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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 neurobehavioral effects, including increased alertness, increased attention, and enhanced mood/euphoria
- Nonmedical use (defined as any use of a prescription stimulant without the advice of a physician) of prescription stimulants has been reported in:
  - 8.1% of adults in a random sample of 10,000 individuals in the United States (Cassidy 2015)
  - 16.7% of adolescents in a nationally representative sample of high school seniors (McCabe 2017)
- Motives for nonmedical use of prescription stimulants include: to feel good/ get high, to enhance alertness/stay 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 T_{max}) of high concentrations (high C_{max}) of drug, a profile that can be achieved with intranasal (IN) administration, among other non-oral routes (Parasrampuria 2007; Spencer 2006; Stoops 2003)
- In abusers of prescription methylphenidate (MPH) products, approximately 40% report IN administration (Cassidy 2015)
- Despite these epidemiological findings, there is a paucity of human laboratory data on the range of doses of IN d-MPH that engender abuse-related effects (Stoops 2003)
  - Such data are important for interpreting epidemiological findings and for evaluating the abuse potential of other stimulant or stimulant-like therapies

OBJECTIVE

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

METHODS

Study design and subjects

- This was a Phase 1, double-blind, single-dose, dose-finding study to determine the human abuse potential of intranasal administration of d-MPH API in healthy, recreational stimulant users
- Subjects (N=6) received all 3 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 male or non-pregnant female recreational stimulant abusers between 18 and 50 years of age
- Subjects must have: 1) had ≥10 lifetime experiences with CNS stimulants (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) insufflated stimulant drugs within 12 weeks prior to Screening
- Written informed consent was obtained. The study protocol 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) E6 Guideline for Good Clinical Practice

Pharmacodynamic Assessments and Analyses

- Visual Analog Scale (VAS) assessments of Drug Liking ("Do you like the drug effect you are feeling now?"), Good Effects ("Does the Drug have Good Effects?"), and Bad Effects ("Does the Drug have Bad Effects?") were performed at 5 minutes post dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4.5, 6, and 8 hours post-dose in each treatment period (study Days 1-3)
- VAS measures for Drug Liking were scored on a bipolar scale of 0-100 points (FDA 2017), where 0 = Strong Disliking, 50 = Neither Like nor Dislike, and 100 = Strong Liking
- 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 (E_{max}), time to maximal effect (TE_{max}), and partial and total area under the effect curves ($AUE_{0\text{-}t}$, where t included all times post-dosing at which the assessments were 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
- As this was a pilot, dose-finding study, no formal sample size calculations were performed and all statistical comparisons were deemed exploratory

RESULTS

Subject Disposition and Demographics

- Six subjects (5 male) were were enrolled and dosed, and completed all 3 treatments
- The most commonly used prior stimulant was cocaine, used by all 6 subjects within the past 6 months a median (range) of 10.5 (5, 25) times and over subjects' lifetimes a median (range) of 100 (20, 300) times

Pharmacodynamic Assessments

- **Figures 1** and **2** show mean Drug Liking (bipolar scale) and Good Effects (unipolar scale) VAS scores, respectively through 8 hours post-dose for 20-, 40-, and 60-mg IN d-MPH
- Drug Liking and Good Effects scores for all doses increased rapidly and peaked within the first hour post-dose and declined to neutral scores (~50) by 3 hours post-dose
- Drug Liking VAS scores fell below 50 from 4.5 h to 8 h post-dose for the 40-mg (range of means over this interval, 43.2-46.8) and 60-mg (range of means over this interval, 33.7-42.2) doses
- Consistent with these scores (i.e., <50) indicating at least some drug disliking, Bad Effects (unipolar scale) were reported across the dose range studied (**Figure 3**)
  - Bad Effects were dose-dependent and most pronounced with the 60-mg dose (mean E_{max} = 41.2). and peaked somewhat later (between 1.5 and 3 h) than Drug Liking and Good Effects

Figure 1. Drug Liking VAS scores following IN administration of d-MPH HCl

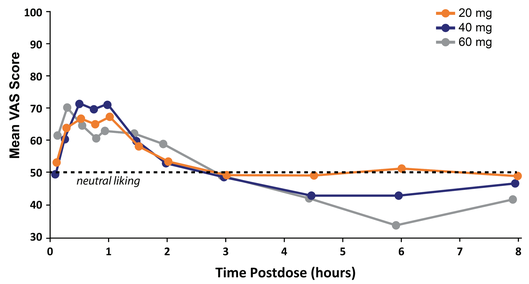


Figure 2. Good Effects VAS scores following IN administration of d-MPH HCl

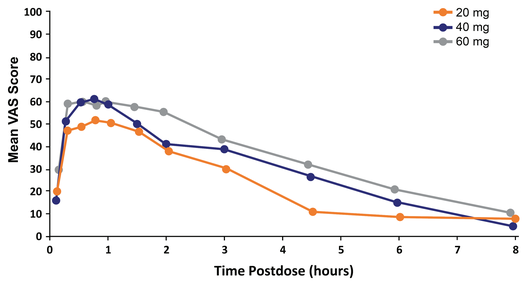
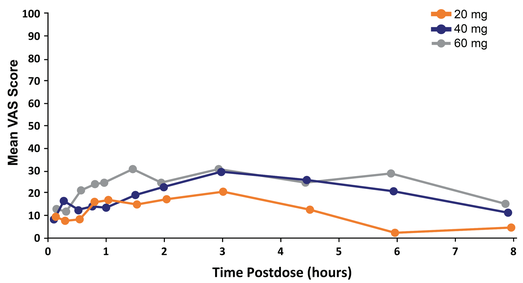


