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Drug Class Update: Antipsychotics
New Drug Evaluation: LYBALVI (olanzapine/samidorphan) oral tablets

Date of Review: August 2025

Date of Last Review: August 2020
April 2021 (pediatrics)
Dates of Literature Search: 1/1/2020-4/22/2025
Brand Name (Manufacturer): LYBALVI (Alkermes, Inc).
Dossier Received: no

Generic Name: olanzapine/samidorphan

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Evidence for antipsychotics was last reviewed by the Oregon Pharmacy & Therapeutic (P&T) Committee in August 2020. This review examines recently published comparative evidence of antipsychotics for major depressive disorder (MDD), schizophrenia, and bipolar disorder. In addition, evidence for the safety and efficacy of LYBALVI (olanzapine/samidorphan) oral tablets for treatment of schizophrenia and bipolar I disorder in adults will be evaluated.

Plain Language Summary:
- Antipsychotics are used to relieve symptoms such as delusions (false beliefs) or hallucinations (seeing or hearing something that is not there) that can occur in people with schizophrenia. In people with bipolar disorder, antipsychotics can help manage mania or depression. When people with major depressive disorder do not respond to antidepressant medicines, certain antipsychotics can be added to help manage the symptoms of depression.
- Most studies of antipsychotic medicines compare their effects to placebo (a sugar pill). No studies have shown that one antipsychotic is better than another in treating mental health symptoms.
- Side effects reported with antipsychotics include tremors, restlessness, muscle stiffness, dizziness, weight gain, diabetes, or sleepiness. Providers will often prescribe the lowest dose that helps with symptoms to reduce risk of these side effects.
- The Food and Drug Administration approved a combination medicine, LYBALVI (olanzapine/samidorphan) for adults with schizophrenia or bipolar I disorder. The antipsychotic in this medication, olanzapine, is effective for symptoms of schizophrenia and bipolar disorder, but it can cause weight gain. Samidorphan is combined with olanzapine to reduce the amount of weight people gain from taking olanzapine. In a 24-week study, people taking samidorphan/olanzapine gained an average of 7 pounds, compared with people taking only olanzapine, who gained 11 pounds.
- The Oregon Health Plan will pay for most antipsychotic medicines for members with a valid prescription. The Oregon Health Authority requires providers to submit documentation before they will pay for an antipsychotic when there are specific safety concerns for the medicine or the member (such as people less than 6 years old).

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Research Questions:

Antipsychotic Class Update

- What is the comparative effectiveness of antipsychotic drugs for people with MDD, schizophrenia, or bipolar disorder?
- What are the harms of antipsychotic drugs for people with MDD, schizophrenia, or bipolar disorder?
- Does effectiveness or safety of antipsychotics vary by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing)?

New Drug Evaluation: Olanzapine/Samidorphan

- What is the effectiveness of olanzapine/samidorphan in treating adults with schizophrenia or bipolar I disorder?
- What are the harms of olanzapine/samidorphan in treating adults with schizophrenia or bipolar I disorder?
- Does the effectiveness or safety of olanzapine/samidorphan vary by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing)?

Conclusions:

- Since the last P & T Committee review, 7 high-quality systematic reviews[1-7] have been published and 6 high-quality guidelines[8-14] have been updated.

<u>Major Depressive Disorder</u>

- A 2024 DERP systematic review identified that adjuvant use of the following second-generation antipsychotics (SGAs) improved symptoms of MDD compared to placebo: aripiprazole (12 RCTs), brexpiprazole (5 RCTs), cariprazine (5 RCTs), olanzapine (1 RCT), olanzapine/fluoxetine (5 RCTs), pimavanserin (2 RCTs), quetiapine (10 RCTs), risperidone (5 RCTs), and ziprasidone (2 RCTs).[2] Moderate-quality evidence showed aripiprazole, brexpiprazole, cariprazine and quetiapine improved results in assessments of depression when compared to placebo.[2]
- Pimavanserin and ziprasidone, which are not approved by the FDA for MDD, have insufficient evidence or appear to be ineffective for use as adjunctive treatments for depression.[2]
- The most common adverse events with adjunct use of SGAs in MDD included akathisia and weight gain.[2] Rates of akathisia were highest with aripiprazole and were slightly lower in patients taking brexpiprazole and cariprazine.[2] Patients taking the olanzapine/fluoxetine combination, quetiapine, ziprasidone, risperidone, and pimavanserin did not experience any significant movement AEs, including akathisia over the 6 to 12 week study periods.[2] When using aripiprazole, there is a moderate risk of akathisia, and patients prescribed olanzapine/fluoxetine should be monitored for weight gain.[2]

<u>Schizophrenia</u>

- A 2025 Drug Effectiveness Review Project (DERP) systemic review evaluating COBENFY (xanomeline/trospium) for schizophrenia found low-quality evidence that xanomeline/trospium is effective in alleviating symptoms of schizophrenia when compared to placebo.[1] Primary adverse effects observed with xanomeline/trospium include gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain and constipation.[1]
- There is insufficient evidence to determine the comparative efficacy of lurasidone versus haloperidol in adults with schizophrenia based on results from 2 RCTs (n=308) that were conducted over 4 to 6 weeks.[3] The evidence is very uncertain about the effects of lurasidone compared with haloperidol on change in mental state as measured by the Brief Psychiatric Rating Scale (BPRS) (mean difference [MD] 3.74, 95% confidence interval [CI] 0.57 to 6.90; 1 RCT, 281 participants; very low-certainty evidence); and the Positive and Negative Syndrome Scale PANSS (MD 6.68, 95% CI 2.45 to 10.91; 1 RCT, 281 participants; very low-certainty evidence). The evidence is also very uncertain about the effects of lurasidone compared to haloperidol on total serious adverse events (RR 0.98, 95% CI 0.37 to 2.60; 2 RCTs, 303 participants; very low certainty of evidence) and on severe adverse events (RR 1.70, 95% CI 0.46 to 6.32; 1 RCT, 281 participants; very low certainty of evidence).[3]

- A 2025 Cochrane review concluded that there was insufficient evidence to examine the effects of switching antipsychotic drugs in adults with schizophrenia who had not responded to initial antipsychotic treatment compared to continuing the same therapy.[4] The evidence is very uncertain regarding the effect of switching antipsychotics on clinically relevant response, quality of life, PANSS score change, duration of hospitalization, and the number of people experiencing at least one adverse effect.[4] Most of the studies were small; only 3 studies had more than 100 patients.[4]
- Compared to oral olanzapine in people with schizophrenia, oral haloperidol may have similar effects on clinically important change in global state using the Clinical Global Impression Scale (CGI) scale (RR 0.84, 95% CI 0.69 to 1.02; I^2 =73%; 6 studies, 3078 participants; very low-certainty evidence) and similar incidence of relapse (RR 1.42, 95% CI 1.00 to 2.02; I^2 =75%; 7 studies, 1499 participants; very low-certainty evidence).[5] Haloperidol may result in more extrapyramidal side effects compared to olanzapine (RR 3.38, 95% CI 2.28 to 5.02; 14 studies, I^2 =72%; 3290 participants; low-certainty evidence), but less weight gain (RR 0.47, 95% CI 0.35 to 0.61; I^2 = 57%; 18 studies, 4302 participants; low-certainty evidence).[5]
- In people with agitation and psychosis related to Alzheimer's disease and vascular dementia, it is uncertain if first-generation antipsychotics (FGAs) improve agitation compared to placebo (standardized mean difference (SMD) -0.36, 95% CI -0.57 to -0.15, 4 studies, n = 361; very low-certainty evidence), but they may have a small improvement for psychosis (SMD -0.29, 95% CI -0.55 to -0.03, 2 studies, n= 240; low-certainty evidence).[6] SGAs probably reduce agitation by a small amount (SMD -0.21, 95% CI -0.30 to -0.12, 7 studies, n = 1971; moderate-certainty evidence), but probably have very little effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03, 12 studies, n = 3364; moderate-certainty evidence) compared with placebo.[6] Both FGAs and SGAs probably increase the risk of somnolence and extrapyramidal symptoms.[6]
- In people with schizophrenia spectrum disorders and antipsychotic-induced weight gain, off-label use of metformin, topiramate, and aripiprazole improved metabolic symptoms, such as weight loss and reduction in waist circumference.[7] Aripiprazole augmentation (SMD = –0.73, 95% CI –0.97 to –0.48, p<0.001; 9 trials, N=813, I^2=68%), topiramate (SMD = –0.72, 95% CI –1.56 to –0.33, p<0.001; 15 trials, N=783, I^2=92.7%), and metformin (SMD = –0.53, 95% CI –0.69 to –0.38, p<0.001; 29 trials, N=1,279, I^2=39.4%) had a medium effect size on the combined outcomes of weight loss and reduction in weight circumference.[7]
- In 2023, the Veterans Affairs (VA)/Department of Defense (DoD) updated guidance for schizophrenia.[8] Because antipsychotics (with the exception of clozapine) have similar efficacy, recommendations were issued for antipsychotics as a class, rather than each medication individually.[8]
    - The VA/DoD recommends antipsychotics other than clozapine for an acute schizophrenia episode, for first-episode psychosis, and for maintenance treatment of schizophrenia to prevent relapses and hospitalization in people who have previously responded to an antipsychotic (Strong Recommendation; Moderate-Quality Evidence).[8]
    - The VA/DoD suggests a trial of another antipsychotic for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication (Weak Recommendation; Very Low-Quality Evidence).[8]
    - The VA/DoD suggests offering long-acting injectable (LAI) antipsychotics to improve medication adherence in individuals with schizophrenia (Weak Recommendation; Very Low-Quality Evidence).
    - The VA/DoD recommends clozapine for people with treatment-resistant schizophrenia (Strong Recommendation; Moderate-Quality Evidence).[8]
    - The VA/DoD suggests augmenting clozapine with another second-generation antipsychotic medication for individuals with treatment-resistant schizophrenia who have not experienced an adequate response to clozapine (Weak Recommendation; Very Low-Quality Evidence).[8]
    - The VA/DoD suggests using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia (Weak Recommendation; Moderate-Quality Evidence).[8]

<u>Bipolar Disorder</u>

- The VA/DoD updated guidance in 2023 for management of bipolar disorder including treatment for: (1) acute mania, (2) acute depression, and (3) maintenance to prevent recurrences of both mania or depression.[9]
  For Treatment of Acute Bipolar Mania, the VA/DoD:
    - suggests lithium or quetiapine as monotherapy (Weak Recommendation; Low-Quality Evidence).[9]

- suggests olanzapine, paliperidone, or risperidone as monotherapy if lithium or quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Very Low-Quality Evidence).[9]
- suggests aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy if the options above are not selected based on patient preference and characteristics (Weak Recommendation; Low-Quality Evidence).[9]
- suggests lithium or valproate in combination with haloperidol, asenapine, quetiapine, olanzapine, or risperidone in individuals who had an unsatisfactory response or a breakthrough episode on monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
- suggests against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
- suggests against brexpiprazole, topiramate, or lamotrigine as a monotherapy (Weak Recommendation; Very Low-Quality Evidence).[9]

For Treatment of Acute Bipolar Depression, the VA/DoD:

- recommends quetiapine as monotherapy (Strong Recommendation; Moderate-Quality Evidence).[9]
- suggests cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy if quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Low-Quality Evidence).[9]
- suggests lamotrigine in combination with lithium or quetiapine (Weak Recommendation; Very-Low Quality Evidence).[9]

Maintenance Treatment to Prevent Relapse:

- To prevent recurrence of mania, the VA/DoD:
  - recommends lithium or quetiapine (Strong Recommendation; Moderate-Quality Evidence).[9]
  - suggests oral olanzapine, oral paliperidone, or LAI risperidone If lithium or quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Low-Quality Evidence).[9]
  - suggests against lamotrigine as monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
  - suggests aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate (Weak Recommendation; Very Low-Quality Evidence).[9]
- To prevent recurrence of bipolar depressive episodes, the VA/DoD:
  - recommends lamotrigine (Strong Recommendation; Moderate-Quality Evidence).[9]
  - suggests lithium or quetiapine as monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
  - suggests olanzapine as monotherapy if lithium or quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Moderate-Quality Evidence).[9]
  - suggests olanzapine, lurasidone, or quetiapine in combination with lithium or valproate (Weak Recommendation; Low-Quality Evidence).[9]

- Guidance updated from the VA/DoD in 2022 suggests adding an SGA for people with MDD who have not responded (< 50% improvement in symptoms) to adequate antidepressant treatment trials (i.e., bupropion, mirtazapine, trazodone, vilazodone, vortioxetine, selective serotonin reuptake inhibitors [SSRIs], or serotonin norepinephrine reuptake inhibitors [SNRIs]) for 6 to 12 weeks (Weak Recommendation; Low-Quality Evidence).[10]
- The Oregon Mental Health Clinical Advisory Group (MHCAG) has developed treatment algorithms for management of schizophrenia,[11] MDD,[14] and bipolar disorder.[12,13] The MHCAG recommendations are similar to the guidance developed by the VA/DoD.

<u>New Indications and Formulations</u>

- December 2021: CAPLYTA (lumateperone) oral capsules received an expanded FDA-approved indication for treatment of depressive episodes associated with bipolar I or II disorder in adults, as monotherapy or as adjunctive therapy with lithium or valproate.[15] Prior to this approval, lumateperone was FDA-approved for the treatment of adults with schizophrenia.[15]
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- December 2021: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for management of schizophrenia in pediatric patents aged 13 to 17 years.[17] Prior to this approval, brexpiprazole was approved for use as adjunctive therapy for treatment of MDD in adults and treatment of schizophrenia in adults.[17]
- December 2022: VRAYLAR (cariprazine) oral capsules were approved as adjunctive therapy to antidepressants for the treatment of MDD in adults.[16] Prior to this approval, cariprazine was FDA-approved for treatment of schizophrenia and bipolar disorder in adults.[16]
- May 2023: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for treatment of agitation associated with dementia due to Alzheimer's disease (AAD).[17] Although the current standard of care for AAD consists of non-pharmacological and off-label pharmacological treatments (e.g., antipsychotics, benzodiazepines, antidepressants, antiepileptics), prior to this approval there were no FDA-approved treatment options for AAD.[18] Brexpiprazole has a boxed warning for increased risk of mortality in elderly patients with dementia-related psychosis, based on a meta-analysis the FDA conducted in 2005.[18]
- April 2024: FANAPT (iloperidone) received an expanded indication for acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.[19] Prior to this approval, iloperidone was FDA-approved to treat schizophrenia in adults.[19]
- March 2024: A new extended-release injectable formulation of risperidone, RISVAN, received FDA-approval for treatment of schizophrenia in adults.[20]
- July 2024: OPIPZA, a new oral film formulation of aripiprazole, received FDA approval for: treatment of schizophrenia in patients ages 13 years and older, adjunctive treatment of MDD in adults, irritability associated with autistic disorder in pediatric patients aged 6 years and older, and treatment of Tourette's disorder in pediatric patients aged 6 years and older.[21]
- July 2024: ERZOFRI, a new formulation of extended-release injectable paliperidone received FDA-approval for treatment of schizophrenia in adults and treatment of schizoaffective disorder in adults as monotherapy or as an adjunct to mood stabilizers or antidepressants.[22]
- There is insufficient evidence to determine if antipsychotic effectiveness or safety varies by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing).

<u>New Drug Evaluation: Olanzapine/Samidorphan</u>

- LYBALVI, a combination of olanzapine and samidorphan, is FDA-approved for adults with schizophrenia or bipolar I disorder as maintenance monotherapy or adjunct to lithium or valproate for acute manic or mixed episodes.[23]
- There is insufficient evidence to compare olanzapine/samidorphan to other therapies for patients with bipolar I disorder. FDA-approval was based upon studies of oral olanzapine.[23]
- In adult patients (n=403) hospitalized with an acute exacerbation of schizophrenia, olanzapine/samidorphan improved symptoms compared with placebo at Week 4 (least square mean [LSM] change in PANSS from baseline, -17.5 vs. -23.9; difference, -6.4; 95% CI -10.0 to -2.8; moderate-quality evidence).[24] There is no MICD for changes in PANSS total score, although response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.[25]
- In clinically stable outpatients (n=561) with schizophrenia, olanzapine/samidorphan had a smaller percent change in body weight over 24 weeks (4.21%) compared to 6.59% with olanzapine (difference, -2.38%; 95% CI, -3.88% to -0.88%; p=0.002; low-quality evidence).[26] The proportions of people with weight gain of 10% or more from baseline was 17.8% in the olanzapine/samidorphan group and 29.8% in the olanzapine group (difference, 12%; 95% CI, -22.8 to -4.6; p=0.003; number needed to treat (NNT) = 8; low-quality evidence).[26]
- The most common adverse effects reported with olanzapine/samidorphan were increased weight, somnolence, dry mouth, and headache.[23] The adverse effects reported in the 4-week ENLIGHTEN-1 trial are presented in **Table 13**. Adverse reactions that led to study discontinuation in ENLIGHTEN-1 included abnormal liver function tests and worsening schizophrenia in 1% of participants.[23] Adverse effects reported in the 24-week ENLIGHTEN-2 trial are summarized in **Table 14**.

