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# Human Abuse Potential of Intravenous Serdexmethylphenidate (SDX), a Novel Prodrug of d-Methylphenidate, in Recreational Stimulant Abusers

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## BACKGROUND

- Serdexmethylphenidate (SDX) is a prodrug of d-methylphenidate (d-MPH) currently being developed as the major pharmaceutical ingredient in an investigational product for the treatment of ADHD
- When taken orally as intended, SDX produces a gradual onset and extended duration of d-MPH exposure that is imparted by the gradual conversion of the prodrug to active d-MPH (Braeckman 2018)
- Currently available prescription stimulant products containing MPH or amphetamine are Schedule II controlled substances due to their high abuse potential, as evidenced by preclinical and clinical studies (Nielsen 1984; de la Garza 1987; Kollins 2001), and epidemiological findings (Cassidy 2015; McCabe 2017, Burtner 2017)
- Prescription stimulant abusers commonly manipulate oral dosage forms to facilitate non-oral routes of administration (e.g., intranasal, intravenous [IV]) that are associated with a rapid and intense "high" (Cassidy 2015; Burtner 2017) and, in turn, chronic abuse and dependence
- Chronic abuse of stimulants, particularly via non-oral routes, can lead to a constellation of health-related problems including cardiovascular and cerebrovascular toxicity, increased likelihood of seizures, increased risk of acquiring blood-borne infections, malnutrition, and miscarriage in pregnant women (Riezzo 2012; Vearrier 2012)
- A comprehensive evaluation of abuse potential is therefore critical for understanding the risk-benefit profile of novel stimulant-like drugs such as SDX

## OBJECTIVES

- To assess the human abuse potential of SDX after a single IV injection and to assess the pharmacokinetics of intact SDX and SDX-derived d-MPH following IV injection

## METHODS

### Study design and subjects

- This was a Phase 1, double blind, single dose, 3 treatment, randomized crossover study of IV administration of SDX API compared with d-MPH HCl API in recreational stimulant users
- Part A (Cohort 1) consisted of a dose escalation phase that determined the optimal IV d-MPH HCl API dose to be used in Part B, based on pharmacodynamic and safety assessments
- In Part B (Cohort 2), subjects who were able to discriminate the optimal dose of IV d-MPH HCl API from placebo were randomized to receive all 3 of the following IV treatments in a randomized, 3-period, crossover design separated by a minimum 72-hour washout period:
  - **Treatment A:** SDX API 30 mg, IV (equivalent to d-MPH HCl, 15 mg, with respect to molar d-MPH)
  - **Treatment B:** d-MPH HCl API 15 mg, IV
  - **Treatment C:** Matching placebo, IV
- Subjects were recreational stimulant users between 18 and 50 years of age with ≥10 lifetime experiences with any stimulant
- Subjects must also have:
  - used stimulants for non-therapeutic purposes ≥5 times within the prior 6 months
  - used cocaine within the prior 6 months
  - had experience with stimulants via a non-oral route of administration
- Written informed consent was obtained. The study protocol was approved by an Institutional Review Board

### Pharmacokinetic Assessments and Analyses

- Blood samples were collected for measurement of plasma concentrations of SDX, d-methylphenidate (d-MPH), l-methylphenidate (l-MPH), and ritalinic acid at pre-dose, at 5 minutes, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 36 hours post-dose
- Primary PK endpoints were maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$), mean systemic exposure ($AUC_{0\text{-}last}$), and mean total systemic exposure ($AUC_{0\text{-}inf}$) (d-MPH only)

### Pharmacodynamic Assessments and Analyses

- At-the-moment, visual analog scale (VAS) assessments were performed at 2 (Drug Liking only) and 5 minutes, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours post dose, and included:
  - Drug Liking ("At this moment, my liking for the drug is?"), assessed on a bipolar, 0-100 point scale, with 0=strong disliking, 50=neither like nor dislike, and 100=strong liking
  - Feeling High ("At this moment, I am feeling high"), assessed on a unipolar, 0-100 point scale, with 0=not at all and 100=extremely
  - Good Effects ("At this moment, I can feel good drug effects"), assessed on a unipolar, 0-100 point scale, with 0=definitely not and 100=definitely yes
- Retrospective VAS assessments, performed 12 and 24 hours postdose, included:
  - Take Drug Again ("I would take this drug again"), assessed on a unipolar, 0-100 point scale, with 0=definitely not and 100=definitely yes
- Pharmacodynamic analyses were performed on the Completers Population, with LS mean or median (as appropriate) differences and associated CIs calculated for each pairwise comparison between treatments
- The primary and key secondary endpoints, Drug Liking $E_{max}$ and Take Drug Again $E_{max}$, respectively, were conducted as one-sided, superiority-type hypothesis tests at a significance level of α=0.05 and reported with 95% confidence intervals (CIs), with margins (δ) defined as shown below:

| Comparison | Null hypothesis ($H_0$) (No difference) | Alternative hypothesis ($H_a$) (Significantly different) |
|---|---|---|
| d-MPH API (B) to Placebo (C) | $\mu_B - \mu_C \leq 15$ (δ1) | $\mu_B - \mu_C > 15$ (δ1) |
| d-MPH API (B) to SDX (A) | $\mu_B - \mu_A \leq 10$ (δ2) | $\mu_B - \mu_A > 10$ (δ2) |
| SDX (A) to Placebo (C) | $\mu_A - \mu_C \geq 11$ (δ3) | $\mu_A - \mu_C < 11$ (δ3) |

