for taxonomy codes)
3. Days covered by antipsychotic in the 6 months following the IE categorized as less than or equal to 30 days or more than 30 days

Chart notes submitted with PA requests were also reviewed.

Results:

The number of members included in this analysis are listed in **Table 1**. After exclusion of members with potentially incomplete claims data, there were 31 members in the 6 months before implementation of the PA and 41 members in the 6 months after implementation of the policy. Eight members were excluded from the post-implementation group because they were already included in the pre-implementation group. Baseline characteristics for these members are described in **Table 2**. Because of the small numbers of members, differences between groups are difficult to quantify. Members were primarily 4 or 5 years of age and enrolled in a CCO at the time of the first claim in the evaluation window. Most members identified as male (>70%) and white (>60%). Risperidone (58%) and aripiprazole (27%) accounted for the majority of claims. Five members had claims for olanzapine (15%). In 4 of these members, olanzapine was prescribed as an antiemetic for cancer.

Table 1. Included population of members with paid claims

Number of included patients	Before	After
Age ≤ 5 years with FFS paid or denied antipsychotic claim	32	51
After exclusion of Medicare, TPL, and limited drug eligibility groups	32	46
After exclusion of non-continuous Medicaid enrollment in the 60-day follow-up period	32	44
After exclusion of non-continuous Medicaid enrollment in 90-day baseline period	31	41
After exclusion of members in Post group who were already in the Pre group	**31**	**33**

Table 2. Baseline characteristics

	Before		**After**	
	31	%	33	%
Age				
2	1	3.2%	2	6.1%
3	4	12.9%	3	9.1%
4	7	22.6%	8	24.2%
5	19	61.3%	20	60.6%
Sex				
Female	7	22.6%	9	27.3%
Male	24	77.4%	24	72.7%
Race				
White	19	61.3%	20	60.6%
Unknown	9	29.0%	8	24.2%
American Indian/Alaskan Native	3	9.7%	2	6.1%
Other	0	0.0%	3	9.1%
Foster Care Enrollment (as of May 2023)	2	6.5%	5	15.2%
Managed Care Enrollment (as of IE)				
FFS		0.0%	2	6.1%
CCO	31	100.0%	31	93.9%
IE Drug				
risperidone	18	58.1%	19	57.6%
aripiprazole	7	22.6%	9	27.3%
olanzapine	3	9.7%	5	15.2%
quetiapine fumarate	3	9.7%	0	0.0%

After implementation of the policy, about half of members had an initial denied claim (n=17, 52%). The current policy allows members to fill 30 days without PA, and an initial denial for these members would indicate that they had claims for an antipsychotic in the prior year. Most members with an initial denied claim had subsequent paid claims.

This policy was implemented in conjunction with a retrospective provider educational initiative in which providers were faxed information about the new policy when a member had their first paid claim for an antipsychotic. The intent of this policy was to avoid interruptions in care by notifying providers of the PA requirement before members had a denied claim. Automated, retrospective faxes to providers notifying them about the policy were successfully transmitted for about 45% of members (n=15). Because of the low success rate with initial faxes, manual efforts were made to call provider offices and re-fax information about the policy.

The most common diagnoses present in medical claims were developmental disorders like autism spectrum disorder, ADHD, psychological development disorders, and language disorders (**Table 3**). Members frequently had more than one mental health diagnosis. Diagnoses related to self-harm, hostility, or violence were present for only one member in each group. There was no change in the number of members with prescriptions from a psychiatrist or neurodevelopmental pediatrician and only slight changes in the number of patients with claims for glucose monitoring or therapy beyond 30 days (**Table 4**).

