Pharmacokinetics of Oral Lisdexamfetamine Dimesylate (LDX; NRP 104) Versus d-Amphetamine Sulfate in Healthy Adults With a History of Stimulant Abuse (NRP104.A01)

Donald Jasinski
The Johns Hopkins University, Baltimore, MD

Suma Krishnan
New River Pharmaceuticals, Blacksburg, VA
LDX
(lisdexamfetamine dimesylate)

- d-amphetamine covalently bonded to l-lysine
- Pharmacologically inactive until cleaved via rate-limiting hydrolysis
- Resistant to manipulation and difficult to extract d-amphetamine
Protocol Objectives

- To determine safety and tolerability of single oral dose of lisdexamfetamine dimesylate (LDX) in 12 healthy adults with histories of stimulant abuse

- To compare PK profile of LDX with d-amphetamine and placebo

- To determine safe and tolerable dosing for further study
Design and Methodology

- Partially randomized, single-blind, dose-escalation study; Subjects on inpatient unit at least 14 days
- Subjects met DSM-IV criteria for stimulant abuse;
- Screening for medical and psychiatric histories; naloxone challenge included
Design and Methodology

- Minimum dosing interval: 48 h
- d-amphetamine and placebo interspersed in random order
- Fasting: 10 h overnight before dosing; ≥4 h after dosing
- Each dosing day: vital sign measures assessed and blood drawn before dosing; 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24 h after dosing
Patient Disposition

- 12 subjects were given at least 1 dose
- 11 subjects completed the study
- 1 subject was discontinued due to “reactive hypertension” after 2nd dose of d-amphetamine sulfate 40 mg
d-amphetamine sulfate 40 mg and lisdexamfetamine dimesylate 100 mg contain equal molar amounts of d-amphetamine base
Cohort 1 and Cohort 2

Cohort 1

Cohort 2
Cohort 3

![Graph showing ng/mL levels over hours with different dose levels: Placebo, 70 mg LDX, 100 mg LDX, 130 mg LDX, 150 mg LDX, and 40 mg d-amp.](image)
# Pharmacokinetics by Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>LDX 100 mg</th>
<th>d-amphetamine sulfate 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$T_{\text{max}}$ $d$-amp (hours)</td>
<td>$C_{\text{max}}$ $d$-amp (ng/mL)</td>
</tr>
<tr>
<td>1</td>
<td>3.78</td>
<td>81.9</td>
</tr>
<tr>
<td>2</td>
<td>4.25</td>
<td>85.0</td>
</tr>
<tr>
<td>3</td>
<td>3.98</td>
<td>104.0</td>
</tr>
</tbody>
</table>
Results

- Dose appeared to attenuate between 130 to 150 mg of lisdexamfetamine
- Doses to 150 mg lisdexamfetamine safe and tolerable for further study
- Prolonged absorption phase as result of rate limiting hydrolysis
A Double-Blind, Randomized, Placebo and Active-Controlled, Six-Period Crossover Study to Evaluate the Likeability, Safety, and Abuse Liability of NRP 104 in Healthy Adult Volunteers with Histories of Stimulant Abuse (NRP104.A03)
Design and Methods

- 30 male and 6 female stimulant abusers
- Six 6X6 balanced Latin squares for crossover design
- Primary variable is maximum score on VAS scale to item “How much do you like the drug effects you are feeling now?”
Drug and doses given orally

- Placebo
- 40 mg d-amphetamine (Schedule II)
- 200 mg diethylpropion (Schedule IV)
  - Pro-drug
  - Subjective and behavioral effects comparable to d-amphetamine 40 mg
- lisdexamfetamine
  - 50 mg (base = d-amp 20 mg)
  - 100 mg (base = d-amp 40 mg)
  - 150 mg (base = d-amp 60 mg)
### Primary Endpoint: Peak Liking Score

**Dependent Variable:** Do you like the drug effect you are feeling now?

<table>
<thead>
<tr>
<th>Drug (I)</th>
<th>Drug (J)</th>
<th>Mean Difference (I - J)</th>
<th>Std. Error</th>
<th>Significance</th>
<th>95% Conf. Interval (Lower Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-amphetamine 40mg</td>
<td>Placebo</td>
<td>4.53*</td>
<td>1.148</td>
<td>&lt; 0.001</td>
<td>1.94</td>
</tr>
<tr>
<td>diethylpropion 200mg</td>
<td>Placebo</td>
<td>4.03*</td>
<td>1.148</td>
<td>0.001</td>
<td>1.44</td>
</tr>
<tr>
<td>LDX 100mg</td>
<td>Placebo</td>
<td>2.14</td>
<td>1.148</td>
<td>0.113</td>
<td>-0.45</td>
</tr>
</tbody>
</table>

Based on observed means

* - The mean difference is significant at the 0.05 level
Primary Endpoint: Peak Liking Score

Dependent Variable: Do you like the drug effect you are feeling now?

<table>
<thead>
<tr>
<th>Drug (I)</th>
<th>Drug (J)</th>
<th>Mean Difference (I - J)</th>
<th>Std. Error</th>
<th>Significance</th>
<th>95% Conf. Interval (Lower Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDX 50mg</td>
<td>Placebo</td>
<td>1.97</td>
<td>1.148</td>
<td>0.148</td>
<td>-0.61</td>
</tr>
<tr>
<td>LDX 100mg</td>
<td>Placebo</td>
<td>2.14</td>
<td>1.148</td>
<td>0.113</td>
<td>-0.45</td>
</tr>
<tr>
<td>LDX 150mg</td>
<td>Placebo</td>
<td>6.06*</td>
<td>1.148</td>
<td>0.001</td>
<td>3.47</td>
</tr>
</tbody>
</table>

Based on observed means
* - The mean difference is significant at the 0.05 level
Peak Liking Scores

- d-amphetamine and diethylpropion
  - 1.5 to 2 hours

- NRP104
  - 3 to 4 hours
**Top Line Results**

- LDX attenuates onset and intensity of liking effects
- Liking effects of LDX 50 and 100mg not significantly different than placebo
- Liking effects of LDX 150 mg greater than placebo but similar to d-amphetamine and diethylpropion however mean peak effect delayed
Top Line Results

- Rate limited hydrolysis of LDX in humans

- Pro-drug attenuates onset and intensity of amphetamine like effects

- Attenuated Liking Scale scores
  - Less reinforcing than equivalent d-amphetamine or diethylpropion
  - Contribute to lesser abuse potential