Figure 3. Bad Effects VAS scores following IN administration of d-MPH HCl

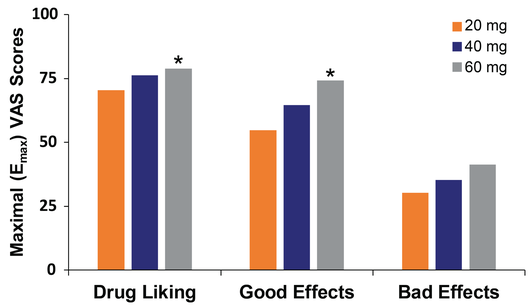


- Descriptive statistics for derived parameters of Drug Liking VAS, Good Effects VAS, and Bad Effects VAS are summarized in **Table 1** and Maximal (E_{max}) VAS scores are depicted graphically in **Figure 4**

Table 1. Descriptive statistics for pharmacodynamic parameters of Drug Liking, Good Effects and Bad Effects following IN administration of d-MPH HCl

Endpoint Mean (SD)	20 mg (N=6)	40 mg (N=6)	60 mg (N=6)
Drug Liking			
E_{max}	70.3 (16.0)	76.3 (16.2)	78.8 (17.2)
TE_{max} (h)	0.7 (0.5)	0.7 (0.3)	0.8 (0.7)
$AUE_{0\text{-}8h}$	25.5 (70.6)	2.5 (124.1)	-18.7 (189.2)
Good Effects			
E_{max}	54.8 (32.2)	64.5 (31.2)	74.2 (24.3)
TE_{max} (h)	0.8 (0.4)	0.8 (0.3)	0.9 (0.7)
$AUE_{0\text{-}8h}$	179.9 (164.7)	237.9 (191.8)	284.2 (220.2)
Bad Effects			
E_{max}	30.3 (28.8)	35.3 (24.3)	41.2 (32.8)
TE_{max} (h)	2.2 (1.7)	3.4 (2.7)	3.6 (2.3)
$AUE_{0\text{-}8h}$	78.0 (103.8)	159.9 (131.0)	190.2 (181.9)

Figure 4. Maximal (E_{max}) VAS scores for pharmacodynamic endpoints following IN administration of d-MPH HCl



* significant difference (p<0.05) between 60- and 20-mg doses
Note: Drug Liking assessed on a bipolar scale where where 0 = Strong Disliking, 50 = Neither Like nor Dislike, and 100 = Strong Liking. Good Effects and Bad Effects assessed on a unipolar scale where 0 = Not at All and 100 = Extremely.

- Pharmacodynamic effects were generally dose-dependent for each of the subjective assessments
- Exploratory statistical comparisons indicated significant differences between the 20-mg and 60-mg dose mean Drug Liking E_{max} (70.3 vs. 78.8, LS mean difference [95% CI] = 8.5 [1.4, 15.6], p=0.0246) and mean Good Effects E_{max} (54.8 vs. 74.2, LS mean difference [95% CI] = 19.3 [8.3, 30.3], p=0.0037)
- Bad Effects were most pronounced with the 60-mg dose (mean E_{max} = 41.2). Bad Effects peaked somewhat later (between 1.5 and 3 h) compared with Drug Liking and Good Effects

Adverse Events

- **Table 2** shows that treatment-emergent adverse events were generally dose-dependent and typical of stimulant administration.
- No serious AEs were reported

Table 2. Treatment-emergent adverse events occurring in ≥2 subjects overall

	d-MPH			
	20 mg (N=6) n (%)	40 mg (N=6) n (%)	60 mg (N=6) n (%)	Overall N=6 n (%)
Nervous System Disorders	2 (33.3)	2 (33.3)	3 (50.0)	5 (83.3)
Headache	2 (33.3)	1 (16.7)	2 (33.3)	4 (66.7)
Psychiatric Disorders	1 (16.7)	3 (50.0)	6 (100.0)	6 (100.0)
Anxiety	0 (0.0)	2 (33.3)	3 (50.0)	4 (66.7)
Restlessness	1 (16.7)	0 (0.0)	3 (50.0)	4 (66.7)
Euphoric mood	0 (0.0)	0 (0.0)	2 (33.3)	2 (33.3)
Hypervigilance	0 (0.0)	2 (33.3)	0 (0.0)	2 (33.3)

CONCLUSIONS

- In recreational stimulant abusers, IN d-MPH HCl produced abuse-related effects that were dose- and time-dependent
- 40 mg d-MPH HCl 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 drug discrimination phase to verify that subjects were able to reliably discern stimulant-like effects from placebo via the IN route, the lack of a placebo control during the Treatment Phase, and the small number of subjects enrolled

Disclosures

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