Table 3. Most common mental health diagnoses (ICD-10 codes beginning with F) in medical claims or submitted with PAs

			Before					After	
			31	%				33	%
Top 10 Mental Health Diagnoses (ICD-10 beginning with F)									
1	F902	Attention-deficit hyperactivity disorder, combined type	13	41.9%	**1**	F840	Autistic disorder	14	42.4%
2	F88	Other disorders of psychological development	12	38.7%	**2**	F902	Attention-deficit hyperactivity disorder, combined type	14	42.4%
3	F840	Autistic disorder	9	29.0%	**3**	F88	Other disorders of psychological development	11	33.3%
4	F919	Conduct disorder, unspecified	8	25.8%	**4**	F802	Mixed receptive-expressive language disorder	9	27.3%
5	F802	Mixed receptive-expressive language disorder	8	25.8%	**5**	F419	Anxiety disorder, unspecified	8	24.2%
6	F3481	Disruptive mood dysregulation disorder	7	22.6%	**6**	F919	Conduct disorder, unspecified	7	21.2%
7	F909	Attention-deficit hyperactivity disorder, unspecified type	7	22.6%	**7**	F909	Attention-deficit hyperactivity disorder, unspecified type	6	18.2%
8	F8089	Other developmental disorders of speech and language	6	19.4%	**8**	F4389	Other reactions to severe stress	5	15.2%
9	F913	Oppositional defiant disorder	6	19.4%	**9**	F4310	Post-traumatic stress disorder, unspecified	5	15.2%
10	F419	Anxiety disorder, unspecified	6	19.4%	**10**	F3481	Disruptive mood dysregulation disorder	4	12.1%
10	F4310	Post-traumatic stress disorder, unspecified	6	19.4%	**10**	F411	Generalized anxiety disorder	4	12.1%
10	F918	Other conduct disorders	4	12.9%	**10**	F918	Other conduct disorders	4	12.1%
10	F809	Developmental disorder of speech and language, unspecified	4	12.9%					
10	F4325	Adjustment disorder w/mixed disturb of emotions and conduct	4	12.9%					

Table 4. Clinical Outcomes

	Before		After	
	31	%	33	%
Glucose monitoring in baseline or follow-up period	11	35.5%	13	39.4%
Psychiatrist or neurodevelopmental prescriber specialty	8	25.8%	8	24.2%
Days covered by antipsychotic in the following 6 months				
0 days		0.0%	4	12.1%
1-30 days	3	9.7%	5	15.2%
>30 days	28	90.3%	24	72.7%

Manual review of profiles

Of the 33 members in the study period after implementation of the safety edit, a PA was ultimately submitted for 24 members (73%; **Table 5**). For 51% of members, long-term antipsychotic therapy was approved. For 18% of members (n=6), a short-term approval was authorized for 3 months to avoid interruptions in therapy and allow the prescriber time to submit additional documentation required for longer approval. Subsequent glucose monitoring was conducted for 4 of these members, and one switched to alternate therapy after a denial for longer-term therapy. Eight members (24%) met criteria for a new start of an antipsychotic and had no subsequent PA requirement. Because the current PA criteria apply only to members who were less than or equal to 5 years of age, 7 members turned 6 years of age before a PA was required and one member had less than 30 days of therapy. A PA was initially denied for one member and no PA was submitted for another member. Manual review of submitted chart notes identified 14 members (42%) with explosive, combative, violent, or self-harmful behavior. Diagnoses documented in chart notes included cancer (n=4), autism (n=10), substance exposure as an infant or *in utero* (n=4), and other developmental disorders (n=8). Overall, diagnostic trends were consistent between medical claims and chart notes except for substance exposure and challenging behavior. These diagnoses were apparent in submitted chart notes but were not identified in medical claims.

