**Methods.** Patients were randomized to placebo + ADT (n=254), cariprazine 1.5 mg/d + ADT (n=252), or cariprazine 3 mg/d + ADT (n=253) for 6 weeks of double-blind treatment. Post hoc analyses evaluated change from baseline to week 6 in MADRS total score in subgroups of patients who had ≥25%–<50% or <25% response to ongoing ADT at baseline, and in subgroups of patients who had inadequate response to 1 or ≥2 ADTs in the current episode. Analyses used a mixed-effects model for repeated measures; least squares mean differences (LSMD) versus placebo with 95% confidence interval (95% CI) were calculated.

**Results.** At baseline, 65.1% (n=486) of patients had an ADT response level between 25%–<50% and 34.9% (n=261) of patients had an ADT response level <25%. Mean MADRS total score reductions were greater for cariprazine 1.5 mg/d + ADT versus placebo + ADT in both ADT response subgroups (25%–<50% ADT response: -14.8 vs -11.9, LSMD [95% CI]=-2.3 [-4.2, -0.3]; <25% response to ADT: (-14.7 vs -11.7, LSMD [95% CI]=-2.6 [-5.5, 0.3]). For cariprazine 3 mg/d + ADT, mean change in MADRS total score was numerically greater versus placebo in both response subgroups (25%–<50% response=-14.2, LSMD [95% CI]=-1.5 [-3.5, 0.4]; <25% response= -12.3, LSMD [95% CI]=-0.74 [-3.6, 2.1]). Approximately 86% (n=644) and 14% (n=105) of patients in this study had inadequate response to 1 ADT or ≥2 ADTs, respectively, during the current episode. The LSMD (95% CI) in MADRS total score change for cariprazine 1.5 mg/d + ADT versus placebo + ADT was -2.3 (-4.1, -0.6) in the subgroup of patients with 1 previous ADT and -3.2 [-7.1, 0.8]) in the subgroup of patients with ≥2 previous ADTs. For cariprazine 3 mg/d + ADT, the LSMD (95% CI) in MADRS total score change versus placebo was -0.7 (-2.5, 1.0) in the 1 previous ADT subgroup and -4.7 (-8.8, -0.6) in the ≥2 previous ADTs subgroup.

**Conclusions.** In these post hoc analyses, cariprazine + ADT was associated with greater reductions in MADRS total score versus placebo regardless of the level of response to ongoing ADT at baseline or number of prior ADT failures in the current episode.

# Categorical Improvement in Depressive Symptom Severity: Results From a Randomized Controlled Trial of Cariprazine for Adjunctive Treatment of MDD

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## Abstract

**Background.** Patients with major depressive disorder (MDD) often do not respond to antidepressant (ADT) monotherapy alone and may require adjunctive treatment to provide adequate symptom relief. Cariprazine (CAR) is a dopamine $D_3$-preferring $D_3/D_2$ and serotonin 5-HT$_{1A}$ receptor partial agonist approved to treat adults with schizophrenia and manic, mixed, or depressive episodes of bipolar I disorder. Post hoc analysis of data from a randomized controlled trial evaluated clinically relevant improvements in depressive symptom severity with adjunctive cariprazine in patients with MDD and inadequate response to ADT monotherapy.

**Methods.** Post hoc analysis evaluated data from a randomized, double-blind, placebo-controlled MDD trial (NCT03738215) in patients treated with CAR (1.5 mg/d or 3 mg/d) + ADT or placebo + ADT; the primary outcome was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Post hoc analysis evaluated category shifts from baseline to week 6 in MADRS severity (normal <6, mild 7–19, moderate 20–34, severe ≥35). MADRS severity shifts were reported as the percentage of patients with no change or worsened severity, 1 category improvement, ≥1 category improvement, and ≥2 category improvement. Examples of categorical shifts in depressive symptoms at week 6 include change from severe at baseline to moderate (1 category improvement) and change from severe at baseline to mild (2 category improvement).

**Results.** Of the 751 patients in the intent-to-treat (ITT) population (CAR: 1.5 mg/d=250, 3.0 mg/d=252; placebo=249), baseline MADRS severity was mild in 1.5%, moderate in 64%, and severe in 35%. Fewer CAR + ADT patients compared to placebo + ADT had no change or worsened MADRS severity at week 6 (CAR: 1.5 mg/d=32%, 3.0 mg/d=33%; placebo=42%). Approximately 68% of patients treated with CAR + ADT demonstrated a MADRS severity improvement of 1 category or greater by week 6 (CAR: 1.5 mg/d=68%, 3.0 mg/d=67%; placebo=58%). A greater percentage of patients in the CAR 1.5 mg/d group also had a 2 or greater category improvement versus CAR 3.0 mg/d or placebo 6 (CAR: 1.5 mg/d=28%, 3.0 mg/d=17%; placebo=19%).

**Conclusions.** In this post hoc analysis, CAR + ADT was associated with a greater proportion of patients with improvements in depressive symptom severity categories compared with placebo + ADT. These results may suggest that CAR + ADT is associated with clinically meaningful depressive symptom improvement in MDD patients.

