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Efficacy and Safety of Newer Antipsychotic Combination Therapies

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The most recent antipsychotics approved by the Food and Drug Administration (FDA) for management of schizophrenia or bipolar disorder include two combination dosage forms: COBENFY™ is a combination of xanomeline and trospium, and is indicated for the treatment of schizophrenia in adults;[1] and LYBALVI® is a combination of olanzapine and samidorphan, and is indicated for adults with schizophrenia or bipolar I disorder as maintenance monotherapy or adjunct to lithium or valproate for acute manic or mixed episodes.[2] This newsletter summarizes the evidence for the FDA approval of these medications and discusse strategies to mitigate weight gain associated with antipsychotic administration.

Traditional first- and second-generation antipsychotics have activity at dopaminergic D2 receptors, but many also impact serotonergic, adrenergic, histaminergic, and muscarinic neurotransmitter systems. The variety of effects across different receptors contribute to many common antipsychotic-induced adverse effects. Common side effects of antipsychotics 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 (e.g., akathisia, dyskinesias, dystonia, parkinsonism) disorders. These adverse effects can limit tolerability to treatment and contribute to treatment discontinuation. Many patients may need to switch therapy because of inadequate symptom improvement or intolerance to adverse effects.

In schizophrenia and bipolar disorder, antipsychotic therapy is intended to improve symptoms, prevent recurrent acute episodes, and limit the impact symptoms have on daily activities and function.

Schizophrenia and Bipolar Disorder

Schizophrenia is a severe 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).[3] Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales.

Bipolar disorder is characterized by episodes of mania, and in the majority of cases, episodes of major depression.[4] 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).[4] After one manic episode, greater than 90% of individuals have recurrent mood episodes, and lifetime suicide risk is estimated to be at least 15-times higher than the general population risk.[5]

The Clinical Global Impression Scale (CGI) evaluates change in disease severity with treatment using a 7-point analogue scale, with lower scores indicating greater improvement of symptoms.[6] The Positive and Negative Syndrome Scale (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).[6] This scale can also be subdivided to assess general psychopathology, positive symptoms, or negative symptoms. The different schizophrenia assessment tools are summarized in **Table 1.**

Table 1. Schizophrenia Assessment Scales[6]

Name	Range	MCID
CGI	1 to 7 points	1 point
CGI-S	1 to 7 points	1 point
PANSS	30 items - ranked 1 to 7 points. Lower score indicates less severity. Total Score: 30-210 points.	20% improvement in score

Abbreviations: CGI = Clinical Global Impression Scale; CGI-S = CGI-Severity; MCID = Minimum Clinically Important Difference; PANSS = Positive and Negative Syndrome Scale

Xanomeline/Trospium (COBENFY™) Efficacy and Safety

Unlike other antipsychotic drugs, xanomeline/trospium does not target dopaminergic D2 receptors. Xanomeline is a muscarinic (or cholinergic) receptor agonist and is administered in combination with trospium, an oral anticholinergic drug, with activity primarily in the peripheral tissues and limited ability to cross the blood brain barrier. The combination allows for cholinergic effects in the central nervous system with reduced adverse cholinergic effects in peripheral tissue.

Compared to placebo, xanomeline/trospium improved symptoms in 3 inpatient, randomized controlled trials (RCTs) enrolling adults with an acute exacerbation or relapse of schizophrenia and moderate-severity symptoms over 5 weeks (**Table 2**).[7-9] The average improvement on the PANSS ranged from -21.6 to -17.4 points for xanomeline/trospium compared to -12.2 to -5.9 points with placebo.[7-9] This improvement meets the current definitons for minimum clinically meaningful changes in symptoms.[10]

Table 2. PANSS Results in the EMERGENT Trials

Trial Name	LSMD change in PANSS after 5 weeks	LSMD Difference (95% CI)
EMERGENT-1[7]	Xano/Trosp: -17.4 Placebo: -5.9	-11.6 (-16.1 to -7.1) p<0.001
EMERGENT-2[9]	Xano/Trosp: -21.2 Placebo: -11.6	-9.6 (-13.9 to -5.2) p<0.0001
EMERGENT-3[8]	Xano/Trosp: -20.6 Placebo: -12.2	-8.4 (-12.4 to -4.3) p<0.001

Abbreviations: CI =confidence interval; LSMD = least squares mean difference; PANSS = Positive and Negative syndrome Scale; Xano/Trosp = Xanomeline/Trospium

There are no direct comparative data to determine whether xanomeline/trospium is more effective or safer than other antipsychotics for treatment of schizophrenia. Preliminary data from an unpublished phase 3 trial indicate that addition of xanomeline/trospium to another antipsychotic will not improve schizophrenia symptoms compared to antipsychotic monotherapy.[11]