- Other secondary endpoints were performed as two-sided, confirmatory hypothesis tests at a significance level of α=0.05 and reported with 95% CIs, with the exception of SDX vs. placebo, which were performed as two-sided hypothesis tests at a significance level of α=0.10 and reported with 90% CI
- Endpoints that were not normally distributed and non-symmetric were analyzed using non-parametric methods

### Safety

- Assessment included incidence adverse events (AEs), physical examination findings, vital signs, electrocardiogram (ECG) parameters, and clinical laboratory tests.

## RESULTS

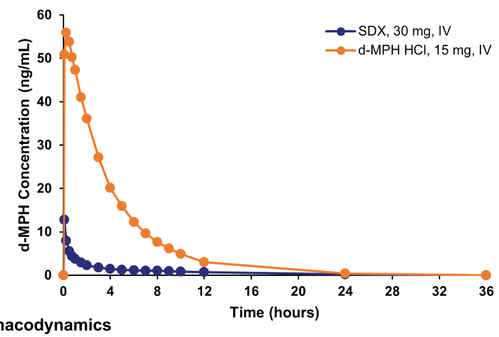
### Subject Disposition and Demographics

- A total of 30 subjects (mean age=32, 80% male) completed all 3 treatment periods and thus comprise the Completer Population

### Pharmacokinetics

- **Figure 1** shows plasma d-MPH concentrations derived from IV SDX and d-MPH HCl
- Peak ($C_{max}$) and overall ($AUC_{inf}$) d-MPH exposure were approximately 21.5% and 12.7% of the exposure observed with d-MPH HCl.

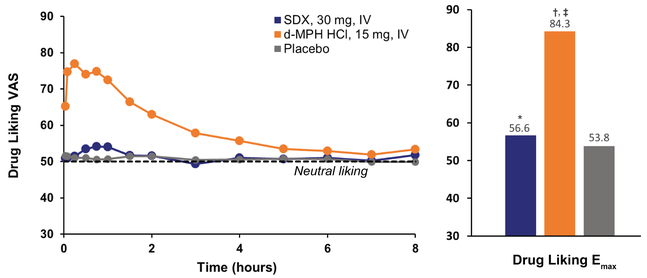
**Figure 1. d-MPH concentrations following IV administration of SDX and d-MPH HCl**




### Pharmacodynamics

- d-MPH HCl produced rapid increases in Drug Liking, with $E_{max}$ scores significantly higher than placebo (LS mean difference [95% CI] = 30.5 [25.9, ∞], p<0.001), thus confirming study validity (**Figure 2**)
- SDX produced little or no increases in Drug Liking scores throughout the testing interval, with $E_{max}$ scores significantly lower than for d-MPH HCl (median difference [95% CI] = 29.0 [22.5, ∞], p=0.001) and non-inferior to placebo (median difference [95% CI] = 0.5 [-∞, 5.5], p=0.001) (**Figure 2**)

**Figure 2. Drug Liking VAS scores over time (left panel) and Drug Liking $E_{max}$ scores (right panel) for IV SDX, d-MPH HCl, and placebo**




* significantly non-inferior to placebo (p=0.001), † significantly higher vs. SDX (p=0.001), ‡ significantly higher vs. placebo (p<0.001)

- Time-dependent VAS scores for Feeling High (**Figure 3**) and Good Effects (data not shown) resembled that for Drug Liking, with d-MPH HCl producing rapid increases in pharmacodynamic effects and SDX producing effects that were generally comparable to placebo
- **Figure 4** shows $E_{max}$ scores for these endpoints and for the retrospective endpoint of Take Drug Again (key secondary endpoint)