- There is insufficient evidence to show that the effectiveness or safety of olanzapine/samidorphan varies by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing).

Recommendations:

- Based on review of recent clinical evidence, no changes to the Preferred Drug List (PDL) are recommended for FGA, SGA, or parenteral antipsychotics.
- After evaluation of medication costs in executive session, no PDL changes are recommended.

Summary of Prior Reviews and Current Policy:

- The last P &T Committee review of antipsychotics drugs was at the August 2020 meeting. No changes to the preferred drug list (PDL) were recommended for oral or parenteral antipsychotics based on efficacy or safety data. After evaluating costs in the executive session, aripiprazole tablets and ziprasidone capsules were designated as preferred on the PDL.
- In the Oregon Health Plan, antipsychotic medications are exempt from traditional PDL requirements. However, clinical PA criteria, which address safety concerns or medically inappropriate use, may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use, for pimavanserin to promote safe use in patients with Parkinson's disease psychosis, for antipsychotics in children to discourage off-label use not supported by compendia, and to ensure safety of xanomeline/trospium in combination with other mental health drugs. The PA criteria for these safety edits are outlined in **Appendix 6**.
- The FGA, SGA, and parenteral antipsychotics included on the Oregon PDL are presented in **Appendix 2.** The preferred FGAs include oral chlorpromazine, fluphenazine, haloperidol, thioridazine, thiothixene, and trifluoperazine. Oral aripiprazole, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone are preferred SGAs on the PDL. Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, paliperidone, risperidone, and trifluoperazine are preferred on the PDL.
- Each quarter, approximately 33,000 patients receive a prescription for an SGA and 1,200 patients have claims for an FGA. Most of the antipsychotic drug use in the Oregon Medicaid population is for preferred oral SGAs, including aripiprazole, quetiapine, and olanzapine. Approximately 5% of antipsychotic drug claims are for parenteral formulations. Paliperidone and aripiprazole are the most frequently prescribed injectable agents in this class.
- Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms for schizophrenia, bipolar mania or MDD. There is insufficient evidence to determine if new formulations of long acting injectable (LAI) aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents.

Background:

Antipsychotic medications are typically categorized as first-generation and second-generation. First generation antipsychotics (FGAs) such as haloperidol and chlorpromazine are dopamine receptor antagonists and block histamine, muscarinic and alpha-1 receptors.[27] Second generation antipsychotics (SGAs) are serotonin-dopamine antagonists, and carry less risk of extrapyramidal symptoms, such as dystonic reactions, akathisia and tardive dyskinesia, that are associated with FGAs.[27] The main adverse effects of SGAs include weight gain, glucose intolerance and hyperprolactinemia.[27] Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.[27] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression and nausea or vomiting.[27]

Major Depressive Disorder

Major depressive disorder is defined as the presence of a depressed mood or a loss of interest or pleasure in normally enjoyable activities that occurs along with at least 4 additional diagnostic criteria or symptoms for at least 2 weeks (see **Appendix 3, Table 17** for specific diagnostic criteria).[28] Based upon functional impairment, severity of symptoms, and level of patient distress, MDD can be assessed as mild, moderate or severe (see **Appendix 3, Table 18** for severity assessments). One-third of patients with MDD have severe MDD, which is more difficult to treat and achieve remission than other forms of MDD.[29]

Major depressive disorder is a common cause of disability, leading to substantial costs to individuals and society.[30,31] Costs to an individual may include emotional suffering, reduced quality of personal relationships, possible adverse effects from treatment, cost of mental health and medical visits and medications, time away from work and lost wages, and cost of transportation.[31] Costs to society may include loss of life, reduced productivity (because of both diminished capacity while at work and absenteeism from work), and increased costs of mental health and medical care.[31] In the United States (U.S.), more than 20% of adults experience MDD in their lifetime, with around 10% experiencing MDD in a given year.[32]

Over 60% of patients with MDD have no response or achieve only a partial response to an antidepressant.[2] Guideline directed therapies to achieve remission in treatment-resistant depression include addition of lithium or a SGA to antidepressant therapy.[33] Antipsychotics are effective adjunctive treatments for patients who have not responded to multiple antidepressant trials.[34] The FDA-approved SGAs for adjunctive treatment of MDD include aripiprazole, brexpiprazole, cariprazine, lurasidone, quetiapine, and the combination of olanzapine with fluoxetine.[27]

Goals of treatment for depression include symptom and function improvement, remission, and relapse prevention.[33] Rating scales used to assess symptom improvement include the 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.[35] The HAM-D is a clinician-rated, 17- item scale with a range of 0 to 52 points, with higher scores indicating more severe depression.[35] Remission is defined being free from depressive symptoms for several months after two or more depressive episodes.[35] Response to therapy is typically defined as a 50% improvement in symptom score from baseline.[35] A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and decreases in HAM-D scores of 3 to 7 points may be clinically significant.[35] Additional outcome assessments for MDD are presented in **Appendix 3, Table 19**.

Schizophrenia

Schizophrenia is a mental health disorder characterized by presence of positive symptoms (delusions, hallucinations, disorganized speech, thought and behavior), negative symptoms (blunted affect, lack of speech or social interactions, anhedonia, and decreased motivation), and cognitive symptoms (impaired executive function, attention, and memory).[36] Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of: 1) at least one positive symptom with 2 or more total symptoms characteristic of schizophrenia and 2) social or occupational disruption in work, relationships, or self-care.[37] Symptoms and social dysfunction generally persist for at least 6 months in the absence of alternative medical causes.[37] Schizophrenia has a lifetime prevalence of about 1%.[38] The prevalence of schizophrenia based on gender, race and ethnicity may vary.[36] Diagnosis of schizophrenia may be 3-5-times more common in Black and Hispanic populations compared to white populations and more common in males than females.[36,39] However, data also shows there may be an increased risk for misdiagnoses of psychiatric conditions in non-white populations.[39]

Onset of schizophrenia symptoms occurs most commonly in early adulthood and can have a significant impact on quality of life, social relationships, and occupational status.[39] Less than 20% of patients who experience first-episode psychosis will remain relapse-free over their lifetime, and at least one-third of patients continue to have symptoms despite treatment.[39] Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, slow symptom onset, and symptom presentation at an earlier age.[39] Schizophrenia has been associated with increased

risk of overall mortality, mortality due to suicide, substance use disorders, cognitive impairment, and chronic medical conditions (e.g., diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease).[39] Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within 1 year after their last episode; most relapses occur when patients stop taking their medication.[26]

Antipsychotic medications are the primary treatment recommended for schizophrenia. Medication selection is dependent on risks for adverse effects, patient preferences, prior treatment response, and availability of a long-acting formulation.[40] All antipsychotic medications are associated with adverse effects that limit medication tolerability and contribute to treatment discontinuation. Adverse effects related to antipsychotic use include sedation, metabolic (e.g., weight gain, diabetes, hypertension, dyslipidemia), cardiovascular (e.g., QT prolongation), hormonal (e.g., elevated prolactin levels, sexual dysfunction), and movement disorders (e.g., akathisia, dyskinesias, dystonia, parkinsonism).[36,39] Antipsychotics with LAI formulations include aripiprazole, risperidone, paliperidone, fluphenazine, and haloperidol. The Oregon Mental Health Clinical Advisory Group recommends that providers consider use of these specific medications because LAI antipsychotics have shown lower risk of hospitalization and relapse when compared to oral antipsychotics.[40] Clozapine is usually recommended for people who have had inadequate response to more than 2 antipsychotics.[40] Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also recommended in conjunction with pharmacological therapy.[40]

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The CGI evaluates disease severity and improvement using a 7-point analog scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimal clinically important difference (MCID).[41] The PANSS evaluates 30 items in patients with schizophrenia. Each item is scored on a 7-point scale, with lower scores indicating less severe symptoms (range 30-210).[41] This scale can also be subdivided to assess general psychopathology (16 items), positive symptoms (7 items), or negative symptoms (7 items). The 7 negative symptom questions are also commonly referred to as the Marder negative factor score.[42] There is no established MCID for the PANSS, though improvements of 16-34% have been correlated to 1 point improvements in CGI-S,[43,44] 4-8 points have been correlated to increases in employment[45] and improvements of 10 points have been correlated with reduced hospitalization.[25] Response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.[25] Additional details about outcomes assessment in schizophrenia are presented in **Appendix 3, Table 20.**

Bipolar Disorder

Bipolar disorder is characterized by episodes of mania and in the majority of cases, episodes of major depression.[46] It is classified as bipolar I disorder (characterized by at least one manic episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes).[46] The World Mental Health Survey Initiative reported lifetime and 12-month prevalence estimates for bipolar disorders of 2.4% and 1.5%, respectively.[47] The prevalence of bipolar I disorder is similar for males and females, while bipolar II disorder occurs more frequently among females.[46] The onset of bipolar disorder typically occurs around 20 years of age.[46] Bipolar disorder is frequently associated with other mental health conditions including anxiety disorder, attention-deficit/hyperactivity disorder (ADHD) and substance use disorders.[46] After one manic episode, greater than 90% of individuals have recurrent mood episodes, and suicide risk is estimated to be at least 15 times higher than the general population risk.[26] Functional impairment is significant. One study found that individuals with bipolar I disorder had severe impairment in occupational functioning about 30% of the time, and individuals with bipolar I disorder attain lower levels of socioeconomic status than members of the general population with equivalent educational levels.[26]

Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.[48] Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.[46] Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy.[46] The recommended pharmacological treatments

for bipolar disorder vary depending on the phase of the disorder (acute mania, acute depression, or maintenance). The mainstay of treatment for acute mania and hypomania is pharmacologic treatment with antipsychotic agents (e.g., aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, ziprasidone) or mood stabilizers (e.g., lithium, divalproex, carbamazepine, lamotrigine).[46] The FDA has approved 4 atypical antipsychotics for the treatment of bipolar depression: quetiapine, lurasidone, cariprazine, and the combination of olanzapine with fluoxetine.[46] Lithium remains one of the most effective drugs for the prevention of both depressive and manic recurrences in bipolar disorder.[46] Quetiapine alone and the combination of quetiapine–lithium or quetiapine–divalproex have also been shown to be effective maintenance treatments for bipolar disorder.[46] Meaningful differences in efficacy among these treatments have not been observed in head-to-head trials.[46]

For patients with bipolar I disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.[48,49] Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a minimum clinically important difference of 1 point).[48,50] Additional details about outcome assessments in bipolar disorder are presented in **Appendix 3, Table 20**.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 5**, which includes dates, search terms and limits used. 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 Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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.

New Systematic Reviews:
Drug Effectiveness Review: Newer Pharmacologic Agents for Treatment of Schizophrenia, Psychosis and Bipolar Disorder
In 2025, DERP published a systemic review of newer pharmacologic agents for treatment of schizophrenia and bipolar disorder.[1] The literature search for this report was completed on November 12, 2024.[1] Nine placebo-controlled RCTs inpatients with schizophrenia met inclusion criteria.[1] Three RCTs evaluated xanomeline/trospium and 6 RCTs evaluated 3 investigational agents: roluperidone, ulotaront, and valbenazine.[1] This evidence summary will focus on the data for the FDA-approved product, xanomeline/trospium, which is a new treatment for psychosis with a different mechanism of action than FGAs and SGAs. Unlike other antipsychotic agents, which antagonize one or more dopamine receptors, this agent is not expected to cause extrapyramidal effects, as it is not known to exhibit antagonist activity on dopamine in the nigrostriatal tracts.[1]

The 3 placebo-controlled RCTs (n=690) that studied xanomeline/trospium had a moderate risk of bias (RoB).[1] DERP assessments of results and certainty of evidence (CoE) include:

- Xanomeline 125 mg/trospium 30 mg reduced the PANSS total score from baseline to week 5 by 8.4% to 10% (3 RCTs, low CoE).[1]
- Xanomeline 125 mg/trospium 30 mg reduced the PANSS positive symptom score from baseline to week 5 by 8% to 12% (3 RCTs, low CoE).[1]

- Xanomeline 125 mg/trospium 30 mg reduced the PANSS negative symptom score from baseline to week 5 by 1.8% to 2.3% (3 RCTs, low CoE).[1]
- Response, measured by a Clinical Global Impression–Improvement (CGI-I) score of 1 or 2, was not significantly different between xanomeline 125 mg/trospium 30 mg and placebo (6% vs. 1%, MD, 4%; 955 CI -3 to 12; 1 RCT; n=182; very low CoE).[1]
- Response, measured by at least a 30% improvement in PANSS scores at endpoint, was greater for xanomeline 125 mg/trospium 30 mg (51% to 55%) compared with placebo (25% to 28%) (2 RCTs, n=508; low CoE).[1]
- The primary AEs with xanomeline/trospium are associated with the muscarinic receptors, leading primarily to gastrointestinal effects such as nausea, vomiting, constipation, and hypersalivation (3 RCTs; moderate CoE).[1]

Drug Effectiveness Review: Second Generation Antipsychotics as Adjuvant Therapy in Treatment of Major Depressive Disorder

In 2024, DERP issued a systematic review that evaluated adjuvant SGAs for treatment of MDD.[2] Literature was searched through October 20, 2023 and 47 RCTs met inclusion criteria.[2] Antipsychotics of interest included aripiprazole (12 RCTs), brexpiprazole (5 RCTs), cariprazine (5 RCTs), olanzapine (1 RCT), olanzapine/fluoxetine (5 RCTs), pimavanserin (2 RCTs), quetiapine (10 RCTs), risperidone (5 RCTs), and ziprasidone (2 RCTs).[2] Pimavanserin, risperidone, and ziprasidone are not FDA-approved as adjunctive therapy for MDD and do not have compendial indications for off-label use in MDD.[27] Limitations to the overall body of evidence included short study durations (most studies were conducted over 6 to 12 weeks) and lack of comparative studies, as most of the RCTs were placebo-controlled in combination with an antidepressant.[2]

Evidence from the 2024 DERP report is summarized below for each of the FDA-approved SGAs. Adjunctive antipsychotic efficacy was evaluated using the MADRS, CGI-I scoring, and treatment response (≥ 50% improvement from baseline on applicable depression scale). Most agents showed a 2 to 3–point improvement in MADRS scores during the first 5 to 8 weeks of treatment.[2] In a clinical setting many practitioners prefer for a patient to experience a 50% or greater reduction in their depression assessments to determine efficacy.[2] Adverse effects were assessed using the Barnes Akathisia Rating Scale (BARS) and change in body weight from baseline.