Table 5. Manual Review of Outcomes of Prior Authorization Status

	Before		After	
Manual review of PA process	31		33	%
Auto-PA for first 30 days (no manual PA requirement)	1	3.2%	8	24.2%
PA Approved > 3 months	1	3.2%	17	51.5%
Short-term PA approval (3 months)	0	0.0%	6	18.2%
No PA submitted and subsequent denied claims	0	0.0%	1	3.0%
Denied PA only	1	3.2%	1	3.0%

Discussion and Limitations:

This analysis is significantly limited by the small numbers of members prescribed antipsychotics. As a claims-based analysis, this evaluation also has several inherent limitations including:

- Before and after study design which is unable to control for potential confounding factors.
- Diagnostic data may be incomplete or not accurately reflect true patient diagnoses. After comparison of diagnoses in medical claims and diagnoses submitted with PAs, we identified that challenging behavior (e.g., aggressive, combative, explosive, violent or self-harmful behavior) was rarely included in medical claims.
- Provider taxonomy, which was used to identify mental health providers, may not actually reflect the true provider specialty or area of practice.
- Use of days' supply on paid claims as a surrogate marker for duration of therapy. Days' supply may not reflect actual member adherence or medication use.
- Use of common codes for psychotherapy and laboratory tests which may not accurately reflect engagement for all types of non-pharmacologic therapies or glucose testing.
- Use of a short follow-up period may result in incomplete data on duration of therapy for some members. In order to maximize the number of people eligible for inclusion, a short follow-up duration (60 days) was chosen. However, based on profile review, members with approval for long-term therapy were inaccurately categorized using this duration. A post-hoc analysis was conducted to evaluate duration of therapy over 6 months instead of 60 days.

The small number of members made it difficult to identify patterns in utilization.

This policy was implemented and designed to avoid interruptions in care for members. Members were allowed to fill 30 days of an antipsychotic without a PA, and a retrospective educational fax was sent at the time of the first claim to notify providers of the PA requirement. If providers requested a PA but did not supply sufficient documentation for long-term approval, 90 days of therapy could be authorized in order to avoid interruptions in care while the provider submitted additional information. During implementation, there were manual efforts to call provider offices and notify providers of the PA requirement. However, despite this, many members still had denied claims for an antipsychotic. It is unclear why providers were unaware of the PA requirement. Potential reasons include:

1. Inaccurate contact information for providers resulting in inability to successfully send a fax notifying the provider of the PA requirement. It is unclear if faxes that were successfully transmitted to a fax number actually reached the provider.
2. Faxes were sent in advance of a denied claim and not at the time of the denial. For members who had intermittent antipsychotic use and had a significant time between their first and second antipsychotic claim, the fax was not temporally associated with the need for a PA request. Retrospective faxes to providers notifying them about the policy were successfully transmitted for about 45% of members (n=15) within the 90 days prior to a denied claim.
3. PA is required for each change in dose or change in drug. In most cases, providers start on a low dose and titrate the antipsychotic if needed to control symptoms. Even when providers submitted an initial PA, subsequent changes in dose or changes in therapy required submission of a new PA.
4. Many PA requests did not include sufficient information to approve long-term therapy. In many cases, a short-term PA was approved in order to give providers time to submit documentation of metabolic monitoring. If providers did not submit this information within 3 months, members may have had subsequent denied claims. Because short-term approval was authorized for most patients, a longer initial treatment duration may be reasonable.

There is insufficient information based on this analysis to determine if the safety edit for antipsychotics in children less than 6 years of age is improving rates of metabolic monitoring, the proportion of providers who consult with a psychiatrist, or the proportion of members who participate in psychotherapy. At the time of this analysis only 3 months of complete follow-up data were available for members in the study, and the small number of people identified for analysis make it difficult to compare differences between groups. However, there were several implementation trends that were apparent after a review of profiles.

