Dose-finding Study of Abuse-Related Effects of Intranasal d-Methylphenidate in Recreational Stimulant Abusers

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BACKGROUND
- Prescription stimulants such as d-amphetamine and methylphenidate (racemic or single d-isomeric forms) produce a range of dose-dependent behavioral and neurobehavioral effects, including increased attention, and enhanced mood/moodlift.
- Nonmedical use (defined as use of a prescription stimulant without the advice of a physician) in recreational stimulant abusers between 18 and 50 years of age.
- Motives for nonmedical use of prescription stimulants include: to feel good/get high, to enhance alertness/day awake, to enhance performance, and/or to experiment (Teter 2006; Cassidy 2015).
- Individuals who abuse stimulants for their reinforcing effects (i.e., to get “high”) tend to prefer a rapid onset (short Tmax) of high concentrations (high Cmax) of drug, a profile that can be achieved with intranasal (IN) administration, among other nonoral routes (Parasuraman 2007; Spencer 2006; Stoops 2003).
- Amphetamines (e.g., d-amphetamine and d-methylphenidate) produce a range of dose-dependent neurobehavioral effects, including increased alertness, increased attention, and enhanced mood/moodlift.

OBJECTIVE
- To determine the optimal intranasal dose of d-methylphenidate (d-MPH) that produces significant psychostimulant effects while minimizing potentially aversive effects that are associated with higher doses of stimulants.

METHODS
Study design and subjects
- There was a Phase 1 study, single-dose, dose-finding study to determine the human abuse potential of intranasal d-MPH API in healthy, recreational stimulant abusers.
- Subjects (N=6) received one of the following intranasal treatments in a randomized 3-period, crossover design separated by a minimum 24-hour washout period:
  - Treatment A: 20 mg d-MPH API powder + 80 mg microcrystalline cellulose (MCC)
  - Treatment B: 40 mg d-MPH API powder + 60 mg MCC
  - Treatment C: 60 mg d-MPH API powder + 40 mg MCC
- Eligible subjects were males or non-pregnant female recreational stimulant abusers between 18 and 50 years of age.
- Subjects must have had 0-10 stimulant drug injections (e.g., amphetamines, cocaine, and MPH), 2) used any stimulant (including cocaine) at least 5 times within the last 6 months prior to the Screening visit, 3) used cocaine within 6 months prior to Screening, and 4) inhaled stimulant drugs within 12 weeks prior to Screening.
- Written informed consent was obtained. The study was approved by an Institutional Review Board (IRB) and the study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonisation (ICH) GCP Guidelines for Good Clinical Practice.

Pharmacodynamic Assessments and Analyses
- Visual Analog Scale (VAS) measures of Drug Liking (“Do you like the drug effect you are feeling now?”) were performed at 5 minutes post dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4.5, 6, 8 hours post dose in each treatment period (study Days 1-5).
- VAS measures for Drug Liking were scored on a bipolar scale of 0-100 points (FDA 2017), where 0 = Not at All and 100 = Extremely.
- VAS measures for Good Effects and Bad Effects were scored on a unipolar scale of 0-100 points (FDA 2017), where 0 = Not at All and 100 = Extremely.
- Maximal effect (Emax) = time to maximal effect (Tmax) and partial and total area under the effect curve (AUCt) across each treatment (AUCt, where I included all times post-dose at which the effect was calculated for each parameter).
- Safety assessments, including adverse events (AEs), vital signs, heart rate, respiratory rate, ECGs, and continuous cardiac telemetry were performed throughout the study.

RESULTS
Subject Disposition and Demographics
- Six subjects (5 male and 1 female) were enrolled and completed all 3 treatments.
- The most commonly used prior stimulant was cocaine, used by all 6 subjects within the past 6 months (range of 10.5, 2.5,1 times) and subjects lifetimes a median (range) of 100 (20, 300) times.

Pharmacodynamic Assessments
- Figures 1 and 2 show dose-finding study of Drug Liking (biologic scale) and Good Effects (unipolar scale) VAS scores, respectively, across 8 hours post-dose for 20-, 40-, and 60-mg doses.
- Drug Liking and Good Effects scores for all doses increased rapidly and peaked within the first hour post-dose and decreased to neutral scores (~50) by 3 hours post-dose.
- Drug Liking VAS scores fell below 4.5 at 2 hours for all 40- (range: 20 mg: n = 60, 40 mg: n = 60, 60 mg: n = 60) mg of dose for the interval, 33.7-42.2) doses.
- Consistent with these scores (i.e., ~50) indicating at least some drug disliking.

Table 1. Descriptive statistics for derived parameters of Drug Liking VAS, Good Effects VAS, and Bad Effects VAS are summarized in Table 1 and Maximal (Emax) VAS scores are depicted graphically in Figure 4.

Table 2. Table 2. Pharmacokinetic parameters of IN d-MPH 20 mg (N=6) and 40 mg (N=6) HCl.

CONCLUSIONS
In recreational stimulant abusers, IN d-MPH HCI produced abuse-related effects that were dose- and time-dependent.
- 20 mg d-MPH HCI produced an optimal balance of Drug Liking/Good Effects and Bad Effects, and therefore was selected as a positive control in the evaluation of the IN human abuse potential of serdexmethylphenidate, a novel prodrug of d-MPH being developed for the treatment of ADHD.
- These findings replicate and extend the limited data reported previously on the abuse-related effects of IN d-MPH.
- These exploratory findings have limitations, including the lack of a direct dose-comparison phase to assess which subjects were able to reliably discern stimulant-like effects from placebo via the IN route, the lack of an active IN comparison during the Treatment Phase, and the small number of subjects enrolled.

Disclosures
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References