Adjunctive Aripiprazole vs. Placebo/Monotherapy

Findings for aripiprazole as adjunctive treatment to ADT versus placebo in MDD were included in 12 RCTs (see **Table 1**).[2] Two of the RCTs were conducted in older adults (aged ≥ 60 years) with treatment-resistant depression.[2] Four of the studies were rated as high risk of bias (RoB), 7 studies were rated as moderate RoB, and 1 study was rated as low RoB.[2] Studies ranged from 6 to 12 weeks in duration.[2] Efficacy outcomes were rated as high CoE due to the large number of studies that showed consistent improvement in assessment scales and treatment response.[2]

Table 1. Adjunctive Aripiprazole Versus Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in Body Weight
Number of RCTs, Total Population	9 RCTs, N = 2,795	8 RCTs, N = 3,874	9 RCTs, N = 3,975	7 RCTs, N = 2,372	11 RCTs, N = 4,208
DERP Certainty of Evidence Assessment	High	High	High	High	High
Notes	MADRS scores typically improved 2 to 3 points during treatment compared	Modest improvement in CGI-I scores compared with placebo.	Aripiprazole showed higher response rates	Aripiprazole showed modestly higher scores in akathisia in short-	Aripiprazole typically showed 1 to 1.5 kg increase in body

	with placebo. (MCID = 2-point increase). DERP meta-analysis from 3 RCTs (n=882) showed more improvement in MADRS scores with aripiprazole vs. placebo (MD, 2.74; 95% CI 0.87 to 4.60; I^2 = 79%).	DERP meta-analysis from 6 RCTs (n=1,856) showed more improvement in the CGI-I score with aripiprazole vs. placebo (MD, 0.30; 95% CI 0.28 to 0.32; I^2 = 20%).	compared to placebo (10% to 28% absolute change). DERP meta-analysis from 8 RCTs (n=2,359) showed higher rates of response with aripiprazole vs. placebo (RR, 1.51; 95% CI 1.33 to 1.71; I^2 = 0%)	term studies. Unknown if this AE resolves with extended therapy.	weight in the first 6 weeks of therapy.
Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio					

Adjunctive Brexpiprazole vs. Placebo/Monotherapy

Five RCTs evaluated brexpiprazole as adjunctive treatment with ADT versus placebo for MDD (see **Table 2**).[2] Two of the studies were rated as high RoB and 3 studies were rated as having a moderate RoB.[2] Most of the RCTs were conducted over 6 to 8 weeks, with one study lasting 24 weeks.[2] Efficacy outcomes were rated as moderate to high CoE due to consistent improvement in MADRS scores, with greater inconsistency for CGI-I assessments.[2]

Table 2. Adjunctive Brexpiprazole Versus Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	5 RCTs, N = 2,829	4 RCTs, N = 2,326	5 RCTs, N = 2,829	3 RCTs, N = 1,932	5 RCTs, N = 2,829
DERP Certainty of Evidence Assessment	High	Moderate	High	Low	High
Notes	MADRS scores typically improved 1.5 to 3 points during treatment compared with placebo. Improvements may not be clinically important for all patients. (MCID = 2-point increase). DERP meta-analysis from 2 RCTs (n=789) showed more improvement in MADRS scores with brexpiprazole vs. placebo (MD, 1.68; 95% CI 0.75 to 2.60; I^2 = 0%).	Modest improvement in CGI-I scores compared with placebo, inconsistent results. DERP meta-analysis from 4 RCTs (n=1,558) showed more improvement in the CGI-I score with brexpiprazole vs. placebo (MD, 1.36; 95% CI 1.12 to 1.65; I^2 = 0%).	Brexpiprazole showed variable response rates compared to placebo (3% to 5% absolute difference).	Brexpiprazole showed modestly higher scores in akathisia in short term studies. Unknown if this AE resolves with extended therapy.	Brexpiprazole typically showed up to 1.6 kg increase in body weight in first 6 weeks of therapy.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

Adjunctive Cariprazine vs. Placebo/Monotherapy

Five RCTs evaluated adjunctive cariprazine with ADT versus placebo in people with MDD (see **Table 3**).[2] Four studies were rated as high RoB due to numerous conflicts of interest by the authors and significant manufacturer involvement in study design, data collection, and assessment.[2] One study was rated as moderate RoB.[2] Three of the studies were Phase 3 trials and 2 of the studies were Phase 2 RCTs.[2] Studies were conducted over 6 to 8 weeks.[2]

Table 3. Adjunctive Cariprazine Versus Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	5 RCTs, N = 3,068	5 RCTs, N = 3,068	5 RCTs, N = 3,068	5 RCTs, N = 3,068	5 RCTs, N = 3,068
DERP Certainty of Evidence Assessment	High	Moderate	High	High	High
Notes	MADRS scores typically improved 1 to 3 points during treatment compared with placebo. Improvements may not be clinically important for all patients. (MCID = 2-point increase). DERP meta-analysis from 4 RCTs (n=1,680) showed more improvement in MADRS scores with cariprazine vs. placebo (MD, 1.26; 95% CI 0.34 to 2.19; I^2 = 0%).	Modest improvement in CGI-I scores compared with placebo, with inconsistent results. DERP meta-analysis from 4 RCTs (n=1,620) showed more improvement in the CGI-I score with cariprazine vs. placebo (MD, 0.2; 95% CI 0.06 to 0.34; I^2 = 0%).	Cariprazine showed higher response rates compared to placebo, but they were not significant (1% to 10% absolute change). DERP meta-analysis from 5 RCTs (n=2,214) showed higher rates of response with cariprazine vs. placebo (RR, 1.18; 95% CI 1.06 to 1.31; I^2 = 0%).	Cariprazine showed modestly higher scores in akathisia severity.	Cariprazine typically showed a 0.4 to 0.9 kg increase in body weight in first 6 weeks of therapy.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

Adjunctive Olanzapine/Fluoxetine vs. Placebo/Monotherapy

Five RCTs evaluated adjunctive olanzapine/fluoxetine versus placebo or fluoxetine monotherapy in people with treatment-resistant depression (see **Table 4**).[2] Four studies were rated as high RoB due to most authors being employees of the manufacturer of olanzapine/fluoxetine and extensive manufacturer involvement in study design and data collection.[2] One small study was rated as moderate RoB.[2] Most studies were conducted over 8 to 12 weeks, and one study was conducted over 27 weeks.[2] There were consistent improvements in MADRS scores (high CoE), but inconsistent adverse event outcome results (low CoE).[2]

Table 4. Adjunctive Olanzapine/Fluoxetine Versus ADT Monotherapy or Fluoxetine Alone[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	5 RCTs, N = 2,077	NR	4 RCTs, N = 1,633	4 RCTs, N = 2,049	5 RCTs, N = 3,068
DERP Certainty of Evidence Assessment	High	NR	High	Low	High
Notes	MADRS scores typically improved 3 to 5 points during treatment compared with placebo. (MCID = 2-point increase). DERP meta-analysis from 2 RCTs (n=709) showed more improvement in MADRS scores with olanzapine/fluoxetine vs. placebo (MD, 3.01; 95% CI 1.47 to 4.55; I^2 = 0%).	NR	Olanzapine/Fluoxetine showed inconsistent results (1% to 18% absolute change). DERP meta-analysis from 4 RCTs (n=1,012) showed higher rates of response with olanzapine/fluoxetine vs. placebo (RR, 1.26; 95% CI 1.04 to 1.52; I^2 = 42%).	Olanzapine/fluoxetine did not increase scores significantly during treatment compared with placebo.	Olanzapine/fluoxetine typically showed up to 6 kg increase in body weight in the first 8 weeks of therapy.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

An additional, small (n=30) RCT compared olanzapine head-to-head with aripiprazole or lithium as augmentation therapy in combination with paroxetine.[2] At 4 weeks, no significant differences in the 17-item Hamilton Depression Rating Scale (HAM-D17) were found between therapies (very low CoE).[2] No harm outcomes were reported in this study.[2]

Adjunctive Quetiapine vs. Placebo/Monotherapy

Eight RCTs evaluated adjunctive quetiapine versus placebo in MDD treatment (see **Table 5**). Two studies were rated as having a high RoB while 6 RCTs were at moderate RoB.[2] Studies were conducted over 6 to 12 weeks.

Table 5. Adjunctive Quetiapine vs. Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight

Number of RCTs, Total Population	5 RCTs, N = 1,159	5 RCTs, N = 1,253	4 RCTs, N = 1,083	2 RCTs, N = 560	7 RCTs, N = 1,329
DERP Certainty of Evidence Assessment	Moderate	Moderate	High	Low	Moderate
Notes	MADRS scores typically improved 3 points during treatment compared with placebo. (MCID = 2-point increase). DERP meta-analysis from 2 RCTs (n=112) showed no differences in MADRS scores between quetiapine and placebo (MD, 1.92; 95% CI -5.57 to 1.74; I^2 = 0%).	Modest 1 point improvement in CGI-I scores compared with placebo. DERP meta-analysis was not conducted for this outcome.	Quetiapine showed higher response rates compared to placebo (10% to 13% absolute change). DERP meta-analysis from 2 RCTs (n=619) showed quetiapine had higher rates of response compared with placebo (RR, 1.26 95% CI 1.08 to 1.47; I^2 = 0%).	No significant differences in akathisia assessments were reported.	Quetiapine typically showed 1 kg increase in body weight in first 6 weeks of therapy

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

Quetiapine vs. Lithium Monotherapy

Two RCTs evaluated adjunctive quetiapine versus lithium in MDD treatment (see **Table 6**). Both studies were rated as having a moderate RoB.[2] These studies were conducted over 6 to 8 weeks.

Table 6. Quetiapine vs Lithium Monotherapy[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	2 RCTs, N = 708	2 RCTs, N = 708	1 RCT, N = 688	NR	1 RCT, N = 688
DERP Certainty of Evidence Assessment	Low	Low	Very Low	NR	Low
Notes	Quetiapine showed a significant improvement in MADRS in 1 study and no difference in 1 study.	Quetiapine showed a significant improvement in CGI-I in 1 study and no difference in 1 study.	There was no difference between groups, with both reporting high response rates.	NR	More participants reported weight gain as an AE in the quetiapine group.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MD = mean difference; RCT = randomized controlled trial

In summary, moderate-quality evidence showed that aripiprazole improved depression outcomes compared with placebo.[2] Brexpiprazole and cariprazine also appear to be efficacious compared with placebo in MDD, based upon the DERP meta-analyses of available moderate-quality evidence.[2] Quetiapine seemed to

show improvement at around 3 points on the MADRS assessment compared with placebo (moderate-quality evidence).[2] Pimavanserin and ziprasidone have insufficient evidence or appear to be ineffective for use as adjunctive treatments for depression.[2]

The most common adverse events seen with SGAs used adjunctively with ADTs included akathisia and weight gain.[2] Rates of akathisia were highest in those on aripiprazole and were slightly lower in patients taking brexpiprazole and cariprazine.[2] Patients taking the olanzapine/fluoxetine combination, quetiapine, ziprasidone, risperidone, and pimavanserin did not experience any significant movement AEs, including akathisia.[2] When using aripiprazole, there is a moderate risk of akathisia, and if using the olanzapine/fluoxetine combination therapy, patients should be monitored for weight gain.[2]

Cochrane: Lurasidone Versus Typical Antipsychotics for Schizophrenia

The purpose of a 2025 Cochrane review was to review the comparative efficacy and safety of lurasidone versus typical antipsychotics in adults with schizophrenia.[3] Literature was searched through April 2024 and 2 RCTs (n=308) met inclusion criteria.[3] A total of 223 participants received lurasidone (20, 40, or 80 mg/day), and 82 participants received haloperidol (up to 10 mg/day).[3] The duration of the follow-up was 4 to 6 weeks.[3] The evidence is very uncertain about the effects of lurasidone compared with haloperidol on change in mental state as measured by the BPRS (MD 3.74, 95% CI 0.57 to 6.90; 1 RCT, 281 participants; very low-certainty evidence); and the PANSS (MD 6.68, 95% CI 2.45 to 10.91; 1 RCT, 281 participants; very low-certainty evidence).[3] The evidence is also very uncertain about the comparative effects of lurasidone and haloperidol on total serious adverse events (RR 0.98, 95% CI 0.37 to 2.60; 2 RCTs, 303 participants; very low certainty of evidence) and on severe adverse events (RR 1.70, 95% CI 0.46 to 6.32; 1 RCT, 281 participants; very low certainty of evidence).[3] The authors concluded there is insufficient evidence to evaluate the comparative efficacy of lurasidone and other antipsychotics in people with schizophrenia.[3]

Cochrane: Switching Antipsychotics Versus Continued Current Treatment in People with Non-Responsive Schizophrenia

A 2025 Cochrane review examined the effects of switching antipsychotic drugs adults with schizophrenia who had not responded to initial antipsychotic treatment.[4] Literature was searched through December 2022.[4] Ten RCTs (n=997) met inclusion criteria.[4] Seven studies were double-blind, 2 were single-blind and one study did not provide any detail regarding blinding.[4] The minimum duration of the ongoing antipsychotic treatment ranged from 3 days to 2 years.[4] The length of the comparison phase varied from 2 weeks to 6 months.[4] In about half of the studies, the methods of randomization, allocation and blinding were poorly reported.[4]

All studies compared switching antipsychotics versus continuation of the same (ongoing) antipsychotic drug. Some studies switched antipsychotics with similar receptor-binding profiles (e.g. from risperidone to paliperidone), while others switched between relatively different drugs (e.g. amisulpride and olanzapine).[4] Few studies clearly described how the antipsychotic drug was switched (e.g. abrupt discontinuation, cross-tapering, or double prescription until efficacy was achieved).[4] All in all, the heterogeneity of the included studies was high, which made pooling data difficult.[4] Trials evaluated a variety of drug switches including changing to clozapine, switching from risperidone to paliperidone, switching between risperidone and olanzapine (or vice versa), switching from fluphenazine to haloperidol, switching from haloperidol to perphenazine, from a FGA to clozapine or to a typical antipsychotic, and switching between olanzapine and amisulpride.[4]

The evidence is very uncertain regarding the effect of switching antipsychotics on clinically relevant response (RR 1.25, 95% CI 0.77 to 2.03; I^2 = 43%; 7 studies, 693 participants), quality of life (MD -1.30, 95% CI -3.44 to 0.84; 1 study, 188 participants), PANSS score change (MD -0.92, 95% CI -4.69 to 2.86; I^2 = 47%; 6 studies, 777 participants), duration of hospitalization (in days) (MD 9.19, 95% CI -8.93 to 27.31; I^2 = 0%; 2 studies, 34 participants) and the number of people experiencing at least one adverse effect (RR 1.29, 95% CI 0.81 to 2.05; I^2 = 36%; 3 studies, 412 participants).[4] Compared to continuing current treatment, switching antipsychotics may result in little to no difference in tolerability, defined as the number of participants leaving the study early due to adverse effects

(RR 0.73, 95% CI 0.24 to 2.26; I^2 = 31%; 6 studies, 672 participants; low-certainty evidence) and leaving the study early for any reason (RR 0.91, 95% CI 0.71 to 1.17; I^2 = 0%; 6 studies, 672 participants; low-certainty evidence).[4]

Overall, the evidence remains highly uncertain regarding the effects of continuing the same therapy or switching to another agent on efficacy and safety outcomes, and no definitive recommendations can currently be made.[4] Most of the studies were small; only 3 studies had more than 100 patients.[4] Although no differences were observed between the 2 strategies (switching medication versus continuation of the same drug) in the key outcomes, including response to the medicines, tolerability (measured as the number of people who left the studies early due to adverse effects), and quality of life, the evidence was very uncertain for most of these outcomes.[4]

Cochrane: Haloperidol Versus Olanzapine for People with Schizophrenia and Schizophrenia-Spectrum Disorders

A 2024 Cochrane review assessed the benefits and harms of oral haloperidol compared to oral olanzapine for people with schizophrenia.[5] Literature was searched through January 2023.[5] Sixty-eight (n=9,132) RCTs comparing haloperidol with olanzapine for adults with schizophrenia and schizophrenia-spectrum disorders met inclusion criteria.[5] Overall, the quality of the included studies was very low to moderate.[5] The most common risks of bias were blinding (performance bias) and selective reporting (reporting bias).[5] Most of the trials (57/68) were short-term RCTs, lasting less than 7 months.[5] The studies were carried out in various settings (e.g., inpatient and outpatient) and used different study populations (e.g., acute episodes of schizophrenia, first-episode schizophrenia, drug-naïve, stable schizophrenia).[5] The doses of haloperidol studied in the included trials was higher than current international best practice guidelines, while the mean doses of olanzapine were in line with guideline recommendations.[5] Most studies were carried out in stable, higher-income settings under controlled conditions and may be less applicable to crisis-affected and low-income settings, where access to specialized clinical mental health care and stable supplies is very often less available.[5]

The main outcomes of interest were clinically important change in global state, relapse, clinically important change in mental state, extrapyramidal side effects, weight increase, clinically important change in quality of life and leaving the study early due to adverse effects.[5] There is only low-certainty comparative evidence which shows no difference between haloperidol and olanzapine in terms of clinically important change in global state using the CGI scale (RR 0.84, 95% CI 0.69 to 1.02; I^2 =73%; 6 studies, 3078 participants; very low-certainty evidence) or incidence of relapse (RR 1.42, 95% CI 1.00 to 2.02; I^2 =75%; 7 studies, 1499 participants; very low-certainty evidence).[5] Haloperidol may reduce the incidence of clinically important change in overall mental state compared to olanzapine (RR 0.70, 95% CI 0.60 to 0.81; I^2 = 0%; 13 studies, 1210 participants; low-certainty evidence).[5] A single study suggests that haloperidol may reduce the incidence of clinically important change in quality of life compared to olanzapine (RR 0.72, 95% CI 0.57 to 0.91; 828 participants; low-certainty evidence).