- At the time a provider submits a PA, we are unable to distinguish between members in foster care and other Medicaid members. Members in foster care have the same PA requirements as all other Medicaid members (even if the Department of Human Services has already reviewed the medication). The retrospective program is able to incorporate foster care enrollment and can help coordinate care for these members.
- Prior authorizations are typically loaded for a specific drug and dose. Titration of medications or switching between medications because of intolerance or lack of benefit increases the administrative burden for providers.
- Prior authorization criteria were only applied for members younger than 6 years of age. Some members turned 6 years of age before the provider submitted information to support long-term antipsychotic use.
- The current policy uses a one-year lookback period to evaluate previous antipsychotic use. If no claims are identified, then 30 days is authorized to allow the prescriber time to submit information needed for ongoing therapy. However, if members use antipsychotics intermittently with a long period between the first and second claims, then the fax notifying the prescriber about the PA requirement was not temporally related to the member's second denied claim. Over 50% of members in this analysis (n=17) had an initial denied claim, despite efforts to notify prescribers about the PA requirement.
- Review of chart notes documented engagement in a wide variety of non-pharmacological therapies for members prescribed antipsychotics. Therapies included play therapy, occupational therapy, school-based therapies, developmental rehabilitation, attachment-based training, parent-child interaction therapy, and applied behavior analysis. Current criteria for use of antipsychotics do not require only referral for psychotherapy and do not require any particular type of non-pharmacologic therapy.

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Appendix 1: Drug Coding

Table A1. Description of PICOs

Population	Medicaid members with a paid or denied FFS claim for antipsychotics in the evaluation window. AND age <=5 years at the time of the IE AND continuous Medicaid enrollment in the baseline (90 day) and follow-up (60 day) periods
Intervention	Continuation of antipsychotic beyond 30 days
Comparators	Members with antipsychotic claims from 10/1/2021 to 3/31/2022 vs. Members with antipsychotic claims from 10/1/2022 to 3/31/2023
Outcomes	Duration of antipsychotic use Glucose monitoring Specialist oversight Administrative burden of PA process – PAs, denied claims

Table A2. Specific Therapeutic Class for second generation antipsychotics

Specific Therapeutic Class	Generic
H7T	clozapine
H7T	risperidone
H7T	olanzapine
H7T	quetiapine fumarate
H7T	ziprasidone HCl
H7T	paliperidone
H7T	asenapine maleate
H7T	iloperidone
H7T	lurasidone HCl
H7T	asenapine
H7T	lumateperone tosylate
H7T	olanzapine/samidorphan malate
H7X	aripiprazole
H7X	brexpiprazole
H8W	cariprazine HCl
H8Y	pimavanserin tartrate

Table A3. Error codes for denied claims

Error Code	Error Status Description	Criteria for Study
513	RECIPIENT NAME AND NUMBER DISAGREE	Exclude
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE	Exclude
2809	DOB IS INVALID	Exclude
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)	Exclude
628	Other Coverage Reject Code Required for OCC 3	Exclude
503	DATE DISPENSED AFTER BILLING DATE	Exclude
643	INVALID OTHER COVERAGE CODE	Exclude
238	RECIPIENT NAME IS MISSING	Exclude
4999	THIS DRUG IS COVERED BY MEDICARE PART D	Exclude
3002	NDC REQUIRES PA	Include
4025	AGE IS NOT ALLOWED FOR NDC	Include
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE	Include

Table A4. Psychiatrist prescriber taxonomies

Taxonomy	Taxonomy Description
2080P0006X	PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS
2080P0008X	PHYSICIAN-PEDIATRICS-NEURODEVELOPMENTAL DISABILITIES
2084A0401X	PSYCHIATRY & NEUROLOGY, ADDICTION MEDICINE
2084B0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-BARIATRIC MEDICINE
2084B0040X	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY
2084D0003X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-DIAGNOSTIC NEUROIMAGING
2084F0202X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY
2084H0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-HOSPICE AND PALLIATIVE MEDICINE
2084N0008X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROMUSCULAR MEDICINE
2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY
2084N0402X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO
2084N0600X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CLINICAL NEUROPHYSIOLOGY
2084P0005X	PHYSICIAN-PSYCHIATRY&NERUOLOGY-NEURODEVELOPMENTAL DISABILITIES
2084P0015X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHOSOMATIC MEDICINE
2084P0800X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY
2084P0802X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-ADDICTION PSYCHIATRY
2084P0804X	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY
2084P0805X	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY
2084P2900X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PAIN MEDICINE
2084S0010X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SPORTS MEDICINE
2084S0012X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SLEEP MEDICINE
2084V0102X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-VASCULAR NEUROLOGY

