obese populations. Both drug combinations displayed these benefits after approximately 7 weeks. OLZ/MET's weight mitigation was largely commensurate with increases in both dosage and duration of treatment. OLZ/SAM's most efficacious dosage was not readily apparent. The maximum reduction in weight gain was achieved when MET was titrated to a daily dose of 2000 mg, although significant prevention of weight gain has been reported with lower doses as well. The mean weight change for OLZ/MET over 24 weeks was +5.5 lbs on 2000 mg per day. The mean weight change for OLZ/SAM over 24 weeks was +7.0 lbs., however, the average dose of OLZ/SAM was not reported. These results were seen in both adult and non-adult populations. OLZ/MET is considerably more affordable in comparison to OLZ/SAM. Other notable differences included dosage flexibility and scheduling, contraindications in select populations, and common side effects, among others.

Conclusions. Weight gain is a serious side effect of many antipsychotics and can greatly impair a patient's quality of health and life. Drug combinations such as OLZ/SAM and OLZ/MET are crucial to help minimize the morbidity caused by medication-induced obesity. Both combinations showed effectiveness in reducing rates of weight gain but these effects were delayed until approximately 7 weeks. OLZ/MET's effectiveness was positively correlated with increased dosages and duration, unlike OLZ/SAM in which no such relation could be convincingly established. OLZ/SAM's relatively high cost is likely prohibitive for many persons, especially considering mental illness' often devastating socioeconomic impact.

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Impact of Cariprazine on Anhedonia Symptoms in Patients with Bipolar I Depression: Pooled Analysis of 3 Pivotal Clinical Trials

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Purpose. Anhedonia characterizes major depressive episodes in bipolar depression and is associated with more severe illness/poor prognosis. These post hoc analyses assess effect of cariprazine 1.5 and 3 mg/d on anhedonia symptoms in patients with bipolar I depression.

Methods. Data were pooled from 3 randomized, double-blind, placebo-controlled bipolar I depression trials in cariprazine. Cariprazine 1.5 and 3 mg/d versus placebo were evaluated in patient subgroups stratified by median baseline MADRS anhedonia score (higher anhedonia=score ≥19; lower anhedonia=score <19). Outcomes included mean change from baseline to week 6 in MADRS total and anhedonia factor score (sum of apparent sadness, reported sadness, concentration, lassitude, and inability to feel items). The proportion of patients with week 6 anhedonia factor response (≥50% improvement from baseline) was also determined. Changes from baseline were analyzed using a mixed-effect model for repeated measures.

Results. There were 760 patients in the higher anhedonia subgroup (placebo=249, cariprazine: 1.5 mg/d=261; 3 mg/d=250) and 623 patients in the lower anhedonia subgroup (placebo=211, cariprazine: 1.5 mg/d=200; 3 mg/d=212). Mean baseline MADRS total score was higher in the higher anhedonia subgroup (total=33.6) than in the lower anhedonia subgroup (total=27.6). Change from baseline to week 6 in MADRS total score was greater for both cariprazine doses versus placebo in the higher anhedonia subgroup (least squares mean difference [LSMD] and 95% confidence interval [CI]: 1.5 mg/d=-3.01 [-4.84, -1.19], *P*=.0012; 3 mg/d: -3.26 [-5.12, -1.40], *P*=.0006); in the lower anhedonia subgroup, cariprazine 1.5 mg/d was statistically significant versus placebo (-2.61 [-4.28, -0.93], *P*=.0024). In the higher anhedonia subgroup at week 6, change from baseline in anhedonia factor score was significant versus placebo for both cariprazine doses (1.5 mg/d=-1.97 [-3.13, -0.81], *P*=.0009; 3 mg/d=-2.07 [-3.26, -0.89], *P*=.0006); in the lower subgroup, the difference was significant versus placebo for cariprazine 1.5 mg/d (-1.70 [-2.77, -0.62], *P*=.0021). After adjusting for changes in other depressive symptoms, LSMDs versus placebo in the anhedonia factor score remained significant for cariprazine 1.5 mg/d (-1.21 [-2.05, -0.36], *P*=.0052) and 3 mg/d (-1.00 [-1.86, -0.14], *P*=.0233) in the higher anhedonia subgroup, and for 1.5 mg/d (-1.06 [-1.92, -0.19], *P*=.0164) in the lower subgroup. In the higher anhedonia subgroup, rates of anhedonia factor response were greater versus placebo (31.7%) for cariprazine 1.5 mg/d (44.8%, *P*=.0028) and 3 mg/d (45.6%, *P*=.0019); in the lower subgroup, response rates were 39.3% for placebo, 48.0% for 1.5 mg/d, and 46.7% for 3 mg/d. Adverse events in ≥5% cariprazine and twice placebo were nausea, akathisia, restlessness, and EPS.

Importance. Those with bipolar depression and anhedonia cariprazine demonstrated a potent antidepressant and antianhedonic effect in higher/lower anhedonia subgroups.