Haloperidol may result in a large increase in extrapyramidal side effects compared to olanzapine (RR 3.38, 95% CI 2.28 to 5.02; 14 studies, I^2 =72%; 3290 participants; low-certainty evidence) and reduced risk of weight gain with haloperidol compared to olanzapine (RR 0.47, 95% CI 0.35 to 0.61; I^2 = 57%; 18 studies, 4302 participants; low-certainty evidence).[5] More people receiving haloperidol left the study early due to adverse effects compared to olanzapine (RR 1.99, 95% CI 1.60 to 2.47; I^2 = 0%; 21 studies, 5047 participants; low-certainty evidence).[5]

In summary, the certainty of the evidence was low to very low for the main outcomes in this review, making it difficult to draw reliable conclusions.[5] It is uncertain if there is a difference between haloperidol and olanzapine in terms of clinically important change in global state and incidence of relapse.[5] While there was a trend towards an increased risk of relapse with haloperidol, evidence was very uncertain and there is considerable discrepancy between some of the studies.[5] Olanzapine may result in a slightly greater overall clinically important change in mental state and in a clinically important change in quality of life.[5] Weight gain was more common with olanzapine (1 in 5 with olanzapine versus 1 in 11 with haloperidol), whereas extrapyramidal side effects were more

common with haloperidol (1 in 3 with haloperidol versus 1 in 6 with olanzapine).[5] Haloperidol likely increases the rate of people leaving the study early due to adverse effects compared with olanzapine (1 in 10 versus 1 in 20).[5] While there is insufficient information to understand the reason for this outcome, it is possible this may be linked to using higher equivalent doses of haloperidol compared to olanzapine in some trials.[5]

Cochrane: Antipsychotics For Agitation and Psychosis in People with Alzheimer's Disease and Vascular Dementia

A 2021 Cochrane review assessed the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.[6] Literature was searched through January 2021.[6] Twenty-four RCTs (n=6,090) met inclusion criteria.[6] Six trials tested an FGA, 4 for agitation and 2 for psychosis.[6] Twenty trials tested an SGA, 8 for agitation and 12 for psychosis.[6] Two trials tested both drug types. Seventeen of 26 comparisons were performed in patients with Alzheimer's disease.[6] The other 9 comparisons also included patients with vascular dementia or mixed dementia.[6] The trials were performed in institutionalized, hospitalized and community-dwelling patients, or a combination of those.[6] Most studies were at high risk of bias in at least one domain.[6]

Overall, 6 trials tested FGA: 4 trials tested haloperidol and 2 trials tested thiothixene.[6] It is uncertain whether FGAs improve agitation compared with placebo (SMD -0.36, 95% CI -0.57 to -0.15, 4 studies, n=361; very low-certainty evidence), but FGAs may improve psychosis slightly (SMD -0.29, 95% CI -0.55 to -0.03, 2 studies, n=240; low-certainty evidence) compared with placebo.[6] These drugs probably increase the risk of somnolence (RR 2.62, 95% CI 1.51 to 4.56, 3 studies, n=466; moderate-certainty evidence) and increase extrapyramidal symptoms (RR 2.26, 95% CI 1.58 to 3.23, 3 studies, n=467; high-certainty evidence).[6] There was no evidence regarding the risk of any adverse event.[6] The risks of serious adverse events (RR 1.32, 95% CI 0.65 to 2.66, 1 study, n=193) and death (RR 1.46, 95% CI 0.54 to 4.00, 6 studies, n=578) may be increased slightly, but these estimates were very imprecise, and the certainty was low.[6]

Twenty RCTs evaluated SGAs including risperidone, olanzapine, aripiprazole, brexpiprazole, and quetiapine.[6] The SGAs probably reduce agitation slightly (SMD -0.21, 95% CI -0.30 to -0.12, 7 studies, n=1971; moderate-certainty evidence) and probably have a very small effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03, 12 studies, n=3364; moderate-certainty evidence) compared with placebo.[6] The SGAs increase the risk of somnolence (RR 1.93, 95% CI 1.57 to 2.39, 13 studies, n=3878; high-certainty evidence) and are probably also associated with slightly increased risk of extrapyramidal symptoms (RR 1.39, 95% CI 1.14 to 1.68, 15 studies, n=4180; moderate-certainty evidence), serious adverse events (RR 1.32, 95% CI 1.09 to 1.61, 15 studies, n= 4316; moderate-certainty evidence) and death (RR 1.36, 95% CI 0.90 to 2.05, 17 studies, n= 5032; moderate-certainty evidence), although the latter estimate was imprecise.[6] The SGAs probably increase risk of any adverse event by a very small amount (RR 1.05, 95% CI 1.02 to 1.09, 11 studies, n=2785; moderate-certainty evidence).[6]

In summary, there is low certainty about the effect of FGAs on psychosis in dementia, due to a small number of studies (only 2 studies), and studies evaluating the effect of FGAs on agitation were too small to provide a precise estimate (4 studies).[6] FGAs might improve psychosis slightly compared with placebo, while the effect on agitation is uncertain.[6] The FGAs probably increase the risk of somnolence and extrapyramidal symptoms.[6] There was no evidence regarding the risk of at least one adverse event, and a slight increase in the risk of a serious adverse event or death.[6]

In contrast, there was a large number of studies that tested the effect of SGAs on psychosis and agitation in dementia (12 and eight studies, respectively), and most studies were relatively large.[6] As a result, the effect estimates are very precise and give certainty that these drugs only have a small effect on agitation and little or no effect on psychosis.[6] The SGAs probably increase the risk of somnolence and extrapyramidal symptoms.[6] The risk of a serious adverse event and the risk of death are slightly increased with SGAs.[6]

The Impact of Pharmacological and Non-Pharmacological Interventions to Improve Physical Health Outcomes in People with Schizophrenia

People with schizophrenia have substantially poorer physical health than the general population, which is often attributed to an interaction between social circumstances, lifestyle factors and treatment effects.[7] Behavioral research has demonstrated that people with schizophrenia are less physically active and exhibit more sedentary behavior than the general population, have a higher quantity but lower quality of dietary food intake, and increased adverse health behaviors, such as smoking.[7] In addition, psychiatric treatment with antipsychotics, mood stabilizers and antidepressants, further increases the risk of physical health conditions.[7] Consequently, people with schizophrenia more frequently have cardio-metabolic diseases, respiratory diseases, chronic pain, fractures, and lower physical fitness than the general population.[7]

A 2019 systematic review evaluated the efficacy for pharmacological and non-pharmacological interventions targeting physical health outcomes among people with schizophrenia spectrum disorders.[7] Literature was searched through June 1, 2018 and 27 meta-analyses (128 RCTs, n=47,231) met inclusion criteria.[7] Only eleven meta-analyses (41%) were rated as high-quality.[7] Seven of the 27 meta-analyses included only double-blind trials (26%).[7] In 16 meta-analyses (59%), the total pooled sample was less than 500 cases, while only five meta-analyses (18%) had a total sample of more than 1,000 participants.[7] Only two meta-analyses (7%) had one included trial with at least 200 participants.[7]

There were meta-analytic data for 17 different pharmacological interventions: aripiprazole augmentation, fluoxetine, metformin, nizatidine, amantadine and memantine, ranitidine, topiramate, dextroamphetamine, famotidine, metformin in combination with sibutramine, orlistat, rosiglitazone, fluvoxamine, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and switching from olanzapine to quetiapine or aripiprazole.[7] Meta-analytic data were available for six different non-pharmacological interventions: individual lifestyle counseling, group lifestyle counseling, cognitive behavioral therapy, psychoeducation, exercise, and dietary interventions.[7]

Individual lifestyle counseling was the most effective intervention for weight reduction (SMD = –0.98, 95% CI –1.15 to –0.81, $p<0.001$; 14 trials, N=411, $I^2=0\%$), followed by exercise interventions alone (SMD = –0.96, 95% CI –1.27 to –0.66, $p<0.001$; 4 trials, N=183, $I^2=0$).[7] Generally, an SMD less than 0.2 is considered negligible, an SMD between 0.2 and less than 0.5 is small, an SMD between 0.5 and less than 0.8 is medium, and an SMD of at least 0.8 is large effect size.[7] Changes in metabolic symptoms, such as weight loss and reduction in waist circumference, were observed with the use of metformin, topiramate, and aripiprazole.[7] A medium effect size was observed for aripiprazole augmentation (SMD = –0.73, 95% CI –0.97 to –0.48, $p<0.001$; 9 trials, N=813, $I^2=68\%$), topiramate (SMD = –0.72, 95% CI –1.56 to –0.33, $p<0.001$; 15 trials, N=783, $I^2=92.7\%$), and metformin (SMD = –0.53, 95% CI –0.69 to –0.38, $p<0.001$; 29 trials, N=1,279, $I^2=39.4\%$).[7] The use of topiramate for antipsychotic-induced weight gain is off-label, and not recommended by guidelines due to its side effect profile.[51] The use of metformin for antipsychotic weight gain is off-label, but listed as a compendial indication in Micromedex.[27] No beneficial effects were found for fluoxetine, ranitidine, orlistat, dextroamphetamine and famotidine for any physical health outcome.[7]

In summary, based on the SMDs and the overall high methodological quality of the original meta-analyses (but with lower quality of the studies included in the meta-analysis), individual lifestyle counseling and exercise interventions showed the largest weight reducing effect, followed by aripiprazole augmentation, topiramate, and metformin.[7]

After review, 69 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

Veterans Administration/Department of Defense: Management of First-Episode Psychosis and Schizophrenia

In 2023, the VA/DoD issued updated guidance for the management of patients with schizophrenia.[8] Pharmacotherapy typically begins with a low dose of a single antipsychotic medication and involves monitoring for symptom response, side effects, and attitudes toward medication at every visit.[8] Consideration of use of a LAI formulation as part of a holistic approach is common practice.[8] Special emphasis on monitoring and managing cardiometabolic risk factors, such as smoking, weight gain, hypertension, dyslipidemia, and pre-diabetes should be part of the treatment plan.[8] There is insufficient evidence to recommend for or against a specific duration for treatment with antipsychotic medication after response or remission for individuals with first-episode psychosis.[8]

Antipsychotic medications share similar efficacy (with the exception of clozapine, which is reserved primarily for the treatment of people who either failed to adequately respond to other antipsychotic medications or for the treatment of suicidality).[8] Therefore, the VA/DoD Work Group considered antipsychotic medications as a class, rather than considering each medication individually.[8] The benefits of antipsychotic medications for the treatment of an acute episode of schizophrenia (e.g., symptom reduction, which is associated with reduced patient distress and increased availability for complementary nonpharmacologic treatments, such as supported employment) and the potential harms of not providing these medications (e.g., increased risk of self-harm or harm to others; impaired work or social functioning or both; decreased quality of life; distress from untreated symptoms; and family burden) outweighed the potential harm of adverse events (e.g., cardiovascular, metabolic, and motor side effects; sedation; and others).[8]

The use of augmenting agents should be considered in addition to lifestyle modifications, including exercise and counseling about lifestyle modifications.[8] Another strategy is to change to an antipsychotic medication that is less likely to cause weight gain and other metabolic side effects.[8] The benefits of using metformin, topiramate, or aripiprazole as an augmenting agent for weight loss slightly outweighed the harms or burdens of use or both.[8] There was concern regarding the adverse cognitive effects of using topiramate including increased risk of congenital anomalies, low birth weight, and low vitamin K with resultant bleeding risk in pregnant women.[8] Metformin was the agent used most frequently in clinical practice.[8]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- The choice of antipsychotic medication should be based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications.
- We recommend the use of an antipsychotic medication other than clozapine for the treatment of an acute episode in individuals with schizophrenia or first-episode psychosis who have previously responded to antipsychotic medications (Strong Recommendation; Moderate-Quality Evidence).[8]
- We recommend the use of an antipsychotic medication for the maintenance treatment of schizophrenia to prevent relapse and hospitalization in individuals with schizophrenia who have responded to treatment (Strong Recommendation; Moderate-Quality Evidence).[8]
- We suggest a trial of another antipsychotic medication for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication (Weak Recommendation; Very Low-Quality Evidence).[8]
- We suggest offering LAI antipsychotics to improve medication adherence in individuals with schizophrenia (Weak Recommendation; Very Low-Quality Evidence).
- We recommend the use of clozapine for individuals with treatment-resistant schizophrenia (Strong Recommendation; Moderate-Quality Evidence).[8]
- We suggest augmenting clozapine with another second-generation antipsychotic medication for individuals with treatment-resistant schizophrenia who have not experienced an adequate response to clozapine (Weak Recommendation; Very Low-Quality Evidence).[8]
- We suggest using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia (Weak Recommendation; Moderate-Quality Evidence).[8]

Veterans Administration/Department of Defense: Management of Bipolar Disorder

The VA/DoD updated guidance for managing patients with bipolar disorder in 2023.[9] There are three distinct phases of the pharmacological management for bipolar disorder, including: (1) treatment for acute mania, (2) treatment for acute depression, and (3) maintenance treatment to prevent recurrences of both mania or depression.[9] It has been common practice to treat individuals experiencing mania or bipolar depression with medications that have evidence of effectiveness for their current episodes and to continue them on agents to which they have responded without considering the impact on long-term outcomes.[9] This approach is often taken even though most individuals with bipolar disorder spend more time in the maintenance and prevention phases than in periods of acute illness.[9] This practice could lead to greater risks for relapses if the medications used to treat acute episodes are not optimal for maintenance.[9] Moreover, if additional medications are added when there are recurrences, it can lead to unnecessary polypharmacy and an increase in the burden of side effects.[9]

As summarized in **Table 7**, there is evidence that some agents (quetiapine, lithium, and olanzapine) are effective for preventing both manic and depressive episodes, others (risperidone and paliperidone) are effective for preventing mania but not depression, and another (lamotrigine) is effective for preventing depression but not mania.[9] Based on these findings, when providers choose monotherapies to treat acute episodes of mania or depression, medications with evidence of effectiveness for the acute episode, a breadth of effectiveness that includes prevention of both mania and depression, and a low side effect burden should be viewed as preferred or first-line treatments.[9]

Table 7. Monotherapies for Bipolar Disorder Management[9]

Medication	Acute Treatment of Mania	Prevention of Mania	Acute Treatment of Bipolar Depression	Prevention of Bipolar Depression
Quetiapine	X	X	X	X
Olanzapine	X	X	X	X
Lithium	X	X		X
Cariprazine	X		X	
Paliperidone	X	X		
Risperidone	X	X		
Aripiprazole	X			
Asenapine	X			
Carbamazepine	X			
Haloperidol	X			
Valproate	X			
Ziprasidone	X			
Lumateperone			X	
Lurasidone			X	
Lamotrigine				X

Planning for the pharmacologic treatment of acute mania should always consider that the treatments effective for acute episodes will most often be continued after the resolution of mania and will form the basis of maintenance treatment to prevent the recurrence of mania.[9] For most individuals receiving treatment for bipolar disorder, prevention of depressive episodes should be considered when formulating any treatment plan.[9] Because lithium and quetiapine have demonstrated efficacy for acute mania, prevention of recurrence of episodes of mania, and prevention of recurrence of depression (with quetiapine additionally having efficacy for acute depression), the VA/DoD Work Group suggested their use as preferred or first-line monotherapies for the treatment of acute mania.[9] The Work Group acknowledged that lithium is approved by the FDA as maintenance monotherapy for bipolar disorder; however, quetiapine is FDA-approved for maintenance treatment only as an adjunct to lithium or valproate.[9] The benefits of lithium and quetiapine as treatments for acute mania and maintenance treatments to prevent both manic and depressive episodes outweighed the potential harms, including the risk of QT corrected for heart rate (QTc) interval prolongation, sedation, and metabolic effects as well as (in the case of lithium) tremor, renal effects, hypothyroidism, and the need for close monitoring.[9]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- We suggest lithium or quetiapine as monotherapy for acute mania (Weak Recommendation; Low-Quality Evidence).[9]
- If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania (Weak Recommendation; Very Low-Quality Evidence).[9]
- If lithium, quetiapine, olanzapine, paliperidone, or risperidone is not selected based on patient preference and characteristics, we suggest aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy for acute mania (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest lithium or valproate in combination with haloperidol, asenapine, quetiapine, olanzapine, or risperidone for acute mania symptoms in individuals who had an unsatisfactory response or a breakthrough episode on monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania (Weak Recommendation; Very Low-Quality Evidence).[9]
- We suggest against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy for acute mania (Weak Recommendation; Low-Quality Evidence).[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics or second-generation antipsychotics, gabapentin, oxcarbazepine, or benzodiazepines as monotherapy or in combination for acute mania.[9]

Management of Bipolar Depression

Evidence from randomized, placebo-controlled clinical trials demonstrates that quetiapine is effective for the acute treatment of bipolar depression.[9] The effectiveness of quetiapine for acute episodes of bipolar depression must be interpreted in the context of its evidence for the prevention of mania and prevention of bipolar depression.[9] When considered together, the breadth of effectiveness is high indicating treatment of bipolar depression with quetiapine can reduce current symptoms, and when continued, can prevent recurrences of depression as well as the onset of mania.[9] The effectiveness for cariprazine, lurasidone, and lumateperone for the treatment of acute episodes of bipolar depression must be interpreted in the context of the current lack of evidence for their effectiveness as monotherapies for maintenance treatment for the prevention of mania or bipolar depression.[9] In this regard, the breadth of effectiveness is lower, and the established benefits for these agents are less comprehensive than those for quetiapine.[9]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- We recommend quetiapine as monotherapy for acute bipolar depression (Strong Recommendation; Moderate-Quality Evidence).[9]