Table A5. Metabolic monitoring for glucose

CPT Code	Description
80048	Blood Test, Basic Group Of Blood Chemicals (Calcium, Total)
80049	Basic Metabolic Panel
80050	General Health Panel
80053	Blood Test, Comprehensive Group Of Blood Chemicals
80054	Comprehensive Metabolic Panel
80065	Metabolic Panel
81506	Endo Assay Seven Anal
82945	Glucose Other Fluid
82947	Assay Glucose Blood Quant
82948	Reagent Strip/Blood Glucose
82950	Glucose Test
82951	Glucose Tolerance Test (Gtt)
82952	Gtt-Added Samples
82953	Glucose-Tolbutamide Test
82954	Glucose, Urine
82961	Glucose Tolerance Test, Intravenous
82962	Glucose Blood Test
83036	Hemoglobin Glycosylated A1c
83037	Hb Glycosylated A1c Home Dev
95249	Cont Gluc Mntr Pt Prov Eqp
95250	Cont Gluc Mntr Phys/Qhp Eqp
95251	Cont Gluc Mntr Analysis I&R
0403T	Diabetes Prev Standard Curr
3044F	Hg A1c Level Lt 7.0%
3045F	Hg A1c Level 7.0-9.0%
3046F	Hemoglobin A1c Level >9.0%
3047F	Hemoglobin A1c Level = 9.0%
3051F	Hg A1c>Equal 7.0%<8.0%
3052F	Hg A1c>Equal 8.0%<Equal 9.0%
3754F	Screening Tests Dm Done
D0411	Hba1c In Office Testing
D0412	Blood Glucose Level Test
G0096	Basic Metabolic Panel (Carbon Dioxide (B

G0098	Comprehensive Metabolic Panel (Albumin-S
G2089	A1c Level 7 To 9%
G8015	Diabetic Pt W/ Hba1c>9%
G8016	Diabetic Pt W/ Hba1c<Or=9%
G8017	Dm Pt Inelig For Hba1c Measu
G8777	Diabetes Screen
TR200	Tracking Only - Hemoglobin A1c - <7.0
TR201	Tracking Only - Hemoglobin A1c - >7 <8.0
TR202	Tracking Only - Hemoglobin A1c - >8 <9.0
TR203	Tracking Only - Hemoglobin A1c - >9.0

Antipsychotics in Children

Goal(s):

- Ensure safe and appropriate use of antipsychotics in children
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Antipsychotic use beyond ~~30~~ 90 days in children 3-~~5~~ 6 years of age
- All antipsychotic use in children 2 years of age or younger

Note: olanzapine can be automatically approved in patients with a recent cancer diagnosis

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Indications and Ages for Oral Second-generation Antipsychotics in Children

FDA-Approved Indications and Ages				
Drug	**Schizophrenia**	**Bipolar I disorder**	**Major depressive disorder (adjunct)**	**Other**
aripiprazole	≥13 yrs	≥10 yrs	≥18 yrs	Irritability associated with Autistic Disorder ≥6 yrs Tourette's Disorder ≥6 yrs
asenapine maleate	≥18 yrs	≥10 yrs		
brexpiprazole	≥13 yrs			
lurasidone HCl	≥13 yrs	≥10 yrs		
olanzapine	≥13 yrs	≥13 yrs	≥18 yrs	
paliperidone	≥12 yrs			Schizoaffective disorder ≥18 yrs
quetiapine fumarate	≥13 yrs	≥10 yrs		Bipolar depression ≥18 yrs
risperidone	≥13 yrs	≥10 yrs		Irritability associated with Autistic Disorder ≥5 yrs