Because xanomeline/trospium is dosed twice daily, providers should consider how patient adherence may impact long-term efficacy. Attrition was high (>20%) during inpatient clinical trials over five weeks,[7-9] and interim analyses of long-term extension studies indicate that over 50% of people had discontinued treatment by 120 days.[12] The primary reasons for discontinuation in outpatient extension studies included withdrawal of consent (18.7%), adverse events (14.9%), loss to follow-up (8.2%), and failure to adhere to protocol requirements (7.4%).[12]

In clinical trials, xanomeline/trospium was associated with significant rates of gastrointestinal adverse events compared to placebo in short-term trials (e.g., nausea, vomiting, dyspepsia, constipation, diarrhea, abdominal pain, and reflux disease).[7-9] Xanomeline/trospium is contraindicated in people with urinary retention, moderate to severe hepatic impairment, gastric retention, or untreated narrow-angle glaucoma.[1] Labeling recommends liver function tests prior to starting treatment and periodically as needed to monitor for liver injury and biliary disease.[1] Short-term trials did not identify an association with akathisia or weight gain, but long-term studies are needed to confirm these findings.

There are insufficient data to evaluate long-term efficacy and safety of xanomeline/trospium and insufficient data in people with comorbid conditions that could increase risk of adverse events. People who were prescribed concomitant mental health drugs were excluded from clinical trials, but there is potential for increased rates of adverse events when used in combination with common antidepressants such as bupropion, fluoxetine, duloxetine, and paroxetine. Studies did not evaluate quality of life, prevention of relapse, return to work and school, improvements in relationships with friends and family, hospital readmission, or mortality.

Olanzapine/Samidorphan (LYBALVI®) Efficacy and Safety

LYBALVI is a fixed dose of the opioid receptor antagonist, samidorphan 10 mg, combined with the antipsychotic, olanzapine 5, 10, 15 or 20 mg to mitigate olanzapine-associated weight gain.[5] The risk of weight gain with olanzapine is generally dose dependent, with higher doses often associated with a greater likelihood of weight gain.[5] The exact mechanism by which samidorphan mitigates olanzapine-associated weight gain is not known.[2]

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.[2] There is insufficient evidence to compare olanzapine/samidorphan to other therapies for patients with bipolar I disorder.

The safety and efficacy of olanzapine/samidorphan for schizophrenia was evaluated in a 4-week, double-blind, phase 3 RCT.[13] 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.[13] The study was designed to compare olanzapine/samidorphan with placebo, not with olanzapine.[13] The primary efficacy endpoint was change in PANSS total score from baseline to Week 4.[13] Compared with placebo, a statistically significant improvement in the change from baseline in PANSS total score at Week 4 was observed with olanzapine/samidorphan (-17.5 vs. -23.9; LSMD, -6.4; 95% CI -10.0 to -2.8; moderate-quality evidence).[13]

Another clinical trial[14] evaluated the weight-mitigation effect of samidorphan on olanzapine in patients with schizophrenia. This was a 24-week, double-blind RCT that compared samidorphan/olanzapine to monotherapy with olanzapine.[14] The efficacy of olanzapine/samidorphan on psychotic symptoms was not evaluated in this study. 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 and a body mass index of only 18-30 kg/m^2.[14] Nearly 40% of participants discontinued the study early.

Over 24 weeks olanzapine/samidorphan resulted in a smaller percent gain in body weight (4.21%) compared to olanzapine (6.59%) (difference, -2.38%; 95% CI, -3.8 to -0.88; p=0.002; low-quality evidence).[14] A clinically significant change in weight is generally defined as a loss or gain of 5% to 10% of total body weight over a period of 6 to 12 months.[15] Weight loss of 5% or greater results in improvements in cardiometabolic risk factors associated with obesity.[16]

Mitigation Strategies to Decrease Weight Gain Associated with Antipsychotics

A 2015 systematic review evaluated drugs commonly associated with weight change.[17] Antipsychotics were identified as a drug class associated with the most weight gain.[17] Olanzapine was associated with the largest gain (2.4 kg), followed by quetiapine (1.1 kg) and risperidone (0.8 kg).[17] A 2024 systematic review evaluated the efficacy of initiating metformin in patients starting antipsychotic therapy to mitigate metabolic side effects associated with antipsychotics.[18] Fourteen studies with 1,126 participants were included.[18] Initiating metformin alongside antipsychotics resulted in an average reduction of 3.12 kg compared with placebo (95% CI -4.22 to -2.01 kg).[18] Metformin also significantly attenuated derangement of fasting glucose levels, total cholesterol, and total triglyceride levels.[18] A 2016 systematic review and meta-analysis found similar results when metformin was used to prevent antipsychotic weight gain.[19] Meta-analysis of 12 published studies with a total of 743 patients found that in patients treated with antipsychotics, metformin treatment resulted in significantly better anthropometric and metabolic parameters than placebo.[19] The mean change in weight with metformin was -3.27 kg (95% CI -4.66 to -1.89; p<0.001).[19] Metformin compared to placebo resulted in significant reduction in body mass index (-1.13 kg/m^2; 95 % CI -1.61 to -0.66) and insulin resistance index (-1.49; 95 % CI -2.40 to -0.59) but not fasting blood sugar (-2.48 mg/dl; 95 % CI -5.54 to 0.57).[19]

