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

Inder Kaul, MD, MPH[1], Leslie Citrome, MD, MPH[2], Sharon Sawchak, RN[1], Judith Kando, PharmD[1], Andrew C. Miller, PhD[1], Steven M. Paul, MD[1] and Stephen K. Brannan, MD[1]

[1]Karuna Therapeutics, Boston, MA and [2]New York Medical College, Valhalla, NY

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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Marder negative factor (KarXT, -3.8; placebo, -1.8 [LSM difference, -2.0; 95% CI, -2.8 to -1.2; P<0.0001; Cohen's d, 0.42]), and CGI-S scores (KarXT, -1.1; placebo, -0.5 [LSM difference, -0.6; 95% CI, -0.8 to -0.4; P<0.0001; Cohen's d, 0.63]).

Conclusions. In pooled analyses from the EMERGENT trials, KarXT demonstrated statistically significant improvements across efficacy measures with consistent and robust effect sizes. These findings support the potential of KarXT to be first in a new class of medications to treat schizophrenia based on muscarinic receptor agonism and without any direct dopamine D_2 receptor blocking activity.

Funding. Karuna Therapeutics

A Review of the Delivery Technologies used in Attention-Deficit/Hyperactivity Disorder Stimulant Medications

Andrew J Cutler, MD[1] and Jacob Hanaie, PharmD, APh[2]

[1]SUNY Upstate Medical University, Lakewood Ranch, FL and [2]Kedren Acute Psychiatric Hospital & Community Mental Health Center and University of Southern California, Los Angeles, CA

Introduction. Multiple pharmaceutical technologies have been developed over the years and applied in the Attention-Deficit/Hyperactivity Disorder (ADHD) treatment space. While the base drugs are either the same or similar, these technologies lead to differences in the medications' properties – including mechanism of release, timing of active drug release, and pharmacokinetic profiles. The technology differences also bring up clinical considerations applicable to patients, including delayed- or extended-release properties so that once daily dosing can be achieved.

This review seeks to make side-by-side comparisons of the technical features of the different technologies used in ADHD medications, not an efficacy comparison. The publication will focus on stimulant medications that use methylphenidate or amphetamine formulations. Gaining an understanding of the technologies' properties and their implications will help clinicians to make more informed decisions when developing their patients' treatment plans to fit their individual needs, and potentially improve adherence.

Methods. Sources including published literature, company websites, filed patents, and prescribing information were reviewed to extract data on the technology used for different ADHD medications. The comparison of the technology in ADHD medications included the drug delivery system, mechanism of drug release, and technology components such as use of resins, beads, complexes, coating or layers. Special considerations that come from these properties were elucidated and framed into a broader clinical context.

Results. Although the medications evaluated were all stimulants containing methylphenidate or amphetamine as the active ingredient, they vary significantly in the technology used to deliver medication to patients. Differences in the technologies used to deliver the stimulants are significant and provide the platform to meet individual patient needs. This side-by-side comparison, describing the specific features and benefits of each technology, will better inform prescribers, leading to better treatment of patients' ADHD.

Conclusions. Clarifying the technologies available among ADHD pharmacotherapies and discussing their implications on patient care may help healthcare professionals better understand the treatment landscape and assist them in clinical decision-making for appropriate ADHD treatment. Knowledge of the mechanism of the technology could improve patients' medication adherence. Additionally, understanding the applications of the technology could also benefit research and clinical programs.

Funding. Tris Pharma

Efficacy of Viloxazine ER (Qelbree) for ADHD in Adults Based on Prior Stimulant Exposure

Greg Mattingly[1,2,3], Joel Young[4,5], Jami Earnest[6], Jennifer Koch[6], Peibing Qin[6] and Jonathan Rubin[6]

[1]St. Charles Psychiatric Associates, St. Charles, MO; [2]Washington University, St. Louis, MO; [3]ADHD Professional Society for ADHD and Related Disorders, Brentwood, TN; [4]Rochester Center for Behavioral Medicine, Rochester, MI; [5]Wayne State University School of Medicine, Detroit, MI and [6]Supernus Pharmaceuticals, Inc., Rockville, MD

Introduction. Although many patients respond equally well to both stimulant and nonstimulant medications for ADHD, some patients respond preferentially to one class over another. Currently, most patients receive a stimulant as first-line therapy; however, nonstimulants present fewer obstacles for prescribers and patients and have low abuse/misuse potential. Still, when patients have suboptimal response to stimulants, physicians may be reticent to switch to a nonstimulant medication due to concerns that the nonstimulant response will be less robust or less preferable for patients. Viloxazine ER (viloxazine extended-release capsules; Qelbree®) is a nonstimulant, FDA-approved treatment for ADHD in children (≥6 years) and adults. This post-hoc analysis of adult Phase 3 trial data (NCT04016779) evaluates response to viloxazine ER (200-600 mg/day) based on whether or not patients reported a history of previous stimulant use.

Methods. For patients randomized to viloxazine in this Phase 3, double-blind, placebo-controlled trial, the change from baseline (CFB) in Adult ADHD Investigator Symptom Rating Scale (AISRS) score (primary trial outcome) was analyzed for prior stimulant users vs. nonusers using MMRM. Prior stimulant use was based on patient-reported medication history recorded upon enrollment. Subjects using stimulants at the time of study screening were required to undergo a ≥1-week washout period prior to randomization.

Results. Of 372 patients treated, 189 received viloxazine ER. Of the patients who received viloxazine ER, 40 reported prior stimulant use and 149 did not. Mean (SD) baseline AISRS scores for prior stimulant users and nonusers were 38.5 (7.40) and 38.3

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