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Impact of Predominant Polarity on Cariprazine Efficacy in Patients with Bipolar I Disorder: A Pooled Analysis

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Purpose. Assess effect of predominant polarity on efficacy of cariprazine in patients with bipolar I (BP-I) disorder. Predominant polarity may be an important clinical consideration in BP-I disorder, with predominant depressive episodes associated with delayed diagnosis and higher rates of suicidality, while predominant manic episodes are associated with younger onset, manic/psychotic first episode, and more substance abuse [1].
Methods. Data were pooled from 3 randomized, double-blind, cariprazine trials in BP-I depression and 3 trials in BP-I mania. Post hoc analyses were performed in subgroups from the bipolar depression studies with/without predominant depression (≥2:1 ratio of prior lifetime depressive to manic episodes), and in subgroups from the bipolar mania studies with and without predominant mania (≥2:1 ratio of prior lifetime manic to depressive episodes). Change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score was evaluated for cariprazine 1.5 and 3 mg/d versus placebo (bipolar depression studies); change from baseline to week 3 in Young Mania Rating Scale total score was evaluated for cariprazine 3-12 mg/d versus placebo (bipolar mania studies). Change from baseline analyzed using mixed-effect model for repeated measures in pooled intent-to-treat population from each indication.
Results. In bipolar depression studies, there were 624 patients (45% of total study population) in the predominantly depressive subgroup (placebo=197, cariprazine: 1.5 mg/d=217; 3 mg/d=210) and 750 patients (55%) in the subgroup without predominant depression (placebo=258, cariprazine: 1.5 mg/d=241; 3 mg/d=251). In the predominant depressive subgroup, LSMDs for MADRS total score change from baseline were significant versus placebo for cariprazine 1.5 mg/d (-2.49 [-4.30, -.68], *P*=.0071) and 3 mg/d (-2.48 [-4.31, -.65], *P*=.0079); in the subgroup without predominant depression, LSMDs were also significant versus placebo for both doses (1.5 mg/d=-3.30 [-5.06, -1.54], *P*=.0002; 3 mg/d=-2.53 [-4.29, -.77], *P*=.0049). In bipolar mania studies, there were 721 patients (73% of total study population) in the predominantly manic episode subgroup (placebo=307, cariprazine 3-12 mg/d =414) and 267 patients (27%) in the subgroup without predominant manic episodes (placebo=102, cariprazine 3-12 mg/d=165). In predominant mania subgroup, LSMD in YMRS total score change from baseline was significant for cariprazine 3-12 mg/d versus placebo (-4.65 [-6.29, -3.02], *P*<.0001); in subgroup without predominant mania, the LSMD for cariprazine versus placebo was also significant (-7.56 [-10.30, -4.82], *P*<.0001).
Importance. Cariprazine was efficacious in treating BP-I mood episodes regardless of predominant polarity for the presenting mood episode. Cariprazine was effective against symptoms of depression in patients with BP-I depression with/without predominant depressive episodes, and against symptoms of mania in patients with BP-I mania with/ without predominant manic episodes.
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Efficacy of KarXT (Xanomeline Trospium) in Schizophrenia: Pooled Results From the Randomized, Double-Blind, Placebo-Controlled EMERGENT Trials

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Introduction. Prior studies demonstrated the antipsychotic activity of the dual M_1/M_4 preferring muscarinic receptor agonist xanomeline in people with schizophrenia and Alzheimer's disease, but its further clinical development was limited primarily by gastrointestinal side effects. KarXT combines xanomeline and the peripherally restricted muscarinic receptor antagonist trospium chloride. KarXT is designed to preserve xanomeline's beneficial central nervous system effects while mitigating side effects due to peripheral muscarinic receptor activation. The efficacy and safety of KarXT in schizophrenia were demonstrated in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials.
Methods. The EMERGENT trials randomized people with a recent worsening of positive symptoms warranting hospitalization, Positive and Negative Syndrome Scale (PANSS) total score ≥80, and Clinical Global Impression–Severity (CGI-S) score ≥4. KarXT dosing (xanomeline/trospium) started at 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID. In each trial, the primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Other efficacy measures included change from baseline to week 5 in PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores. Data from the EMERGENT trials were pooled, and efficacy analyses were conducted in the modified intent-to-treat population, defined as all randomized participants who received ≥1 trial drug dose and had a baseline and ≥1 postbaseline PANSS assessment.
Results. The pooled analyses included 640 participants (KarXT, n=314; placebo, n=326). Across trials, KarXT was associated with a significantly greater reduction in PANSS total score at week 5 compared with placebo (KarXT, -19.4; placebo, -9.6 [least squares mean (LSM) difference, -9.9; 95% CI, -12.4 to -7.3; *P*<0.0001; Cohen's *d*, 0.65]). At week 5, KarXT was also associated with a significantly greater reduction than placebo in PANSS positive subscale (KarXT, -6.3; placebo, -3.1 [LSM difference, -3.2; 95% CI, -4.1 to -2.4; *P*<0.0001; Cohen's *d*, 0.67]), PANSS negative subscale (KarXT, -3.0; placebo, -1.3 [LSM difference, -1.7; 95% CI, -2.4 to -1.0; *P*<0.0001; Cohen's *d*, 0.40]), PANSS

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