Guidance from the British Association for Psychopharmacology recommends metformin as an adjunct to attenuate or reduce weight gain following antipsychotic medication (strong recommendation, high-quality evidence).[20] Lifestyle interventions should be fully explored and the other interventions be considered, including switching antipsychotics, if possible.[20]

Metformin has been compared to lifestyle intervention for weight reduction in a large 3-year RCT of people at high risk of diabetes in the general population.[20] Metformin led to a modest 2 kg reduction in weight over the short- and long-term but was less effective than intensive lifestyle intervention (high-quality evidence).[20] In people taking antipsychotic medications, short-term trials have shown that metformin reduces weight gain, compared to placebo, by approximately 3 kg (high-quality evidence).

Clinical trials of atomoxetine, dextroamphetamine, famotidine, fluoxetine, fluvoxamine and nizatidine have failed to show benefit in mitigating weight gain in individuals on antipsychotic treatment (moderate-quality evidence).[20] Three out of four RCTs of topiramate as an adjunct to antipsychotics reported statistically significant weight loss, ranging from 1.5 kg to 5 kg.[20] One RCT supports an effect to attenuate weight gain in people with a first episode of psychosis (moderate-quality evidence).[20] However, the risk–benefit profile of topiramate is severely limited by its adverse effects including paresthesias, dizziness, drowsiness, and nausea (moderate-quality evidence).[20]

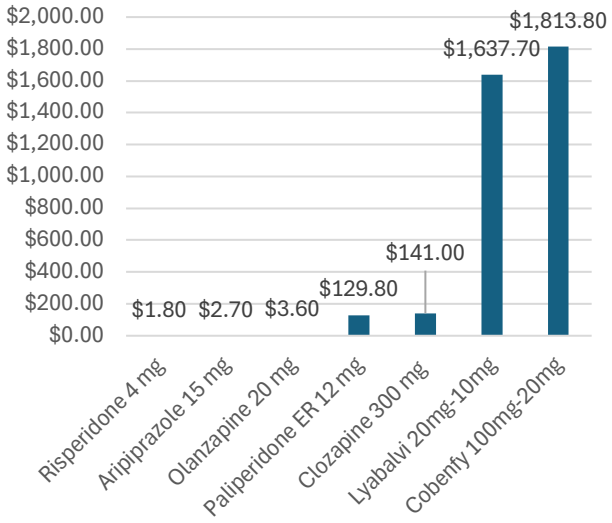
Oregon Health Plan Policies

In the Oregon Health Plan, antipsychotic medications are exempt from traditional Preferred Drug List (PDL) requirements. However, clinical prior authorization (PA) criteria, which address safety concerns or medically inappropriate use, may be implemented as safety edits. 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. **Figure 1** illustrates the comparative monthly costs for oral antipyschotics that are recommended to treat schizophrenia and bipolar disorder.

For treatment of schizophrenia, the Oregon Mental Health Clinical Advisory Group (MHCAG) recommends that providers consider use of antipsychotics with an available long-acting formulations (e.g., aripiprazole, risperidone, or paliperidone, or alternatively fluphenazine or haloperidol if a first-generation agent is needed) because long-acting injectable formulations improve adherence and lower risk of hospitalization and relapse when compared to oral formulations.[21] Clozapine is recommended for people who have had inadequate response to two different antipsychotics.[21]

For treatment of bipolar disorder, antipsychotics can be prescribed as maintenance monotherapy or adjunct to lithium or valproate for acute manic or mixed episodes. In 2019, the MHCAG evaluated bipolar disorder and developed a treatment algorithm for Acute Bipolar Depression[22] and acute bipolar mania.[23]

Figure 1. Comparative Monthly Costs for Selected Oral Antipsychotics



Based on Myers and Stauffer Provider Resources for Drug Pricing[24]

Conclusions

The evidence for xanomeline/trospium is limited to short-term, inpatient trials. Current evidence does not include Important outcomes such long-term efficacy, safety and adherence in outpatient settings. There is no direct comparative evidence data of xanomeline/trospium with other antipsychotics and no published data in combination with other antipsychotics. Unpublished data show no benefit to combination use. For this reason, OHP has implemented clinical prior authorization criteria to ensure safety if xanomeline/trospium is prescribed in combination with other mental health medications.

The antipsychotic component of LYBALVI, olanzapine, is effective for managing symptoms of schizophrenia and bipolar disorder, but it can cause weight gain. Samidorphan, when combined with olanzapine modestly reduces weight gain over 24 weeks compared to olanzapine alone (+7 pounds vs. +11 pounds, respectively).

Metformin is effective in attenuating weight gain in people starting antipsychotic treatment, and may improve other metabolic indicators such as insulin resistance.

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