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for use of olanzapine as an antiemetic associated with cancer or chemotherapy?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Has the patient been screened for diabetes (blood glucose or A1C) within the last 12 months?	**Yes:** Go to #5	**No:** Go to #4
4. Is there documented clinical rationale for lack of metabolic monitoring (e.g. combative behaviors requiring sedation) OR documentation of patient weight before and after initiation of treatment? Note: Caregivers failing to take patients to the laboratory is not a clinical rationale for lack of monitoring.	**Yes:** Document rationale. Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Annual metabolic screening or consistent evaluation for rapid weight gain is required for chronic use of antipsychotics. Refer denied requests to the OHA for follow-up. ~~A single 90- day continuation of therapy may be granted upon request to allow for laboratory testing.~~
5. Is the patient engaged in, been referred for, or have documented inability to access evidence based first-line non-pharmacological therapy (e.g., applied behavior analysis therapy for autism, parent behavioral therapy, or parent child interaction therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. ~~A single 90- day continuation of therapy may be granted upon request to allow time for engagement.~~

Approval Criteria		
6. Is the drug prescribed by or in consultation with a child psychiatrist or developmental pediatrician?	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Go to #7
7. Is there detailed documentation regarding risk/benefit assessment and the decision to prescribe antipsychotic therapy? A thorough assessment should include ALL the following: a. Multidisciplinary review including a mental health specialist b. Mental health assessment including documentation of diagnoses, symptoms, and disease severity c. Discussion and consideration of first-line non-pharmacological therapies d. Assessment of antipsychotic risks and monitoring strategies e. Specific therapeutic goals of antipsychotic therapy, and for ongoing therapy, discussion of progress toward or achievement of therapeutic goals (or reasons for lack of progress and remediation strategies) f. Anticipated duration of therapy g. Detailed follow-up plan	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. ~~A single 90- day continuation of therapy may be granted upon request to allow for submission of required documentation.~~

P&T/DUR Review: 6/21(SS)
Implementation: 10/1/22

Recognition and Management of Antipsychotic-induced Movement Disorders

Antipsychotic-induced movement disorders that are more commonly seen in clinical practice include parkinsonism, akathisia, tardive dyskinesia and acute dystonia. The prevalence of antipsychotic-induced movement disorders may be about 37% (95% CI, 18-55%), where 20% of people on an antipsychotic medication experience parkinsonism, 11% experience akathisia, and 7% experience tardive dyskinesia.[1] Acute syndromes manifest within days or weeks, whereas tardive syndromes might develop after months or years of antipsychotic treatment. These movement disorders can cause a lot of distress and stigma, which leads to poor medication adherence, poorer quality of life and increased morbidity and mortality.[2]

Parkinsonism

Symptoms of antipsychotic-induced parkinsonism develop within a few weeks of starting or increasing the dosage of medication, and may include parkinsonian tremor, muscular rigidity, loss of movement or difficulty initiating movement (akinesia), or slow movement (bradykinesia).[3] Parkinsonism may also affect emotional and cognitive function even in the absence of motor symptoms.[3] Differential diagnoses include tardive dyskinesia, agitation, and anxiety.

Treatment [3]

- **Lower the dose of antipsychotic medication** after weighing benefits of reduced parkinsonism with potential for an increase in psychotic symptoms.
- **Switch to another antipsychotic medication** with a lower likelihood of parkinsonism (see Side Effect Profiles of Second-generation Antipsychotic Medications).
    - Clozapine may be considered for individuals highly sensitive to antipsychotic-induced parkinsonism
- Add an anticholinergic medication. A short-term course may alleviate symptoms until the necessary medication changes are made; if a change in dose or change in medication is not possible, the anticholinergic medication may be needed on a long-term basis.
    - **Benztropine**, **trihexyphenidyl** or **diphenhydramine** are recommended.
    - Anticholinergic medications can negatively impact patient's quality of life and cognition, especially in older individuals.
    - Other side effects include dry mouth, blurred vision, precipitation of angle-closure glaucoma, constipation, tachycardia, and urinary retention.
    - Anticholinergic toxicity results in delirium, somnolence and hallucinations.
    - **Amantadine** is an alternative when an anticholinergic medication is not an option for an individual.