- If quetiapine is not selected based on patient preference and characteristics, we suggest cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy for acute bipolar depression (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression (Weak Recommendation; Very-Low Quality Evidence).[9]
- There is insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression.[9]
- There is insufficient evidence to recommend for or against ketamine or esketamine as either a monotherapy or an adjunctive therapy for acute bipolar depression.[9]
- There is insufficient evidence to recommend for or against antidepressants to augment treatment with second-generation antipsychotics or mood stabilizers for acute bipolar depression.[9]

Preventing Symptom Recurrence

Evidence from recent systematic reviews suggests that lithium and quetiapine are the most effective maintenance medications to prevent recurrence of mania.[9] The efficacy of both medications appears to be similar, but each has unique advantages and disadvantages that would be relevant individual patients.[9] The systematic evidence review conducted to inform this guideline provides some support for LAI olanzapine, paliperidone, and risperidone as maintenance medications for the prevention of recurrence of mania, but this support is weaker than that for lithium and quetiapine.[9] Evidence does not support the use of lamotrigine to prevent recurrence of mania.[9] However, the evidence does support the use of lamotrigine to prevent bipolar depressive episodes.[9] Evidence suggests using the following antipsychotics in combination with lithium or valproate as maintenance medication for the prevention of recurrence of mania: aripiprazole, olanzapine, quetiapine, and ziprasidone.[9]

Evidence suggests that treatment with lithium, quetiapine, or olanzapine can help prevent the recurrence of depressive episodes in individuals with bipolar disorder.[9] Evidence regarding which of the 3 medications is the most efficacious is mixed, though there is some evidence that quetiapine and olanzapine performed better than other SGAs in the prevention of depression.[9] The body of evidence had some limitations because no studies directly compared the effectiveness of these medications against each other, so ascertaining whether one of these medications is more effective than the other is difficult.[9] The benefits of using lithium or quetiapine to prevent depressive episodes and for their effects on other outcomes (e.g., to decrease the risk of suicide, hospitalization) outweighed the potential harm of medication side effects.[9] The benefits of using olanzapine to prevent depressive episodes and other outcomes slightly outweighed the potential harm of medication side effects.[9]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- We recommend lithium or quetiapine for the prevention of recurrence of mania (Strong Recommendation; Moderate-Quality Evidence).[9]
- If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest oral olanzapine, oral paliperidone, or risperidone long-acting injectable for the prevention of recurrence of mania (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate for the prevention of recurrence of mania (Weak Recommendation; Very Low-Quality Evidence).[9]
- We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes (Strong Recommendation; Moderate-Quality Evidence).[9]
- We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes (Weak Recommendation; Low-Quality Evidence).[9]

- If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes (Weak Recommendation; Moderate-Quality Evidence).[9]
- We suggest olanzapine, lurasidone, or quetiapine in combination with lithium or valproate for the prevention of recurrence of bipolar depressive episodes (Weak Recommendation; Low-Quality Evidence).[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics, second-generation antipsychotics, and anticonvulsants (including valproate) for the prevention of recurrence of mania.[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants (including valproate) as monotherapies for the prevention of recurrence of bipolar depressive episodes.[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants in combination with a mood stabilizer for the prevention of recurrence of bipolar depressive episodes.[9]

Safety Concerns

- For individuals with bipolar disorder who are or might become pregnant and are stabilized on lithium, we suggest continued treatment with lithium at the lowest effective dose in a framework that includes psychoeducation and shared decision making (Weak Recommendation; Very Low-Quality Evidence).[9]
- We recommend against valproate, carbamazepine, or topiramate in the treatment of bipolar disorder in individuals of child-bearing potential (Strong Recommendation; Very-Low Quality Evidence).[9]

Veterans Administration/Department of Defense: Management of Major Depressive Disorder

The VA/DoD updated guidance for managing patients with MDD in 2022.[10] Treatment options include adding an SGA for patients who have not responded (<50% improvement in symptoms) to adequate antidepressant treatment trials (i.e. bupropion, mirtazapine, trazodone, vilazodone, vortioxetine, SSRIs, SNRIs) for 6 to 12 weeks.[10] Five atypical antipsychotics are FDA-approved for MDD as adjunctive treatment: aripiprazole, brexpiprazole, cariprazine, lurasidone, and quetiapine.[27] Olanzapine is approved for the treatment of acute treatment-resistant MDD when used in combination with fluoxetine, but olanzapine by itself is not indicated for treatment-resistant depression.[10] Other SGAs such as cariprazine and risperidone, while not indicated, are used off-label for augmentation.[10]

While there is a significant benefit with augmentation using SGAs, there is also the potential for significant side effects.[10] Fair-quality evidence found that compared to placebo, aripiprazole had an increased incidence of akathisia and weight gain; olanzapine had an increased incidence of weight gain and sedation; quetiapine had more weight gain and sedation; and risperidone had greater, but not statistically significant, weight gain when compared to antidepressants plus placebo.[10] While the risk is generally lower than FGAs, another significant adverse effect associated with SGAs is tardive dyskinesia.[10] Due to the possibility of additional side effects and the potential for drug-drug interactions with augmentation, SGAs require appropriate monitoring (e.g., glucose, complete blood count, hepatic panel, lipid panel, body mass index, waist circumference, blood pressure, involuntary movements/tardive dyskinesia, slit lamp exam [quetiapine-only]).[10]

VA/DoD pharmacologic recommendation and strength of evidence:

- For patients with MDD who have demonstrated partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered):
  - Switching to another antidepressant (including tricyclic antidepressants, monoamine oxidase inhibitors, esketamine, ketamine, or nefazodone)
  - Switching to psychotherapy
  - Augmenting with psychotherapy

- Augmenting with an SGA (Weak Recommendation; Low-Quality Evidence).[10]

Oregon Health Authority: Mental Health Clinical Advisory Group

The MHCAG has developed treatment algorithms and clinical practice recommendations to guide clinicians, patients, and caregivers in several mental health disorders. Specific algorithms were developed for schizophrenia, MDD, and bipolar disorder and are summarized below.

- In 2023, updated recommendations for management of schizophrenia were reviewed by the MHCAG.[11] Two algorithms were developed to guide treatment with either FGA or SGA medications. They can be accessed here: MHCAG Treatment of Schizophrenia with Antipsychotic Medications
  - Choice of treatment should be based on the side effect profiles of medications, the individual's treatment-related preferences, and prior treatment response.[11]
  - When initially choosing an oral antipsychotic medication for maintenance treatment, discuss the feasibility of using a LAI formulation long-term with the patient.[11] The oral and LAI formulations of a specific medication are comparable, so trial the oral formulation first to assure efficacy and tolerability.[11]
  - People who do not respond to two trials of antipsychotic medication with adequate dosage, duration, and adherence should be offered clozapine. Clozapine is associated with better outcomes in people whose condition has not sufficiently responded to other antipsychotic medications.[11]

- In 2023, the MHCAG updated recommendations for the treatment of MDD.[14] The algorithm can be accessed here: MHCAG Medication Algorithm for the Treatment of Major Depressive Disorder
  - Recommended first-line agents include SSRIs, SNRIs, bupropion, and mirtazapine.[14]
  - Second-generation antipsychotics include those with FDA approval as adjunct treatment (aripiprazole, brexpiprazole, quetiapine, and olanzapine in combination with fluoxetine) and risperidone (with evidence to support off-label use).[14]

- In 2019, MHCAG evaluated bipolar disorder and developed an algorithm for managing acute bipolar depression[13] and another algorithm for managing acute bipolar mania.[12] They can be accessed here: MHCAG Acute Bipolar Depression Algorithm and MHCAG Acute Bipolar Mania Algorithm.
  - Bipolar depression management recommendations:
    - First-line monotherapy medication options for treatment of bipolar depression include lamotrigine, lithium, or quetiapine.[13]
    - Second-line monotherapy medications include cariprazine, divalproex, and lurasidone.[13]
    - Combination therapy with lamotrigine and another treatment medication is recommended as a second-line alternative option.[13] Other options include:
      - Combination of lurasidone and lithium OR divalproex
      - Combination of olanzapine and fluoxetine
      - Bupropion OR a combination of SSRI and another bipolar medication treatment.[13]
    - Aripiprazole should be avoided in treatment of acute bipolar depression due to evidence of ineffectiveness.[13]
    - Antidepressant monotherapy should also be avoided due to ineffectiveness and the risk of triggering a manic or mixed episode.[13]
  - Acute bipolar mania management recommendations:
    - First-line combination therapy recommendations are quetiapine combined with lithium OR quetiapine combined with divalproex.[12]
    - Second-line monotherapy options include: aripiprazole, asenapine, cariprazine, risperidone, and ziprasidone.[12]
    - Lamotrigine should be avoided for treatment of acute mania only.[12]

New Formulations and Indications:

New Formulations

- March 2024: A new extended-release injectable formulation of risperidone, RISVAN, received FDA-approval for treatment of schizophrenia in adults.[20] The manufacturer recommends that tolerability to this medication should be established with oral risperidone prior to initiating treatment with the extended-release risperidone intramuscular injection.[20] The recommended dose is 75 mg (for maintenance of 3 mg orally once daily) to 100 mg (for maintenance of 4 mg orally once daily) injected once monthly.[20] Patients who are stable on oral risperidone less than 3 mg per day or higher than 4 mg per day may not be candidates for this formulation.[20] Neither a loading dose or supplemental oral risperidone is recommended.[20] Other risperidone LAI injections include RISPERIDAL CONSTA, which is administered every 2 weeks; PERSERIS, which is administered once a month; and UZEDY, which can be administered at 1- and 2-month dosing intervals.

  One 12-week placebo-controlled trial evaluated the safety and efficacy of RISVAN in adults with schizophrenia (Study 1; NCT03160521).[20] This study compared extended-release risperidone injection (75 mg and 100 mg intramuscular every 4 weeks) with placebo in adults (aged 18 to 65 years) experiencing acute exacerbations of schizophrenia.[20] Patients were required to have a PANSS total score of 80 to 120 (moderate to severely ill) for study inclusion.[20] The primary endpoint was the change in PANSS total score from baseline to end of study at Day 85. Both risperidone 75- and 100-mg doses demonstrated a statistically and clinically significant improvement in PANSS total score compared with placebo (see **Table 8**).[20]

  Table 8. Mean Change from Baseline in PANSS Total Score at day 85 with ER Risperidone in Adults with Schizophrenia[20]

Treatment Group (n = number of patients)	Mean Baseline PANSS Score	LSM Change from Baseline	Placebo-Subtracted Difference (95% CI)
Extended-release risperidone 75 mg injection (n=129)	96.3	-24.6	-13.0 (-17.3 to -8.8)
Extended-release risperidone 100 mg injection (n=129)	96.1	-24.7	-13.3 (-17.6 to -8.9)
Placebo (n=132)	96.4	-11.0	-
Abbreviations: CI = confidence interval; ER = extended release; LSM = least squares mean; mg = milligrams; PANSS = Positive and Negative Syndrome Scale			

  Adverse reactions that led to discontinuation in risperidone-treated patients in this trial included: abscess limb (0.3%), skin infection (0.3%), fall (0.3%), humerus fracture (0.3%), liver function test increased (0.3%), neutrophil count decreased (0.3%), mental impairment (0.3%), erectile dysfunction (0.3%), galactorrhea (0.3%), lactation disorder (0.3%), and pruritus (0.3%).[20] The most frequently reported adverse reactions (≥5% and twice placebo) were blood prolactin increase, hyperprolactinemia, akathisia, headache, sedation (including somnolence), weight increased, injection site pain, and increased alanine aminotransferase.[20]

- July 2024: OPIPZA, a new oral film formulation of aripiprazole, received FDA approval for treatment of schizophrenia in patients ages 13 years and older, adjunctive treatment of MDD in adults, irritability associated with autistic disorder in pediatric patients aged 6 years and older, and treatment of Tourette's disorder in pediatric patients aged 6 years and older.[21] Daily dosing depends upon the indication, age, and weight (for pediatric patients). The safety and efficacy of aripiprazole oral film in the FDA-approved indications is based on studies of another oral aripiprazole product.[21]

- July 2024: ERZOFRI, a new formulation of extended-release injectable paliperidone received FDA-approval for treatment of schizophrenia in adults and treatment of schizoaffective disorder in adults as monotherapy or as an adjunct to mood stabilizers or antidepressants.[22] The recommended dose is 351 mg

as an initial dose followed by 39 mg to 234 mg once a month via provider-administered intramuscular injection.[22] The safety and efficacy of this new extended-release paliperidone product is based upon studies of a different once-a-month paliperidone extended-release injectable suspension.[22]

New Indications

- December 2021: CAPLYTA (lumateperone) oral capsules received an expanded FDA-approved indication for treatment of depressive episodes associated with bipolar I or II disorder in adults, as monotherapy or as adjunctive therapy with lithium or valproate.[15] Prior to this approval, lumateperone was FDA-approved for the treatment of adults with schizophrenia.[15]

  The efficacy of lumateperone monotherapy was evaluated in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adults who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 3; NCT03249376).[15] The primary efficacy measure was the change from baseline in MADRS total score at Week 6.[15] A total of 381 patients were randomized to receive lumateperone 42 mg or placebo.[15] Demographic and baseline characteristics were similar for both groups.[15] The median age was 45 years, 58% were female, 91% were White, and 8% were Black.[15] Compared to the placebo group, patients randomized to lumateperone showed a statistically significant improvement from baseline to Day 43 in the MADRS total score (least squares mean [LSM] change, -12.1 vs. -16.7; difference; -4.6; 95% CI -6.3 to -2.8).[15]

  The efficacy of lumateperone, as adjunctive therapy with lithium or valproate, was assessed in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 4; NCT02600507). The primary efficacy measure was the change from baseline in MADRS total score at Week 6. A total of 529 patients were randomized to receive lumateperone 28 mg (two-thirds the recommended daily dose), lumateperone 42 mg, or placebo.[15] Demographic and baseline characteristics were similar for the lumateperone and placebo groups.[15] The median age was 46 years, 58% were female, 88% were White, and 11% were Black.[15] Compared to the placebo group, patients randomized to adjunctive lumateperone 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score (LSM change -14.5 vs. -16.9; difference -2.4; 95% CI -4.4 to -0.4).[15] The treatment effect in the lumateperone 28 mg group vs. placebo was not statistically significant.[15]

- December 2022: VRAYLAR (cariprazine) oral capsules were approved as adjunctive therapy to antidepressants for the treatment of MDD in adults.[16] Prior to this approval, cariprazine was FDA-approved for treatment of schizophrenia and bipolar disorder in adults.[16] The safety and efficacy of cariprazine as adjunctive therapy in MDD was evaluated in 2 RCTs conducted in adults. The mean age of enrolled patients was 45 years, 72% were female and 85% were White.[16] The primary endpoint was change from baseline in MADRS total score to Week 6 compared with placebo.[16] In study 1, the treatment effect on MADRS improvement was statistically significant with cariprazine 1.5 mg per day, but not for 3 mg per day (see **Table 9**). In study 2, the MADRS improvement with cariprazine 2 to 4.5 mg per day (mean dose = 2.6 mg) was statistically significant compared to placebo, but not for doses of cariprazine 1 to 2 mg per day (see **Table 9**).