**Figure 3. Feeling High VAS scores over time for IV SDX, d-MPH HCl, and placebo**

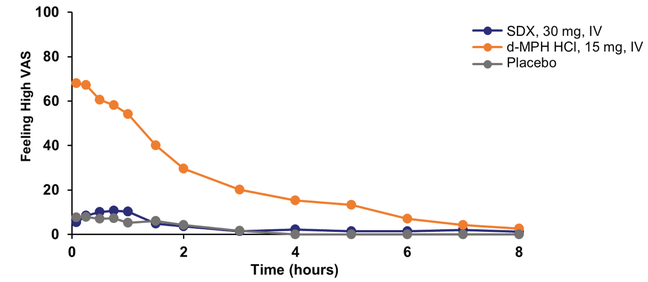
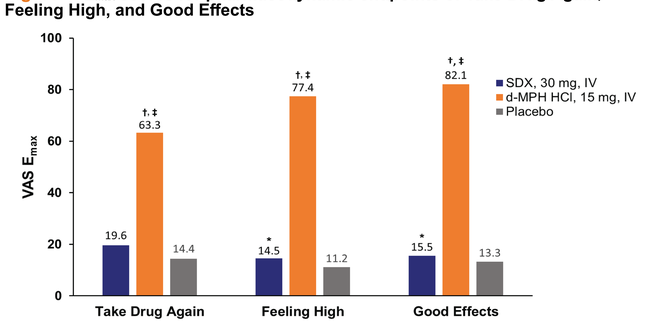



**Figure 4. $E_{max}$ scores for pharmacodynamic endpoints of Take Drug Again, Feeling High, and Good Effects**




Take Drug Again: † significantly higher vs. SDX (p<0.001), ‡ significantly higher vs. placebo (p<0.001)
Feeling High: * statistically similar to placebo (p=0.655), † significantly higher vs. SDX (p<0.001), ‡ significantly higher vs. placebo (p<0.001)
Good Effects: * statistically similar to placebo (p=0.789), † significantly higher vs. SDX (p<0.001), ‡ significantly higher vs. placebo (p<0.001)

### Tolerability and Safety

- **Table 2**, showing the most common AEs during the Treatment Phase, indicates that AEs typical of stimulants (euphoric mood, hypervigilance, heart rate increased) were more common during d-MPH HCl vs. SDX treatment
- There were no clinically significant clinical laboratory values, ECG results, or out-of-range vital signs following IV SDX

**Table 2. Adverse Events Occurring in ≥5% of Subjects in the Treatment Phase of Part B (Safety Population)**

| MedDRA System Organ Class<br>*Preferred Term* | SDX (N=31) | d-MPH HCl (N=30) | Placebo (N=31) |
|---|---|---|---|
| **Cardiac disorders** | | | |
| Palpitations | 0 (0.0) | 2 (6.7) | 0 (0.0) |
| Sinus tachycardia | 0 (0.0) | 4 (13.3) | 0 (0.0) |
| Tachycardia | 0 (0.0) | 4 (13.3) | 0 (0.0) |
| **Gastrointestinal disorders** | | | |
| Dry mouth | 0 (0.0) | 6 (20.0) | 0 (0.0) |
| Nausea | 0 (0.0) | 3 (10.0) | 0 (0.0) |
| **General disorders and administration site conditions** | | | |
| Energy increased | 2 (6.5) | 1 (3.3) | 1 (3.2) |
| Feeling abnormal | 1 (3.2) | 2 (6.7) | 0 (0.0) |
| Feeling hot | 2 (6.5) | 6 (20.0) | 2 (6.5) |
| Feeling jittery | 0 (0.0) | 2 (6.7) | 0 (0.0) |
| Feeling of relaxation | 0 (0.0) | 1 (3.3) | 2 (6.5) |
| **Investigations** | | | |
| Heart rate increased | 0 (0.0) | 5 (16.7) | 0 (0.0) |
| **Nervous system disorders** | | | |
| Headache | 1 (3.2) | 1 (3.3) | 2 (6.5) |
| Paraesthesia | 0 (0.0) | 2 (6.7) | 1 (3.2) |
| Somnolence | 1 (3.2) | 4 (13.3) | 0 (0.0) |
| **Psychiatric disorders** | | | |
| Change in sustained attention | 0 (0.0) | 2 (6.7) | 0 (0.0) |
| Euphoric mood | 4 (12.9) | 17 (56.7) | 2 (6.5) |
| Hypervigilance | 4 (12.9) | 10 (33.3) | 2 (6.5) |
| **Skin and subcutaneous tissue disorders** | | | |
| Hyperhidrosis | 1 (3.2) | 4 (13.3) | 0 (0.0) |

## CONCLUSIONS

- IV administration of the SDX yielded minimal exposure to d-MPH
- Consistent with these findings, IV SDX produced effects that were statistically similar to IV placebo on multiple abuse-related endpoints
- The performance of SDX following IV administration appears to confirm the rational chemical design of the prodrug and suggests that SDX, as a prodrug of d-MPH, is unlikely to be attractive for intravenous abuse

## Disclosures

RB, SG, TCM, ACB, and AS are employees and shareholders of KemPharm, Inc. BS and DK are employees of Vince & Associates. This study was funded by KemPharm, Inc., Coralville, IA, USA. Design support was provided by Research Triangle Graphics, LLC.

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