Evidence

Overall quality of evidence is low because of lack of data from clinical trials; however, sufficient evidence from a large amount of real-world clinical experience suggests these treatment options may be useful for antipsychotic-induced parkinsonism. No studies are available to suggest that one option is more effective than another option, but adding an anticholinergic may result in undesirable side effects. Individualize treatment based on patient preferences.

Akathisia

Akathisia can be difficult to diagnose and should be distinguished from psychomotor agitation associated with psychosis so that unnecessary increasing of the dose of antipsychotic medication is avoided.[3] People with akathisia have subjective complaints about feeling restless, with signs of excessive movements like fidgeting their legs, rocking on their feet, pacing, or a general inability to sit or stand still. Akathisia can develop within a few weeks of starting or increasing a dose of an antipsychotic medication. Most patients are bothered by akathisia, and some can be very distressed by it. It is a frequent cause of nonadherence to antipsychotic treatment.[3]

Treatment [3]

- **Lower the dose of antipsychotic medication** after weighing benefits of reduced akathisia with potential for an increase in psychotic symptoms.

- **Switch to another antipsychotic medication** with a lower likelihood of akathisia (see Side Effect Profiles of Second-generation Antipsychotic Medications).
- Add a benzodiazepine like **lorazepam** or **clonazepam** or the beta-blocker **propranolol**.

Evidence

Overall quality of evidence is low because of lack of data from clinical trials; however, sufficient evidence from a large amount of real-world clinical experience suggests these treatment options may be useful for antipsychotic-induced akathisia. No studies are available to suggest that one option is more effective than another option, but adding a benzodiazepine may result in undesirable side effects. Individualize treatment based on patient preferences.

Tardive Dyskinesia

Tardive dyskinesia is a persistent, involuntary movement disorder typically characterized by orofacial symptoms of grimacing, chewing and tongue movements.[4] Symptoms may begin weeks after starting antipsychotic treatment and may persist despite reducing the dose or discontinuing the antipsychotic medication.[5]

Tardive dyskinesia is a risk after exposure to antipsychotic medication. Risk is higher with first-generation medications than with second-generation agents, and risk increases with higher doses, longer duration of treatment, advancing age and female sex.[6,7] Diagnosis is complicated because symptoms fluctuate, and may be influenced by psychosocial factors. In addition, Huntington's disease is one of the most important differential diagnoses of tardive dyskinesia, where psychiatric disease can precede the development of hyperkinetic movements by several years.[2]

Most patients who develop tardive dyskinesia have mild symptoms. In people who develop moderate or severe symptoms, a complete assessment should be conducted, including a neurological examination, history of motor symptoms, past and current medication and drug use history, and laboratory testing (liver function tests, thyroid function tests, serum calcium, complete blood count and antiphospholipid antibodies).[3] If dyskinetic movements have begun or have increased after decreasing the dose of an antipsychotic medication, assess the longitudinal course of symptoms for up to several months because spontaneous reductions or resolution of dyskinesia may occur.[3] A validated evaluation tool like the Abnormal Involuntary Movement Scale (AIMS) is important to correctly diagnose tardive dyskinesia.