  The FDA recommended dosing for cariprazine as adjunctive therapy to antidepressants for MDD is a starting dose of 1.5 mg once daily with a recommended maintenance dose of 3 mg once daily.[16] In people with schizophrenia, the recommended maintenance dose of cariprazine is 1.5 to 6 mg once daily.[16] For bipolar mania, the recommended cariprazine maintenance dose is 3 mg to 6 mg once daily. [16]

Table 9. Change in MADRS with Adjunctive Cariprazine in Adults with MDD over 6 Weeks[16]

Treatment Group (n = number of patients)	Mean Baseline MADRS Score	LSM Change from Baseline	Placebo-Subtracted Difference (95% CI)

Study 1			
Cariprazine 1.5 mg/day + ADT (n=250)	32.8	-14.1	-2.5 (-4.2 to -0.9)
Cariprazine 3 mg/day + ADT (n=252)	32.7	-13.1	-1.5 (-3.2 to 0.1)
Placebo + ADT (n=249)	31.9	-11.5	-
Study 2			
Cariprazine 1 to 2 mg/day + ADT (n=273)	29.0	-13.4	-0.9 (-2.4 to 0.6)
Cariprazine 2 to 4.5 mg/day + ADT	29.3	-14.6	-2.2 (-3.7 to -0.6)
Placebo	28.9	-12.5	-
Abbreviations: ADT = antidepressant therapy; CI = confidence interval; LSM = least squares mean; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; mg = milligrams			

The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in cariprazine-treated patients and at least twice the rate of placebo was akathisia (2%).[16] Overall, 6% of the patients who received cariprazine discontinued treatment due to an adverse reaction, compared with 3% of placebo-treated patients in these trials.[16] The most common adverse effects observed in the two 6-week trials included akathisia, extrapyramidal symptoms, nausea, and insomnia.[16]

- December 2021: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for management of schizophrenia in pediatric patents aged 13 to 17 years.[17] Prior to this approval, brexpiprazole was approved for use as adjunctive therapy for treatment of MDD in adults and treatment of schizophrenia in adults.[17] Safety and effectiveness of brexpiprazole for treatment of schizophrenia in pediatric patients 13 years of age and older is supported by evidence from studies in adults with schizophrenia, pharmacokinetic data from adults and pediatric patients, and safety data in pediatric patients 13 to 17 years of age.[17] Adverse reactions reported in clinical studies for this age group were generally similar to those observed in adult patients.[17]

- May 2023: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for treatment of agitation associated with dementia due to Alzheimer's disease (AAD).[17] Prior to this approval there were no FDA-approved treatment options for AAD.[18] Like all antipsychotics, brexpiprazole has a boxed warning for increased risk of mortality in elderly patients with dementia-related psychosis, based on a meta-analysis the FDA conducted in 2005.[18]

  Two multi-center, double-blind, placebo-controlled, phase 3 RCTs evaluated brexpiprazole over a 12-week treatment period in patients with AAD.[18,52] Study 1 (n=433) used fixed brexpiprazole 1 mg and 2 mg once daily dosing, while Study 2 (n=270) employed flexible brexpiprazole dosing (0.5 mg to 2 mg once daily).[52] Eligible patients were 55 to 90 years of age, with a diagnosis of AAD and a Mini-Mental State Examination (MMSE) score of 5 to 22.[52] The mean age of enrolled patients was 74 years, 58% were female, and 95% were White.[52] Two-thirds (67%) of enrolled patients were institutionalized, with moderate cognitive impairment (mean MMSE score = 62).[18] In general, demographic characteristics were similar between males and females, age groups, and race groups across treatment arms.[18]

  The primary endpoint for both studies was the mean change from baseline in the Cohen Mansfield Agitation Inventory (CMAI) at Week 12.[18,52] The purpose of the CMAI is to assess the frequency of agitated behaviors in elderly patients and was originally developed for use in the nursing home, but has since been expanded for use in community dwelling patients with AAD.[52] The CMAI-Long Form is a caregivers' rating instrument consisting of 29 items all rated on a 1 to 7 scale with 1 being the "best" rating (no occurrence) and 7 being the "worst" rating (frequency of several times an hour).[18] The CMAI Total Score is the sum of ratings for all 29 items and ranges from 29 to 203.[52] Higher scores indicate more frequent agitated behaviors.[52] The key secondary efficacy measure was the Clinical Global Impression – Severity of illness (CGI-S) score as related to agitation.[52] MCIDs were not established for either outcome measurement.

In Study 1, brexpiprazole 2 mg had a small improvement in CMAI total score from baseline to Week 12 compared with placebo (see **Table 10**).[52] The brexpiprazole 1 mg group did not show meaningful difference from placebo on the primary efficacy endpoint (see **Table 10**).[52] In Study 2, there was no difference between brexpiprazole and placebo in the CMAI change from baseline at Week 12.[52] Changes from baseline in the CGI-S score at Week 12 were not statistically significant between brexpiprazole and placebo in either study.[52]

Table 10. Effects Of Brexpiprazole On Symptoms Of Agitation (CMAI Change From Baseline at Week 12)[52]

Dose (number of patients)	Baseline Mean CMAI score	Change from baseline at Week 12	Adjusted Mean Difference
Study 1			
Brexpiprazole 2 mg (n=138)	71.0	-21.6	-3.77 (95% CI, -7.38 to -0.17) p = 0.04
Brexpiprazole 1 mg (n=134)	70.5	-17.6	0.23 (95% CI, -3.40 to 3.86) p = 0.90
Placebo (n=131)	72.2	-17.8	-
Study 2			
Brexpiprazole 0.5 to 2 mg (n=131)	71.5	-18.9	-2.34 (95% CI, -5.49 to 0.82) p = 0.15
Placebo (n=135)	68.6	-16.5	-
Abbreviations: CI = confidence interval; CMAI = Cohen-Mansfield Agitation Inventory; mg = milligram			

In study 1, treatment-emergent adverse events (TEAEs) with incidence of 5% or more among patients receiving brexpiprazole 2 mg/day were headache (9.3% versus 8.1% with placebo), insomnia (5.7% versus 4.4%), dizziness (5.7% versus 3.0%), and urinary tract infection (5.0% versus 1.5%).[52] In Study 2, TEAEs with incidence of 5% among patients receiving brexpiprazole 0.5–2 mg/day were headache (7.6% versus 12.4% with placebo) and somnolence (6.1% versus 3.6%).[52] In both studies, the majority of TEAEs were mild or moderate in severity.[52]

- April 2024: FANAPT (iloperidone) received an expanded indication for acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.[19] Prior to this approval, iloperidone was FDA-approved to treat schizophrenia in adults.[19] The efficacy of iloperidone in the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults was evaluated in one multicenter, randomized, double-blind, placebo-controlled, 4-week study that enrolled patients who met the DSM-5 criteria for bipolar I disorder, manic or mixed type (Study 1; NCT04819776).[19] The median age was 46 years, 45% were female, 64% were White, and 28% were Black.[19] The primary endpoint was change in manic symptoms assessed with the Young Mania Rating Scale (YMRS) total score from baseline to Day 28 (n=392). Iloperidone 24 mg/day was superior to placebo with a LSM change in YMRS score of -10.0 versus -14.0 (difference -4.0 (95% CI -5.70 to -2.25)).[19] In this trial, the following adverse reactions occurred in 5% or more incidence in the patients treated with iloperidone and at least twice the placebo rate: tachycardia, dizziness, dry mouth, hepatic enzymes increased, nasal congestion, weight increased, hypotension, and somnolence.[19]

New FDA Safety Alerts:

Table 11. Description of new FDA Safety Alerts[53]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Brexpiprazole	REXULTI	5/10/23	Warnings and Precautions	Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis *without* agitation associated with Alzheimer's disease.
Brexpiprazole	REXULTI	5/7/24	Pediatric Use	**Schizophrenia** The safety and effectiveness of REXULTI for the treatment of schizophrenia has not been established in pediatric patients less than 13 years of age. **Irritability Associated with Autism Spectrum Disorder** The safety and effectiveness of REXULTI for the treatment of irritability associated with autism spectrum disorder have not been established in pediatric patients. Effectiveness was not demonstrated, in an 8-week, double-blind, placebo-controlled, flexible-dose clinical study conducted in 119 REXULTI-treated pediatric patients 5 to 17 years of age with irritability associated with autism spectrum disorder diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria. In this study, somnolence (including sedation) occurred at a higher rate than reported in other REXULTI studies evaluating adults and elderly patients (16% in REXULTI-treated pediatric patients versus 5% for placebo). The mean increase in age-and-gender adjusted body weight z-score from baseline to last visit was 0.3 for REXULTI-treated patients versus 0.1 for placebo-treated patients. Increases in age-and-gender adjusted body weight z-score of at least 0.5 SD from baseline was higher in REXULTI-treated patients versus placebo (19% versus 5%).
Clozapine	CLOZARIL	1/22/25	Boxed Warning	Pericarditis added to the boxed warning statement about the risk of myocarditis, pericarditis, cardiomyopathy and mitral valve incompetence: Fatal myocarditis and cardiomyopathy have occurred with CLOZARIL treatment. Discontinue CLOZARIL and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with CLOZARIL-related myocarditis or cardiomyopathy should not be rechallenged with CLOZARIL. Consider the possibility of myocarditis, pericarditis, or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur.

Olanzapine Olanzapine/Fluoxetine Olanzapine/Samidorphan Quetiapine Ziprasidone	ZYPREXA SYMBYAX LYBALVI SEROQUEL GEODON	1/22/25	Warnings and Precautions	**Hyperprolactinemia** Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.
Ziprasidone	GEODON	1/22/25	Contraindications Warnings and Precautions	Ziprasidone is contraindicated in patients taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome. **Serotonin Syndrome** Ziprasidone can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, tramadol, meperidine, methadone, lithium, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., monoamine oxidase inhibitors (MAOIs).
Aripiprazole	ABILIFY	1/22/25	Use in Specific Populations	**Lactation** Aripiprazole is present in human breast milk. Based on published case reports and pharmacovigilance reports, aripiprazole exposure during pregnancy and/or the postpartum period can lead to variable effects on milk supply in the post-partum period, including clinically relevant decreases in milk supply which may be reversible with discontinuation of the drug. There are also reports of aripiprazole exposure during pregnancy and no maternal milk supply in the post-partum period. Effects on milk supply are likely mediated through decreases in prolactin levels, which have been observed. Monitor the breastfed infant for dehydration and lack of appropriate weight gain.
Olanzapine/Samidorphan	LYBALVI	1/22/25	Use in Specific Populations	**Lactation** Clinical Considerations: Infants exposed to LYBALVI should be monitored for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements). Data: A single dose milk-only lactation study was conducted in 12 healthy adult lactating women. Following a 5 mg/10 mg oral dose of olanzapine and samidorphan, the mean quantities in human milk were detected to be 0.002 mg

				and 0.006 mg, respectively. The calculated weight-adjusted infant daily oral dose for olanzapine (~ 0.0005 mg/kg) and samidorphan (0.001 mg/kg) was less than 1% of the weight-adjusted maternal dose for olanzapine (0.07 mg/kg) and samidorphan (0.15 mg/kg), respectively.

Randomized Controlled Trials:

A total of 571 citations were manually reviewed from the initial literature search. After further review, 570 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 4**.

Table 12. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Reif, et al.[54] ESCAPE-TRD OL, single-blind, MC Phase 3 RCT	1.Esketamine nasal spray flexibly dosed: 18-64 yrs: 56 or 84 mg 65-74 yrs: 28 mg Administered twice weekly during Weeks 1-4, then weekly during Weeks 5-8, and weekly or every 2 weeks during Weeks 9 to 32 + ADT Vs. 2. Quetiapine extended-release oral 150-300 mg/day + ADT	1. n=336 2. n=340 Adults aged 18 to 74 yrs with MDD with no response to ADT	Remission: MADRS score $\leq$ 10 at Week 8	1. n=91; 27.1% 2. n=60; 17.6% Difference: 9.5%; p=0.003 OR 1.74; 95% CI 1.20 to 2.52 Esketamine was superior to quetiapine in achieving remission at Week 8	-Open label, single bind (raters unaware of patient assignments) -Trial designed and coordinated by the manufacturer of esketamine -Each medication had a distinct adverse effect profile, which could have led to unblinding by the raters
Abbreviations: ADT = antidepressant therapy; CI = confidence interval; MADRS = Montgomery-Åsberg Depression Scale; MC = multi-center; MDD = major depressive disorder; mg = milligrams; OL = open label; OR = odds ratio; RCT = randomized controlled trial; yrs = years					

New Drug Evaluation: LYBALVI (olanzapine/samidorphan)
LYBALVI, a combination of olanzapine and samidorphan (an opioid receptor antagonist), is indicated for treatment of schizophrenia in adults, and maintenance monotherapy for bipolar I disorder in adults, and acute treatment of manic or mixed episodes of bipolar I disorder as monotherapy or adjunct to lithium or valproate.[23] A fixed dose of samidorphan 10 mg is combined with olanzapine 5, 10, 15 or 20 mg to mitigate olanzapine-associated weight gain.[26] The risk of weight gain with olanzapine is generally dose dependent, with higher doses often associated with a greater likelihood of weight gain.[26] The exact mechanism by which samidorphan mitigates olanzapine-associated weight gain is not known.[23] As with other oral antipsychotics, olanzapine/samidorphan carries a black box warning of increased mortality in elderly patients with dementia-related psychosis.[23] It is contraindicated in patients using opioids or undergoing acute opioid withdrawal.[23]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The efficacy of olanzapine/samidorphan in the treatment of adult patients with bipolar I disorder is based upon studies of orally administered olanzapine as monotherapy and adjunctive therapy to lithium or valproate.[23] One clinical trial evaluated the safety and efficacy of olanzapine/samidorphan in schizophrenia (ENLIGHTEN-1)[24] and another clinical trial (ENLIGHTEN-2)[26] evaluated the weight-mitigation effect of samidorphan on olanzapine in patients with schizophrenia. Both studies are described and evaluated below in **Table 16**.

The efficacy of olanzapine/samidorphan for schizophrenia in adults was assessed in a 4-week, double-blind, placebo-controlled, phase 3 RCT (ENLIGHTEN-1).[24] Adult patients (n=403) with an acute exacerbation of schizophrenia were randomized in a 1:1:1 ratio to olanzapine/samidorphan, olanzapine monotherapy, or placebo.[24] Patients assigned to olanzapine/samidorphan could receive either 10 mg/10 mg or 20 mg/10 mg once a day, and patients assigned to olanzapine could receive either 10 mg or 20 mg a day.[24] The study was designed to compare olanzapine/samidorphan with placebo, not with olanzapine.[24]
Eligible patients were 18 to 70 years of age, with a body mass index (BMI) of 18.0–40.0 kg/m^2, PANSS total score of 80 or more, and a score of 4 or more on at least 3 of the selected Positive Scale items (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution).[24] Patients were also required to have a Clinical Global Impression-Severity (CGI-S) score of 4 or more.[24] For the first 2 weeks of the study, patients were hospitalized and dose titration was permitted. In the last 2 weeks of the RCT, patients could be treated as inpatients or outpatients with a fixed dose of study medication. Approximately 89% of enrolled subjects were hospitalized for the entire study.[24] Sixty-one percent of enrolled patients were male and 69% were White, with an average age of 41 years and mean baseline BMI of 26.6 kg/m^2.[24]

The primary efficacy endpoint was change from baseline in PANSS total score at Week 4.[24] Compared with patients on placebo, a statistically significant improvement in the change from baseline in PANSS total score at Week 4 was observed in patients treated with olanzapine/samidorphan (LSM change, -17.5 vs. -23.9; difference, -6.4; 95% CI -10.0 to -2.8).[24] There is no MICD for changes in PANSS total score, although response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.[25] The inclusion of samidorphan did not negatively impact the antipsychotic efficacy of olanzapine, and PANSS scores were similar in people randomized to olanzapine and olanzapine/samidorphan.

A second study (ENLIGHTEN-2) evaluated the weight-mitigation effect of samidorphan. In this 24-week, double-blind, phase 3 RCT, once daily olanzapine/samidorphan (10 mg/10 mg) or (20 mg/10 mg) was compared to once daily olanzapine 10 mg or 20 mg in clinically stable outpatients (n=561) with

schizophrenia.[26] The efficacy of olanzapine/samidorphan on psychotic symptoms was not evaluated in this study.[26] Most of the patients were African American males with average age of 40 years old and a mean baseline BMI 25.45 kg/m^2.[26] Co-primary endpoints were the percent change from baseline in body weight and the proportion of subjects with 10% or more weight gain from baseline at Week 24. The percent change in body weight from baseline to week 24 was 4.21% with olanzapine/samidorphan and 6.59% with olanzapine (difference, -2.38%; 95% CI -3.88% to -0.88%; p=0.002).[26] The proportions of subjects with weight gain of 10% or more from baseline was 17.8% in the olanzapine/samidorphan group and 29.8% in the olanzapine group (difference 12%; 95% CI -22.8 to -4.6; p=0.003; NNT = 8).[26]

Study Limitations:
ENLIGHTEN-1 was a short-term, 4-week study. High placebo response was observed in PANSS improvement (LSM improvement =-17.5), which is consistent with reported trends in placebo-controlled schizophrenia trials.[24] ENLIGHTEN-2 restricted BMI to 18-30 kg/m^2 in patients with long history of illness and may have inadvertently included patients relatively resistant to antipsychotic associated weight gain. In addition, almost 40% of patients discontinued the study early and no adherence measures were performed.

