# Evaluation of Dermal Irritation with the Dextroamphetamine Transdermal System (d-ATS) in Healthy Adults and Patients with ADHD

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**Background.** The d-ATS patch was developed as an alternative to oral amphetamine formulations for attention-deficit hyperactivity disorder (ADHD). The US Food & Drug Administration (FDA) recommends evaluating irritation of transdermal patches under intended (rotating application sites) and exaggerated use (repeated application to one site). These studies assessed irritation after d-ATS application.

**Methods.** *Intended Use:* In **Study 1**, adults with ADHD, d-ATS was applied daily (9-hour application) for 4 weeks rotated between 5 sites (left/right: hip, flank, chest, upper arm, upper back), with irritation assessed on Days 1, 7, 14, 27, and 28. In **Study 2**, children and adolescents with ADHD, d-ATS was applied daily (9 hours) for 5 weeks to the hip (left or right), with irritation assessed daily.

*Exaggerated Use:* In **Study 3**, adults with ADHD, d-ATS was applied daily (9 hours) to the hip (repeated application to one site) for 4 weeks, with irritation assessed daily. In **Study 4**, healthy adults, 1 d-ATS and 1 placebo patch were applied daily (24 hours) for 21 days to the back (repeated application to 1 site), with irritation assessed daily.

Irritation was assessed by a trained evaluator 30-60 min after patch removal using Berger and Bowman Dermal Response (0-7, with 7 being the worst reaction) and Other Effects (0-3, with 3 being the worst reaction) scores. Dermal Response and Other Effects scores were added together for the combined score. A combined score of ≥3 was considered clinically meaningful irritation.

**Results.** *Intended Use:* In Study 1 (N=15), meaningful irritation after patch removal was reported in 9/15 subjects (60%). The mean (SD) combined score was 1.05 (0.21), with no treatment-emergent adverse events at the application site. In Study 2 (N=110), all combined irritation scores were ≤3 for d-ATS, with a combined score of 3 reported by 2% of patients. There were no discontinuations due to dermal reactions in either study.

*Exaggerated Use:* In Study 3 (N=20), meaningful irritation was reported in 19/20 subjects (95%). The mean (SD) combined score was 1.63 (0.78). In Study 4, mean (SD) combined scores were 2.1 (0.73) for d-ATS and 1.3 (0.69) for placebo (N=206 for both), with no discontinuations due to dermal reactions.

**Conclusions.** These results support previous findings that d-ATS is safe and well tolerated for ADHD. After intended use, irritation was minimal and did not cause study discontinuations.

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# Cariprazine as Adjunctive Treatment for Major Depressive Disorder: Benefit and Risk Assessment Using Number Needed to Treat and Number Needed to Harm

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**Purpose.** This post hoc analysis investigated efficacy and tolerability of adjunctive cariprazine (CAR) in patients with major depressive disorder (MDD) using evidence-based medicine metrics of number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

**Methods.** Data sources were five completed Phase II/III, 6-8 week, randomized, double-blind, placebo-controlled studies. Efficacy outcomes included acute response (≥50% decrease from baseline on the Montgomery-Åsberg Depression Rating Scale [MADRS] total score). Tolerability outcomes included commonly occurring adverse events (AEs) and rates of discontinuation because of an AE, with data pooled across all studies for the CAR 1-2 mg/day plus 1.5 mg/day dose groups, 2-4.5 mg/day plus 3 mg/day dose groups, and for all groups where CAR dose was ≥1 mg/day. NNT and NNH were calculated for adjunctive CAR vs. adjunctive placebo.

**Results.** MADRS response rates at Week 8 for CAR 2-4.5 mg/day vs. placebo were 134/271 (49.4%) vs. 101/264 (38.3%), resulting in a NNT of 9 (95% CI 6-36). In study NCT03738215, MADRS response rates at Week 6 for CAR 1.5 mg/day vs. placebo were 110/250 (44.0%) vs. 87/249 (34.9%), resulting in a NNT of 11 (95% CI 6-193). For the pooled CAR ≥1 mg/day group, MADRS response rates at Week 6 were 765/1887 (40.5%) for CAR vs. 354/1101 (32.2%) for placebo, resulting in a NNT of 12 (95% CI 9-21). For the pooled CAR ≥1 mg/day group, rates of akathisia vs. placebo were 209/1893 (11.0%) vs. 25/1108 (2.3%) for placebo, resulting in a NNH of 12 (95% CI 10-14). This appears dose related as the NNH for akathisia vs. placebo was 24 (95% CI 17-43) for the 1-2 mg/day plus 1.5 mg/day dose groups, and 9 (95% CI 7-11) for the 2-4.5 mg/day plus 3 mg/day dose groups. For the pooled CAR ≥1 mg/day group, rates of discontinuation because of an AE vs. placebo were 122/1893 (6.4%) vs. 26/1108 (2.3%) for placebo, resulting in a NNH of 25 (95% CI 19-38). This appears dose related as the NNH for discontinuation because of an AE vs. placebo was 94 (ns) for the 1-2 mg/day plus 1.5 mg/day dose groups, and 17 (95% CI 13-28) for the 2-4.5 mg/day plus 3 mg/day dose groups. For the pooled CAR ≥1 mg/d group, rates of weight gain ≥7% from baseline vs. placebo were 35/1893 (1.8%) vs. 12/1108 (1.1%) for placebo, resulting in a NNH of 131 (ns). LHH comparing MADRS response vs. discontinuation because of an AE is >1, and >>1 for the lower dose range. Indirect comparisons of the above results with that of the effect sizes seen in positive studies of other adjunctive antipsychotic treatments vs. adjunctive placebo in MDD demonstrate similar values for NNT for response, and

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