Treatment [3,4,6]

- Add a vesicular monoamine transporter-2 (VMAT-2) inhibitor **valbenazine** or **deutetrabenazine** in adults with moderate to severe tardive dyskinesia:
    - **Valbenazine (INGREZZA)** is dosed once daily.
        - Initiate ag 40 mg/day and increase to 80 mg/day after 1 week.
        - Major substrate of CYP3A4; avoid in patients on a CYP3A4 inducer; use 40 mg/day dose in patients on a CYP3A4 inhibitor.
        - Do not exceed 40 mg/day in people who are poor CYP2D6 metabolizers.
        - Not recommended in people with severe renal impairment.
    - **Deutetrabenazine** extended-release formulation (**AUSTEDO XR**) is dosed once daily.
        - Initiate at 12 mg/day and increase by 6 mg each week. A dose response should be observed, with higher doses and longer duration of use.
        - Doses of 24 mg/day and 36 mg/day provide similar response.
        - Assess ECG in patients at risk for QTc prolongation if dose exceeds 24 mg/day.
        - Do not exceed 36 mg/day in people with poor CYP2D6 metabolism.
        - Administer dose with food; tablets must be swallowed whole.
        - Contraindicated in people with hepatic impairment.
    - These medications are very expensive, so verify insurance coverage and prior authorization criteria. Discount cards (eg, ArrayrRx discount card) are available and may be helpful for uninsured or underinsured individuals.
    - It is helpful to diagnose moderate to severe tardive dyskinesia using the Abnormal Involuntary Movement Scale (AIMS), which can be performed by any clinician with appropriate training.[8]

        - Obtain a baseline score and reassess symptoms with the AIMS after 6 weeks of treatment.
        - Discontinue if no clinically meaningful improvement is documented (i.e., about 2-point reduction[9,10]).
- Consult with psychiatric services before discontinuing the offending antipsychotic medication or switching to a different agent with low risk for tardive dyskinesia, such as clozapine.

Evidence

Evidence for reducing symptoms of tardive dyskinesia by lowering the antipsychotic dose or switching to another antipsychotic is insufficient.[5] It is therefore our recommendation that the clinician consult closely with a psychiatrist or movement disorder specialist before making changes to the antipsychotic regimen. There is moderate quality evidence, however, that deutetrabenazine and valbenazine reduce the total AIMS score, which is the tool used to assess the efficacy of the VMAT-2 inhibitor.[6] With regard to safety, there is also moderate quality evidence that both VMAT-2 inhibitors are generally well tolerated.[6] No studies have directly compared VMAT-2 inhibitors, so it is unclear if there are differences in efficacy or safety between them.

Acute Dystonia

Acute antipsychotic-induced dystonia is characterized by uncontrollable movement (twisting or repetitive) or abnormal posturing of the neck (head tilt and rotation) due to prolonged or intermittent muscle contraction.[7] It is painful and can be quite distressing to the patient. Acute dystonia is sudden in onset, either after starting treatment or increasing the dose.[7] Upon observation, its appearance is dramatic and may be incorrectly attributed to catatonic signs or unusual behavior on the part of the patient, or misdiagnosed as seizure activity.[3]

Treatment [3]

- **IM diphenhydramine** (or administer IV if life-threatening laryngospasm present).
- **IM benztropine** is an alternative option.
- Transition to a short-term course of a long-acting oral anticholinergic medication like **benztropine** or **trihexyphenidyl** once acute dystonia resolved and the dose of the offending medication is reduced, or the medication is switched.
    - Anticholinergic medications can negatively impact patient's quality of life and cognition.
    - Other side effects include dry mouth, blurred vision, precipitation of angle-closure glaucoma, constipation, tachycardia, and urinary retention.
    - Be aware of anticholinergic toxicity with delirium, somnolence and hallucinations.

Evidence

Overall quality of evidence is low because of lack of data from clinical trials; however, sufficient evidence from a large amount of real-world clinical experience suggests these treatment options may be useful to reverse acute dystonia. Most cases observed have been with use of high doses of high-potency FGAs. No studies are available to suggest that these anticholinergic medications differ in their effectiveness or safety when used to treat acute dystonia.

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