Effects of Oral Naltrexone on Oral d-Amphetamine and Smoked Cocaine in Humans

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Conflicts of Interest

- None
1% of the world population reports abuse of illicit or prescription amphetamines (SAMSHA, 2009)

No FDA approved pharmacotherapy for amphetamine dependence
Preclinical and clinical research suggest that naltrexone (NTX) may decrease the abuse liability of amphetamines

- Jayaram-Lindstrom et al. (2004, 2008)
- Jiminez-Gomez et al. (2010)
“Feel the drug”

Non-abusers

0 mg NTX + 30 mg AMPH

50 mg NTX + 30 mg AMPH

N=12
Jayaram-Lindstrom et al., 2004

Non-abusers

0 mg NTX + 30 mg AMPH

50 mg NTX + 30 mg AMPH

N=12
Jayaram-Lindstrom et al., 2004

Non-abusers

N=12

0 mg NTX + 30 mg AMPH

50 mg NTX + 30 mg AMPH
Amph dep + ADHD

N=20
Amph dep + ADHD

N=20

Jayaram-Lindstrom et al., 2008
Amph dep + ADHD

N=20
Amph dependent, seeking treatment

N=40 per group

Retention: no difference
Craving: lower in NTX group
Jimenez-Gomez et al., 2010

Graph showing the proportion of control responses per minute as a function of naltrexone dose (mg/kg) for Amphetamine (filled circles) and Ethanol (open circles).
No difference in $[^{11}\text{C}]$carfentanil binding

N=10

Individual $[^{11}\text{C}]$carfentanil BP values for the ventral striatum (1=baseline, 2=placebo, 3=amphetamine)
Background

- The literature is ambiguous regarding the ability of NTX to alter the abuse liability of cocaine
  - Kosten et al. (1992)
  - Walsh et al. (1996)
  - Sofuoglu et al. (2003)
Goal

Directly compare the effects of naltrexone on the abuse liabilities of amphetamine and cocaine
Hypotheses

- Naltrexone would reduce the positive subjective effects of amphetamine but not cocaine

- Naltrexone would produce comparable effects on the physiological responses produced by amphetamine and cocaine
## Methods

- Non-treatment seeking cocaine abusers (n=9 completers; data shown for first 4)
- Double-blind, placebo-controlled, within-subject crossover design
- 10 sessions with at least 1 day in between

### Measures

<table>
<thead>
<tr>
<th>Acute Pre-treatment</th>
<th>Stimulant Challenge</th>
<th>Measures</th>
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</thead>
<tbody>
<tr>
<td>Oral naltrexone (NTX)</td>
<td><strong>Oral d-amphetamine</strong></td>
<td>Subjective effects (VAS)</td>
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<tr>
<td>0, 12.5, or 50 mg (1-hr prior to stimulant administration)</td>
<td>0, 10, and 20 mg (1-hr inter-dose interval)</td>
<td>Vital signs (HR and BP)</td>
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<td><strong>Smoked cocaine</strong></td>
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<td>0, 12.5, 25, and 50 mg (14-min inter-dose interval)</td>
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<td><strong>Placebo</strong></td>
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Subjective Effects

*All p< 0.001
Conclusions

- NTX attenuates the positive subjective effects of oral d-amphetamine but not cocaine.
- NTX had no effect on cardiovascular measures for either drug.
- Effectiveness of NTX 12.5 mg suggests that sustained-release formulations could be effective in treating amphetamine abuse.
- Opioid system involvement in abuse potential of amphetamine but not cocaine?
Implications

- Maintenance on stimulant medications may be useful for treating stimulant dependence.
- However, this approach has met with resistance because the maintenance medications themselves have abuse liability.
- NTX may selectively alter the abuse liability of amphetamine (and methylphenidate; see Zhu et al., 2011).
- Thus, NTX in combination with stimulants may reduce their abuse liability when used for the treatment of cocaine dependence and/or ADHD.
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