Clinical Safety:
The safety of olanzapine/samidorphan was evaluated in 1262 patients (18 to 67 years of age) diagnosed with schizophrenia in 4 double-blind, controlled studies and 3 long-term safety extension studies of up to 3 years of duration.[23] The most common adverse effects reported with olanzapine/samidorphan were increased weight, somnolence, dry mouth, and headache.[23] The adverse effects reported in the 4-week ENLIGHTEN-1 trial are presented in **Table 13**. Adverse reactions that led to study discontinuation in ENLIGHTEN-1 included abnormal liver function tests and worsening schizophrenia in 1% of participants.[23] Adverse effects reported in the 24-week ENLIGHTEN-2 trial are summarized in **Table 14**. Adverse reactions that led to discontinuation of olanzapine/samidorphan in more than one patient in the ENLIGHTEN-2 RCT included somnolence (2%), increased weight(2%), neutropenia (2%), increased glycosylated hemoglobin (1%), worsening schizophrenia (1%), and abnormal liver function test abnormal (1%).[23]

Table 13. Adverse Reactions Reported in ≥ 2% of Olanzapine/Samidorphan-Treated Patients and Greater than Placebo Over 4 Weeks[23]

Adverse Reaction	Placebo (n=134)	Olanzapine/Samidorphan (n=134)
Increased Weight	3%	19%
Somnolence	2%	9%
Dry Mouth	1%	7%
Headache	3%	6%
Increased Blood Insulin	1%	3%
Sedation	0%	2%
Dizziness	1%	2%
Decreased Neutrophil Count	0%	2%

Table 14. Adverse Reactions Reported in ≥ 5% of Olanzapine/Samidorphan-Treated and Olanzapine-Treated Patients Over 24 Weeks[23,26]

Adverse Reaction	Olanzapine (n=276)	Olanzapine/Samidorphan (n=274)
Increased Weight	36%	25%
Somnolence	18%	21%

Dry Mouth	8%	13%
Increased Appetite	12%	11%
Increased Waist Circumference	8%	6%
Increased Blood Creatinine Phosphokinase	4%	5%

Other safety considerations:
Olanzapine/samidorphan may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.[23] This medication is not recommended for use in patients with end-stage renal disease (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m^2).[23] Use with strong CYP3A4 inducers should be avoided due to potential drug interactions.[23]

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduction of psychosis symptoms
2) Improved quality of life or function
3) No significant weight gain
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint(s):
1) LSM improvement in PANSS score from baseline to week 4
2) Change in body weight
3) Proportion of people with ≥ 10% change in body weight

Table 15. Pharmacology and Pharmacokinetic Properties.[23]

Parameter	
Mechanism of Action	Olanzapine: second generation antipsychotic -dopamine and serotonin antagonist Samidorphan: opioid receptor antagonist
Absolute Oral Bioavailability	Olanzapine: NA Samidorphan: 69%
Protein Binding	Olanzapine: 93% Samidorphan: 23%-33%
Elimination	Olanzapine: Hepatic Samidorphan: Hepatic
Half-Life	Olanzapine: 35-52 hours Samidorphan: 7-11 hours
Metabolism	Olanzapine: CYP1A2, UGT1A4, CYP2D6 Samidorphan: CY3A4, CYP3A5, CYP2C19, CYP2C8
Abbreviations: CYP=cytochrome P450; NA = Not Applicable; UGT=Uridine 5'-diphospho-glucuronosyltransferase	

Table 16. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Potkin, et al.[24] ENLIGHTEN-1 Phase 3, DB, MC RCT	1. Olanzapine/ Samidorphan: 10 mg/10mg or 20mg/10mg orally once a day 2. Olanzapine 10 or 20mg orally once a day 3. Placebo orally once a day	Demographics: -Mean age: 41 yrs -Male: 61% -Race White: 69% Black: 28% Asian: 1% Other: 1.7% -Mean BMI: 26.6 kg/m^2 Key Inclusion Criteria: -Adults aged 18-70 yrs with diagnosis of acute schizophrenia or relapse of schizophrenia symptoms -BMI 18-40 kg/m^2 -PANSS score > 80 -CGI-S score ≥ 4 Key Exclusion Criteria: -History of treatment-resistant schizophrenia - Less than 1 yr since onset of symptoms -History of diabetes - Opioid agonist use with 14 days of screening -Use of olanzapine, chlorpromazine, thioridazine, or long-acting injectable antipsychotic within 12 months of screening -Use of clozapine within 6 months of screening	ITT: 1. 132 2. 132 3. 133 PP: 1. 122 2. 119 3. 111 Attrition: 1. 12 (9%) 2. 14 (10.5%) 3. 23 (17.2%)	Primary Endpoint: LSM improvement in PANSS score from baseline to Week 4 in ITT population 1.-23.9 2.-22.8 3.-17.5 Difference 1 vs 3 = -6.4 95% CI -10.0 to -2.8 P<0.001 Difference 2 vs. 3 = -5.3 95% CI -8.9 to -1.7 P=0.004 Secondary Endpoint: LSM change in CGI-S from baseline to Week 4 1. -1.21 2. -1.27 3. -0.84 Difference 1 vs 3 = -0.38 95% CI -0.61 to -0.14 P=0.002 Difference 2 vs 3 = -0.44 95% CI -0.67 to -0.20 P<0.001	NA NA NA NA	Any Adverse Effect 1. 73 (54.5%) 2. 73 (54.9%) 3. 60 (44.8%) Serious Adverse Effects 1. 1 (0.7%) 2. 1 (0.8%) 3. 0 Weight Gain 1. 25 (18.7%) 2. 19 (14.3%) 3. 4 (3.0%) p-values and 95% CI NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IWRS. Baseline characteristics were balanced between groups. Performance Bias: Low. All study medications were single, coated, bi-layer tablets. Patients and investigators blinded to treatment assignments. Detection Bias: Unclear. Method of blinding of outcome assessors not described. Attrition Bias: High. More placebo-treated patients withdrew compared to active treatment arms due to lack of efficacy, withdrawal by patients, or adverse effects. Missing data was imputed using the last observation carried forward. Reporting Bias: Low. Protocol available on-line. All outcomes reported as planned. Other Bias: Unclear. Trial funded by manufacturer. The manufacturer was also involved in design, data collection and analysis. The primary author has received research support from manufacturer. **Applicability**: Patient: Patients who were experiencing acute schizophrenia episode or relapse were included in this trial. Patients with bipolar disorder were not included in this trial. Intervention: Samidorphan dosing determined in Phase 2 trials. Olanzapine dosing is within FDA-approved therapeutic ranges. Comparator: Placebo is an appropriate comparator for efficacy. Outcomes: PANSS and CGI scores are validated outcomes used in other schizophrenia trials. Setting: A total of 38.4% of the patients were from the United States. All other patients were from Bulgaria, Ukraine, or Serbia.
2. Correll, et al[55] ENLIGHTEN-2	1. Olanzapine/ Samidorphan: 10 mg/10 mg and 20 mg/10 mg orally once a day	Demographics: -Mean age: 40.2 yrs -Male: 72.7% -Race White: 23.3% Black: 71.3%	ITT: 1. 276 2. 274 PP:	Co-Primary Endpoints: LSM percent change from baseline in body weight at Week 24 1. 4.21% 2. 6.59%	NA	Any Adverse Effect 1. 203 (74.1%) 2. 227 (82.2%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Randomized 1:1. Method of randomization not described. Baseline characteristics were balanced between groups. Performance Bias: Low. Patients, investigators, and outcomes assessors blinded to treatment assignment.

Phase 3 MC, DB, RCT	2. Olanzapine 10 mg and 20 mg orally once a day	Asian: 1.5% Key Inclusion Criteria: -Adults aged 18-55 yrs with diagnosis of schizophrenia -BMI 18-30 kg/m^2 -Stable body weight (≤ 5% self-reported change for ≥ 3 mos prior to study entry) Key Exclusion Criteria: -History of treatment-resistant schizophrenia - Less than 1 yr since onset of symptoms - Naïve to antipsychotic medications - Opioid agonist use with 14 days of screening	1. 176 2. 176 Attrition: 1. 98 (36%) 2. 100 (36%)	Difference: -2.38 95% CI -3.88 to -0.88 P=0.003 Co-Primary Endpoints: Proportion of patients with ≥ 10% weight gain at Week 24 1. 47 (17.8%) 2. 81 (29.8%) Difference: -12% 95% CI -22.8 to -4.6 P=0.003 Secondary Endpoints: Proportion of patients with ≥ 7% weight gain at Week 24 1. 73 (27.5%) 2. 116 (42.7%) Difference: -15.9% 95% CI -25.3 to -6.5 P=0.001	12%/8 15.9%/7	Serious Adverse Events: 1. 10 (3.6%) 2. 7 (2.5%) Adverse Events Leading to Treatment Discontinuation 1. 33 (12%) 2. 27 (9.8%) 95% CI and p value NR	NA	Medication supplied in identical formulations for both study arms. Detection Bias: Low. Assessors were blinded to treatment assignment. Attrition Bias: High. Only 64% of enrolled patients completed the 24-week trial. Attrition rates were due to AEs, withdrawal, loss to follow-up. Missing data were imputed using a multiple imputation regression method. Reporting Bias: Low. Protocol available online at clinical trials.gov website. All outcomes reported as planned. Other Bias: Unclear. Funded by manufacturer. **Applicability**: Patient: BMI restricted to a range of 18-30 kg/m^2 may have selected patients resistant to antipsychotic weight gain. Patients older than 55 years excluded from study, limiting applicability to older patients. Intervention: Dosing determined in Phase 2 and Phase 3 RCTs. Comparator: Active comparator of olanzapine is appropriate to determine impact on weight gain. Outcomes: RCT primarily evaluated the proportion of patients with weight gain in the 2 different treatment arms. Setting: 54 sites in the United States

Abbreviations: AE = adverse events; ARR = absolute risk reduction; BMI = body mass index; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; DB = double blind; ITT = intention to treat; IWRS = interactive web response system; LSM = least squares mean; MC = multi-center; mg = milligram; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PANSS = Positive and Negative Syndrome Scale ; PP = per protocol; RCT = randomized controlled trial; yrs = years

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21. OPIPZA (aripiprazole) oral film. Prescribing Information. Hazlet, NJ; Carwin Pharmaceutical Associates; March 2025.
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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LYBALVI® (olanzapine and samidorphan) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis. (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions (5.17) 1/2025

INDICATIONS AND USAGE

LYBALVI is a combination of olanzapine, an atypical antipsychotic, and samidorphan, an opioid antagonist, indicated for the treatment of:

- Schizophrenia in adults (1)
- Bipolar I disorder in adults (1)
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

DOSAGE AND ADMINISTRATION

Indication	Recommended Starting Dose (olanzapine/samidorphan)	Recommended Dose (olanzapine/samidorphan)
Schizophrenia (2.2)	5 mg/10 mg or 10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder (manic or mixed episodes) (2.3)	10 mg/10 mg or 15 mg/10 mg	5 mg/10 mg 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder adjunct to lithium or valproate (2.3)	10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg

- See the full prescribing information for the recommended titration and maximum recommended dosage. (2.2, 2.3)
- Administer LYBALVI once daily with or without food. Do not divide tablets or combine strengths. (2.4)
- Recommended starting dosage is 5 mg/10 mg once daily in patients who have a predisposition to hypotensive reactions, have potential for slower metabolism of olanzapine, or may be more pharmacodynamically sensitive to olanzapine. (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg. (3)

CONTRAINDICATIONS

- Patients using opioids. (4)
- Patients undergoing acute opioid withdrawal. (4)
- If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for those products. (4)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis*: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities). (5.2)
- *Precipitation of Opioid Withdrawal in Patients Who are Dependent on Opioids*: LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids to avoid precipitation of opioid withdrawal. (2.1, 5.3)
- *Vulnerability to Life-Threatening Opioid Overdose*:
  - *Risk of Opioid Overdose from Attempts to Overcome LYBALVI Opioid Blockade:* Attempts to overcome LYBALVI opioid blockade with high or repeated doses of opioids may lead to fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued. (5.4)
  - *Risk of Resuming Opioids in Patients with Prior Opioid Use*: Patients with a history of chronic opioid use prior to LYBALVI treatment may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. (5.4)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring. (5.5)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*: Discontinue if DRESS is suspected. (5.6)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.7)
- *Tardive Dyskinesia*: Discontinue if clinically appropriate. (5.8)
- *Orthostatic Hypotension and Syncope*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.9)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors. (5.11)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.13)
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery. (5.14)
- *Anticholinergic (Antimuscarinic) Effects:* Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. (5.16)
- *Hyperprolactinemia*: May elevate prolactin levels. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and at least twice placebo):

- *Schizophrenia (LYBALVI):* weight increased, somnolence, dry mouth, and headache. (6.1)
- *Bipolar I Disorder, Manic or Mixed Episodes (olanzapine):* somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, tremor. (6.1)
- *Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine):* dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Strong CYP3A4 Inducers*: Not recommended. (7.1)
- *Strong CYP1A2 Inhibitors*: Consider dosage reduction of olanzapine component of LYBALVI. (7.1)
- *CYP1A2 Inducer*: Consider dosage increase of the olanzapine component of LYBALVI. (7.1)
- *CNS Acting Drugs*: May potentiate orthostatic hypotension. (7.1)
- *Anticholinergic Drugs:* Can increase risk for severe gastrointestinal adverse reactions. (7.1)
- *Antihypertensive Agents*: Monitor blood pressure. (7.2)
- *Levodopa and Dopamine Agonists*: Not recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Renal Impairment:* Use is not recommended in patients with end-stage renal disease. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2025

Appendix 2: Current Preferred Drug List

Second Generation Antipsychotics

Generic	Brand	Form	PDL
aripiprazole	ABILIFY	TABLET	Y
aripiprazole	ARIPIPRAZOLE	TABLET	Y
asenapine maleate	ASENAPINE MALEATE	TAB SUBL	Y
asenapine maleate	SAPHRIS	TAB SUBL	Y
cariprazine HCl	VRAYLAR	CAPSULE	Y
clozapine	CLOZAPINE	TABLET	Y
clozapine	CLOZARIL	TABLET	Y
lurasidone HCl	LATUDA	TABLET	Y
lurasidone HCl	LURASIDONE HCL	TABLET	Y
olanzapine	OLANZAPINE	TABLET	Y
olanzapine	ZYPREXA	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE ER	TAB ER 24H	Y
quetiapine fumarate	SEROQUEL XR	TAB ER 24H	Y
quetiapine fumarate	SEROQUEL XR	TAB24HDSPK	Y
quetiapine fumarate	QUETIAPINE FUMARATE	TABLET	Y
quetiapine fumarate	SEROQUEL	TABLET	Y
risperidone	RISPERDAL	SOLUTION	Y
risperidone	RISPERIDONE	SOLUTION	Y
risperidone	RISPERDAL	TABLET	Y
risperidone	RISPERIDONE	TABLET	Y
ziprasidone HCl	GEODON	CAPSULE	Y
ziprasidone HCl	ZIPRASIDONE HCL	CAPSULE	Y
aripiprazole	OPIPZA	FILM	V
aripiprazole	ARIPIPRAZOLE	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	TABSENSSTR	V
aripiprazole	ABILIFY MYCITE	TABSENSTPD	V
asenapine	SECUADO	PATCH TD24	V
brexpiprazole	REXULTI	TAB DS PK	V
brexpiprazole	REXULTI	TABLET	V
clozapine	VERSACLOZ	ORAL SUSP	V
clozapine	CLOZAPINE ODT	TAB RAPDIS	V
iloperidone	FANAPT	TAB DS PK	V
iloperidone	FANAPT	TABLET	V
lumateperone tosylate	CAPLYTA	CAPSULE	V
olanzapine	OLANZAPINE ODT	TAB RAPDIS	V

olanzapine	ZYPREXA ZYDIS	TAB RAPDIS	V
olanzapine/samidorphan malate	LYBALVI	TABLET	V
paliperidone	INVEGA	TAB ER 24	V
paliperidone	PALIPERIDONE ER	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	CAPSULE	V
pimavanserin tartrate	NUPLAZID	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE	TABLET	V
risperidone	RISPERIDONE	SYRINGE	V
risperidone	RISPERIDONE ODT	TAB RAPDIS	V
xanomeline tart/trospium chlor	COBENFY STARTER PACK	CAP DS PK	V
xanomeline tart/trospium chlor	COBENFY	CAPSULE	V