# Vilazodone-Induced Glycolimia

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## Abstract

**Introduction.** Glycolimia is observed in a plethora of medical conditions including burning mouth syndrome, opioid withdrawal, as well as from a variety of medications including vortioxetine, l-methylfolate, lisdexamfetamine, and gabapentin. While vilazodone, an antidepressant with agonist like effects on 5-HT1A receptors, has been found to induce hyperglycemia, it has not heretofore been reported to induce glycolimia. Such a case is described.

**Method.** Case study: A 60-year-old, left-handed (pathological) male presented with a past history of depression, minimally

responsive to a variety of antidepressant medications, was begun on vilazodone, initially 20 mg and gradually increased to 60 mg a day. On 60 mg a day he noticed severe cravings for sweets, which he had never experienced prior to starting vilazodone. He found he had increased consumption, craving sweet foods including cookies and candy. For instance, in a typical day, he would eat eight Oreos, chocolate-covered graham crackers, one pint of ice cream a day, and he would crave sweets even after feeling satiated after consuming a meal. Along with this increased eating, he gained 20 pounds over the 3 months while on the vilazodone. Upon discontinuing the vilazodone, although the weight didn't change, the sweet cravings resolved.

**Results.** Abnormalities on: Neurological examination: Mental status examination: Immediate recall: able to remember 6 digits forwards and 3 digits backwards. Motor examination: Drift testing: right inward drift. Gait examination: unstable tandem gait. Neuropsychiatric examination: Go-No-Go test: 6/6 (normal). Animal Fluency Test: 22 (normal).

**Discussion.** There are myriad mechanisms whereby vilazodone may have induced glycolimia. Possibly due to its antidepressant effects, it increased hedonics, generating appetitive behaviors, including enhanced socialization, sexual, and other consumptive behaviors, including eating. Peradventure it may have enhanced motivation and socialization. Along with socialization, there is escalation in social intercourse, with accompanying commensalism. Along with such consumptive behaviors, we could anticipate glycolimia. As a 5-HT1A receptor agonist, possibly vilazodone may have acted on the arcuate pro-opiomelanocortin neurons associated with hyperphagia, with modulation of energy homeostasis in the serotonin pathway. Alternatively, vilazodone may have triggered an enhanced insulin response with secondary reduction in blood sugar, leading to a homeostatic behavioral response of increased glucose intake. In those who are treated with vilazodone, query as to glycolimia is warranted and warning as to potential manifestations of hyperglycemia should be entertained.

# Population Pharmacokinetic-Pharmacodynamic Modeling of Variable Wear Times for a Dextroamphetamine Transdermal System

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**Abstract**

**Introduction.** The Dextroamphetamine Transdermal System (d-ATS) was developed as an alternative to oral amphetamine (AMP) formulations for ADHD. In a pivotal study, d-ATS met primary and secondary efficacy endpoints for ADHD in children and adolescents. Study subjects wore d-ATS for 9 hours, and an improvement in Swanson, Kotkin, Agler, M-Flynn, and Pelham scale (SKAMP) total score was observed from 2 through 12 hours after application. Patients with ADHD may need varying durations of treatment for symptoms from day to day. This analysis describes the exposure-response (E-R) relationship for d-ATS and explores possible outcomes for wear times ≤9 hours under varying assumptions.

**Methods.** A population pharmacokinetic (PK) model was developed to describe AMP disposition following d-ATS administration. This model was used to construct a population pharmacokinetic/pharmacodynamic (PK/PD) model from SKAMP total score data from two pediatric clinical studies to characterize onset and duration of effect after d-ATS administration. The integrated PK/PD model was used to describe the d-ATS E-R relationship and simulate the potential onset and duration of effect of d-ATS in response to various removal times (when <9 hours) by utilizing SKAMP scores as the efficacy measure. Subject-level AMP PK and SKAMP profiles were simulated for d-ATS removal at 4–9 hours post-application under different assumptions for AMP absorption after early patch removal. Modifications were made to the original population PK model to simulate patch removal.

**Results.** Data from 81 children and 41 adolescents, 6–17 years old, were included. The model provided a reasonable description of the SKAMP score over time, showing an initial decline ~2 hours after patch application. In approximately 50% of children and adolescents, the maximum decline in SKAMP scores was observed within the first 4 hours after patch application. Earlier simulated d-ATS removal times were associated with reduced systemic exposure and earlier return to near-baseline scores across the range of assumptions tested.

Under different assumptions, the graphs changed modestly but not dramatically. For example, with moderate/conservative assumptions, following a 9-hour wear time, SKAMP scores returned to within 90% of baseline value in ~49% of subjects by 12 hours and ~80% of subjects by 16 hours. Following a 4-hour wear time, percentages were ~74% by 12 hours and ~95% by 16 hours.

**Conclusions.** Simulation results suggest that the duration of d-ATS efficacy may be related to wear time, which can be adjusted according to treatment needs, consistent with published observations for another transdermal stimulant. The d-ATS patch provides the ability to control medication exposure by shortening wear time, allowing treatment duration to be individualized and optimized in ADHD patients who have varying schedules and needs.

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