Injectable Antipsychotics

Generic	Brand	Form	PDL
aripiprazole	ABILIFY ASIMTUFII	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	SUSER VIAL	Y
aripiprazole lauroxil	ARISTADA	SUSER SYR	Y
aripiprazole lauroxil, submicr.	ARISTADA INITIO	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	AMPUL	Y
chlorpromazine HCl	THORAZINE	AMPUL	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	VIAL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALDOL DECANOATE 50	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	VIAL	Y
haloperidol lactate	HALOPERIDOL LACTATE	SYRINGE	Y
haloperidol lactate	HALOPERIDOL LACTATE	VIAL	Y
paliperidone palmitate	ERZOFRI	SYRINGE	Y
paliperidone palmitate	INVEGA HAFYERA	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	SYRINGE	Y
risperidone	PERSERIS	SUSER SYR	Y
risperidone	UZEDY	SUSER SYR	Y
risperidone microspheres	RISPERDAL CONSTA	VIAL	Y
risperidone microspheres	RISPERIDONE ER	VIAL	Y
risperidone microspheres	RYKINDO	VIAL	Y

trifluoperazine HCl	STELAZINE	VIAL	Y
olanzapine	OLANZAPINE	VIAL	V
olanzapine	ZYPREXA	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	VIAL	V
ziprasidone mesylate	GEODON	VIAL	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	VIAL	V

First Generation Antipsychotics

Generic	Brand	Form	PDL
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ELIXIR	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	TABLET	Y
fluphenazine HCl	PROLIXIN	TABLET	Y
haloperidol	HALOPERIDOL	TABLET	Y
haloperidol lactate	HALOPERIDOL LACTATE	ORAL CONC	Y
loxapine succinate	LOXAPINE	CAPSULE	Y
loxapine succinate	LOXAPINE SUCCINATE	CAPSULE	Y
perphenazine	PERPHENAZINE	TABLET	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL CONC	Y
thioridazine HCl	THIORIDAZINE HCL	TABLET	Y
thiothixene	THIOTHIXENE	CAPSULE	Y
thiothixene HCl	THIOTHIXENE HCL	ORAL CONC	Y
trifluoperazine HCl	STELAZINE	TABLET	Y
trifluoperazine HCl	TRIFLUOPERAZINE HCL	TABLET	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	TABLET	V
chlorpromazine HCl	THORAZINE	TABLET	V
loxapine	ADASUVE	AER POW BA	V
pimozide	PIMOZIDE	TABLET	V

Appendix 3: Diagnostic Criteria and Assessments in Select Mental Health Conditions

Table 17. Diagnostic Criteria for Major Depressive Disorder[28]

DSM-5 Criteria for MDD (must have all A-E below)
A. Depressive Symptoms: ≥5 symptoms during the same two-week period that are a change from previous functioning. Depressed mood (1) and/or loss of interest/pleasure (2) must be present. Exclude symptoms clearly attributable to another medical condition. 1. Depressed mood. Most of the day, nearly every day. May be subjective (e.g., feels sad, empty, hopeless) or observed by others (e.g., appears tearful). In children and adolescents, it can be irritable. 2. Loss of interest/pleasure. Markedly diminished interest/pleasure in all (or almost all) activities most of the day, nearly every day. May be subjective or observed by others. 3. Weight loss or gain. Significant weight loss (without dieting) or gain (change of >5% body weight in a month) or decrease or increase in appetite nearly every day. In children, it may be failure to gain weight as expected. 4. Insomnia or hypersomnia: Nearly every day. 5. Psychomotor agitation or retardation. Nearly every day and observable by others (not merely subjectively restless or slow). 6. Fatigue or loss of energy. Nearly every day. 7. Feeling worthless or excessive/inappropriate guilt. Nearly every day. Guilt may be delusional. Not merely self-reproach or guilt about being sick. 8. Decreased concentration. Nearly every day. May be indecisiveness. May be subjective or observed by others. 9. Thoughts of death/suicide. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or suicide attempt, or a specific plan for suicide.
B. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. Episode not attributable to the physiological effects of a substance or another medical condition.
D. Episode not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. No history of manic or hypomanic episode (exclusion does not apply if all manic-like or hypomanic-like episodes are substance-induced or are attributable to physiological effects of another medical condition).
Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MDD = major depressive disorder

Table 18. Categories of MDD Symptom Severity[33]

Instrument	None	Mild	Moderate	Severe/Very Severe
HAM-D17	0-7	8-13	14-19	20-25 or ≥26
HAM-D21	0-8	9-15	16-22	23-28 or ≥ 29
HAM-D24	0-9	10-18	19-26	27-34 or ≥ 35
MADRS	0-6	7-19	20-34	≥ 35
BDI	0-9	10-18	19-20	≥ 30
PHQ-9	0-4	5-9	10-19	20-27
QID-SR	0-5	6-10	11-15	16-20 or ≥ 21

Abbreviations: Abbreviations: BDI = Beck Depression Inventory; HAM-D = Hamilton Rating Scale for Depression (with 17, 21, or 24 items); MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; PHQ-9 = Patient Health Questionnaire (9-item depression module); QID-SR = Quick Inventory of Depressive Symptomatology—Self-Report

Table 19. Assessments in Major Depressive Disorder[2]

Assessment	Description
Efficacy Scales	
Clinical Global Impressions-Severity (CGI-S) scale	Assesses overall severity of mental illness on a 7-point scale: • 1 = Not ill • 2 = Borderline ill • 3 = Mildly ill • 4 = Moderately ill • 5 = Markedly ill • 6 = Severely ill • 7 = Extremely severely ill
Clinical Global Impressions-Improvement (CGI-I) scale	Assesses overall improvement of condition on a 7-point scale, compared to baseline: • 1 = Very much improved • 2 = Much improved • 3 = Minimally improved • 4 = No change from baseline • 5 = Minimally worse • 6 = Much worse • 7 = Very much worse
Hamilton Depression Rating Scale (HAM-D17)	17-item scale; ratings cover symptom severity experienced over the past week. Items are scored from 0 (absent) to 4 (very severe) or 0 (absent) to 2 (definite), depending on the item. Total score of: • ≥ 23 = very severe depression • 19 to 22 = severe depression • 14 to 18 = moderate depression • 8 to 13 = mild depression • 0 to 7 = normal Total score ranges from 0 to 52. Minimal clinically important difference (MCID) = 3-to-7-point improvement
Hamilton Anxiety Rating Scale (HAM-A)	14-item scale; assesses the severity of anxiety symptoms. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0 to 56. Scoring: • 1 to 17 = mild • 18 to 24 =mild to moderate

	• 25 to 30 = moderate to severe • Score < 7 = remission of condition
Montgomery-Åsberg Depression Rating Scale (MADRS)	65-item scale assesses 10 most commonly occurring symptoms in adult patients on a 0 to 6 scale, with higher scores indicating more severe symptoms: • Apparent sadness • Reported sadness • Inner tension • Reduced sleep • Reduced appetite • Concentration difficulty • Lassitude • Inability to feel • Pessimistic thoughts • Suicidal thoughts Minimal clinically important difference (MCID) = 2-point improvement
Adverse Event Scales	
Abnormal Involuntary Movement Scale (AIMS)	12-item scale; assesses abnormal movements in patients taking neuroleptic medications. Items are rated 0 to 4, with higher scores indicating more severe movements. Domains assessed include: • Facial and oral movements • Extremity movements • Trunk movements • Global judgements • Mental status
Barnes Akathisia Rating Scale (BARS)	4 item assessment to screen for akathisia (inability to remain still) with 0 = normal to 3 = severe. A low score indicates low levels of akathisia. • Objective akathisia: (scale 0 to 3) • Subjective akathisia: (scale 0 to 3) • Distress of patient (scale 0 to 3) • Global score (scale 0 to 5) with higher numbers associated with increased severity; ≥ 2 indicates presence of akathisia.

Table 20. Assessments in Schizophrenia, Psychosis, and Bipolar Disorder[1]

Assessment	Description
Efficacy Scales	
Brief Negative Symptom Scale (BNSS)	13-item scale with questions organized into 6 subscales for assessing: • Anhedonia (loss of interest or pleasure) • Distress • Asociality (social withdrawal or lack of interest in socializing) • Avolition (lack of motivation)

	• Blunted affect (reduced emotional expression) • Alogia (decreased speech or difficulty speaking) Items are scored on a 0 to 6 scale, with 0 indicating the symptom is absent and 6 indicating the symptom is severe. Items are summed. Total scores range between 0 and 78, with higher scores indicating more severe symptoms.
Brief Psychiatric Rating Scale (BPRS)	18 symptoms including hostility, suspiciousness, hallucination, and grandiosity are scored on a range from 1 (not present) to 7 (extremely severe). Clinical administered, based on patient's behavior over the previous 2-3 days. Final score ranges from o to 126. The higher the score, the more severe the pathology. Mildly ill = score of 31 Moderately ill = score of 41 Markedly ill = score of 53 "Minimally improved" interpretation was associated with a percentage BPRS reduction of 24, 27 and 30% at weeks 1, 2 and 4, respectively.
Calgary Depression Scale for Schizophrenia (CDSS)	9-item scale with questions assessing: • Depression • Hopelessness • Self-deprecation • Guilt • Sleep • Suicidal ideation Items are scored on a 0 to 3 scale with total scores ranging between 0 and 27. Higher scores indicate more severe depression.
Positive and Negative Symptom Scale (PANSS)	30-item scale cutoff scores do not clearly indicate the severity of illness. The range of possible scores is 30 to 210 (usual range is 60 to 150). A low score indicates less severity. • < 5 very low • 6 to 25 low • 26 to 74 moderate • 75 to 94 high • > 95 very high Subscales include positive, negative, and general psychopathology, rated on a scale of 1 (not present) to 7 (extremely severe).
Sheehan Disability Scale (SDS)	Assesses functional impairment in 3 main domains: • Work/school (scale 0 to 10) • Social life (scale 0 to 10) • Family life/home responsibilities (scale 0 to 10) Higher scores indicate more severe impairment.
Adverse Event Scales	
Columbia Suicide Severity Rating Scale (CSSRS)	6-item scale designed for all ages. Items are scored yes or no in reference to suicidal thoughts, actions, or plan. • Any score of yes designates the need for a referral • A score of yes on items 4, 5, or 6 designates need for immediate suicide precautions
Simpson Angus Scale (SAS)	10-item scale used to screen for extrapyramidal side effects (drug-induced movement). Items are rated on a continuum of 0 to 4:

	• 0 = absence • 4 = most extreme form of the condition Up to 3 is considered within normal range.

Appendix 4: Abstracts

Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression.[56]

Background: In treatment-resistant depression, commonly defined as a lack of response to two or more consecutive treatments during the current depressive episode, the percentage of patients with remission is low and the percentage with relapse is high. The efficacy and safety of esketamine nasal spray as compared with extended-release quetiapine augmentation therapy, both in combination with ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), in patients with treatment-resistant depression are unknown.

Methods: In an open-label, single-blind (with raters unaware of group assignments), multicenter, phase 3b, randomized, active-controlled trial, we assigned patients, in a 1:1 ratio, to receive flexible doses (according to the summary of product characteristics) of esketamine nasal spray (esketamine group) or extended-release quetiapine (quetiapine group), both in combination with an SSRI or SNRI. The primary end point was remission, defined as a score of 10 or less on the Montgomery-Åsberg Depression Rating Scale (MADRS), at week 8 (scores range from 0 to 60, with higher scores indicating more severe depression). The key secondary end point was no relapse through week 32 after remission at week 8. All patients were included in the analysis; patients who discontinued the trial treatment were considered as having had an unfavorable outcome (i.e., they were grouped with patients who did not have remission or who had a relapse). Analyses of the primary and key secondary end points were adjusted for age and number of treatment failures.

Results: Overall, 336 patients were assigned to the esketamine group and 340 to the quetiapine group. More patients in the esketamine group than in the quetiapine group had remission at week 8 (91 of 336 patients [27.1%] vs. 60 of 340 patients [17.6%]; P = 0.003) and had no relapse through week 32 after remission at week 8 (73 of 336 patients [21.7%] vs. 48 of 340 patients [14.1%]). Over 32 weeks of follow-up, the percentage of patients with remission, the percentage of patients with a treatment response, and the change in the MADRS score from baseline favored esketamine nasal spray. The adverse events were consistent with the established safety profiles of the trial treatments.

Conclusions: In patients with treatment-resistant depression, esketamine nasal spray plus an SSRI or SNRI was superior to extended-release quetiapine plus an SSRI or SNRI with respect to remission at week 8. (Funded by Janssen EMEA; ESCAPE-TRD ClinicalTrials.gov number, NCT04338321.).

Appendix 5: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to April 22, 2025>

1	Aripiprazole/tu [Therapeutic Use]	587
2	Antipsychotic Agents/tu [Therapeutic Use]	34269
3	asenapine.mp.	535
4	cariprazine.mp.	534
5	Clozapine/tu [Therapeutic Use]	4398
6	Lurasidone Hydrochloride/tu [Therapeutic Use]	146
7	Olanzapine/tu [Therapeutic Use]	507
8	Quetiapine Fumarate/tu [Therapeutic Use]	505
9	Risperidone/tu [Therapeutic Use]	4050
10	ziprasidone.mp.	2232
11	brexpiprazole.mp.	471
12	iloperidone.mp.	254
13	lumateperone.mp.	100
14	Paliperidone Palmitate/tu [Therapeutic Use]	256
15	pimavanserin.mp.	373
16	xanomeline.mp.	259
17	Chlorpromazine/tu [Therapeutic Use]	3876
18	Fluphenazine/tu [Therapeutic Use]	893
19	Haloperidol/tu [Therapeutic Use]	4093
20	Trifluoperazine/tu [Therapeutic Use]	465
21	Loxapine/tu [Therapeutic Use]	154
22	Perphenazine/tu [Therapeutic Use]	461
23	Thioridazine/tu [Therapeutic Use]	771
24	Thiothixene/tu [Therapeutic Use]	210
25	Pimozide/tu [Therapeutic Use]	466
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	46510
27	limit 26 to (english language and humans and yr="2020 -Current")	4826
28	limit 27 to (clinical trial, phase iii or guideline or meta-analysis or practice guideline or "systematic review")	571

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 60 days in children 3-6 years of age
- All antipsychotic use in children 2 years of age or younger
- For quetiapine requests in children ≥7 years of age, see criteria for Low Dose Quetiapine

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.
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.
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

Approval Criteria		
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.

P&T/DUR Review: 8/25; 2/24 (SS); 6/21(SS)
Implementation: 4/1/24; 10/1/22

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine, immediate- and extended-release

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- For any requests in children ≤6 years of age, see criteria for Antipsychotics in Children
- Auto-PA approvals for people 7 and older:
    - Patients with a claim for a second-generation antipsychotic in the last 6 months
    - Patients with prior claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider
    - Extended-release formulations in patients with claims for a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor in the last 90 days

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Table 1. Adults (age ≥18 years) with FDA-approved or Compendia-supported Indications

Bipolar Disorder	
Major Depressive Disorder (MDD)	Adjunctive therapy with antidepressants for MDD
Schizophrenia	
Bipolar Mania	
Bipolar Depression	
Generalized Anxiety Disorder (GAD)	Adjunctive therapy with SSRI/SNRI

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. Is the request for an evidence-supported diagnosis (Table 1 or Table 2)?	**Yes:** Go to #2	No: Pass to RPh. Deny; medical appropriateness.
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy (at ≤50 mg) longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *8/25; 6/23 (SS); 4/21 (SF); 8/20; 3/19; 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *7/1/23; 1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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 the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
4. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
5. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
6. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *8/25; 8/20(SF); 3/19 (DM); 9/18; 3/18; 01/17*
Implementation: *4/1/17*

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:

Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long-term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

P&T Review: *8/25; 10/23 (DM); 2/22 (DM); 9/18 (DM); 9/17; 9/16; 5/05*
Implementation: *10/13/16; 11/18/04*

Xanomeline-trospium (COBENFY) Safety Edit

Goal(s):

- Promote safe use of xanomeline-trospium in combination with other mental health drugs for schizophrenia.

Length of Authorization:

Up to 12 months

Requires PA:

- Xanomeline-trospium
- Auto-approval requests for people with a claim for xanomeline-trospium in the last 6 months

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 xanomeline-trospium prescribed for an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the intent to prescribe xanomeline-trospium in conjunction with another antipsychotic medication?	**Yes:** Go to #4	**No:** Go to #5
4. Is there documentation or provider attestation that the benefits of therapy (e.g. symptom improvement, social function, number of hospitalizations, etc.) outweigh potential risks of combination treatment (e.g. hepatic impairment, biliary disease, gastrointestinal and anticholinergic effects, etc.)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is there documentation or provider attestation that the patient does not have any of the following conditions? • Concurrent antidepressant that inhibits CYP2D6 (e.g., bupropion, fluoxetine, paroxetine, or duloxetine) • Urinary retention (e.g., benign prostatic hyperplasia, diabetic cystopathy) • Untreated narrow-angle glaucoma • Impaired gastric motility (e.g., gastrointestinal obstructive disorders) • Mild, moderate or severe hepatic impairment, biliary disease, or elevated liver function tests • Moderate or severe renal impairment or estimated glomerular filtration rate (eGFR) <60 mL/min	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/25; 2/2025 (SS)
Implementation: 3/10/25