Naltrexone treatment for amphetamine dependence

Group Pompidou 2010-05-10

Johan Franck, MD PhD
Karolinska Institutet
Stockholm
Amphetamine abuse in Sweden (pop. 9m)

- 1930s Prescription Benzedrine
- 1970s Illicit (racemic) amphetamine epidemic
- 2000s Sudden increase in meth-amphetamine
Lack of pharmacological treatment

- 35 million abusers of amphetamines world wide

- Sweden: 30 000 “heavy drug users” - 50% have amphetamine as drug of choice

- No evidence based pharmacological treatment dependence
## Pharmacological treatments largely negative

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Reference</th>
<th>Medication</th>
<th>Sample size</th>
<th>Result</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine transporter</strong></td>
<td>Elkashef et al., 2007</td>
<td>Bupropion</td>
<td>151</td>
<td>+</td>
<td>(only in a subgroup)</td>
</tr>
<tr>
<td></td>
<td>Tiihonen et al., 2007</td>
<td>Methylphenidate</td>
<td>53</td>
<td>+</td>
<td>(secondary finding)</td>
</tr>
<tr>
<td><strong>Glutamate</strong></td>
<td>Shearer et al., 2009</td>
<td>Modafinil</td>
<td>80</td>
<td>+</td>
<td>(better outcome in the medication compliant group)</td>
</tr>
<tr>
<td><strong>GABAergic</strong></td>
<td>Brodie et al., 2005</td>
<td>Gamma vinyl-GABA</td>
<td>30</td>
<td>+</td>
<td>(but strong side effect profile)</td>
</tr>
<tr>
<td></td>
<td>Johnson et al., 2007</td>
<td>Topiramate</td>
<td>10</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heinzerling et al., 2007</td>
<td>Baclofen and Gabapentin</td>
<td>340</td>
<td>+</td>
<td>(only for baclofen)</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td>Bakti et al., 1999</td>
<td>Fluoxetine</td>
<td>64</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shoptaw et al., 2006</td>
<td>Sertraline</td>
<td>414</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>Bakti et al., 2001</td>
<td>Amlodipine</td>
<td>77</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td>Galloway et al., 1996</td>
<td>Imipramine</td>
<td>32</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>5HT-3 antagonist</strong></td>
<td>Johnson et al., 2004</td>
<td>Ondansetron</td>
<td>150</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Interaction between Dopamine and Opioids

- Opioid receptor stimulation modulates dopamine release
- Dopamine release modulates opioid peptide expression
- Opioid peptide mRNA colocalize in postsynaptic neurons expressing dopamine receptors
Early naltrexone/naloxone studies

- Reduces amphetamine-induced locomotor activity
  

- Reduces intra-cranial self-stimulation induced by amphetamine
  
  Holtzman 1976; Schaefer and Michael 1990

- Attenuates amphetamine-induced extracellular dopamine release in striatum and N.Acc
  
  Hooks et al. 1992; Schad et al. 1995
Conditioned Place Preference

- Context-drug associative learning model
- Repeated association between the drug and a specific context leads to increased time spent in the drug-associated context in the absence of the drug

Locomotor activity

- Sensitization of response as a marker of addictive property

Self-administration i.v.

- Models relapse in humans
The effect of NTX on amphetamine-induced reinstatement of conditioned place preference

Haggkvist et al. (2009) Addiction Biology
The effect of NTX on locomotor activity on reinstatement

Haggkvist et al. (2009) Addiction Biology
The effect of NTX on AMPH-induced expression of sensitization

---

**Distance Travelled**

- **Vehicle**
- **NTX**

Distance (m):

- 0
- 200
- 400
- 600
- 800
- 1000
- 1200
- 1400

**Statistical Significance**:

- ***p<0.001**
- *p<0.05**
- #p=0.07
The effect of NTX on context-induced conditioned locomotor response

Distance Travelled

- **Vehicle**
- **NTX**

![Bar chart showing distance travelled with error bars.](chart)

**p<0.01
*p<0.05**
Amphetamine Self-administration and Reinstatement

- 100 pellets 20 minutes

Catheter i.v. One week recovery

0.1mg/kg/infusion 2h/day 20 days

Saline 20 days

Amph 0.5 mg/kg NTX pre-treatment (0, 0.3, 1.0 or 3.0 mg/kg)
The effect of NTX on amphetamine-induced self-administration behaviour

Haggkvist et al. (2009)
Behavioural Brain Research 197(1):219-24
Effect of naltrexone on operant responding for food

Summary: Animal models, effect of NTX

- **Conditioned Place Preference**: No effect of NTX on acquisition, expression or reinstatement; Reduction of locomotor behaviour at reinstatement.

- **Behavioral Sensitization**: Amphetamine-induced sensitization; Context-induced locomotor response.

- **Self administration**: Reinstatement induced by amphetamine.
Human Studies

- Human laboratory studies
  - Acute interaction of NTX and amphetamine
    - Healthy subjects
    - Amphetamine dependent patients
    - Controlled laboratory setting
    - Standard test batteries

- Outpatient clinical trials
  - Effect of chronic treatment with naltrexone
    - Amphetamine dependent patients
    - Outpatient setting
    - Open label trial
    - Randomized placebo controlled trial

- Study compounds
  - Naltrexone hydrochloride =50mg p.o.
  - Dexamphetamine =30mg p.o.
Effect of NTX on Amphetamine-Induced Subjective Effects: Drug Naïve Subjects

Effect of NTX on Amphetamine-Induced Subjective Effects: Amphetamine Dependent Subjects

Jayaram-Lindstrom et al. (2008) Neuropsychopharmacology
Effect of Acute Dose of NTX on Craving for Amphetamine (post-priming dose)

Jayaram-Lindstrom et al. (2008) Neuropsychopharmacology
Effect of NTX on the HPA Axis

Jayaram-Lindstrom et al. (2008) Neuropsychopharmacology
Placebo Controlled RCT of NTX for Amphetamine Dependence

294 screened

80 Randomized

Excluded (by reason)
97 - inability to attain abstinence
77 - dependent on other drugs
40 - refusal to comply

40 Naltrexone

11 Dropped out

29 Completers

40 Placebo

14 Dropped out

26 Completers

<table>
<thead>
<tr>
<th>Assessment/Procedure</th>
<th>Screening</th>
<th>Inclusion</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASI interview</td>
<td></td>
<td>X</td>
<td>X (week 12)</td>
</tr>
<tr>
<td>DSM-IV interview</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timeline Follow Back</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood samples (w 4, 8 &amp; 12)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Urine toxicology test</strong></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>2 times a week</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication dispensal</strong></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(Naltrexone 50mg (once week in blister of 7 capsules))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapse prevention therapy</strong></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(once a week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Craving scale</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>b) Adverse events</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone n=40</th>
<th>Placebo n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>39.3 (8.1)</td>
<td>39.6 (9.3)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>77.5%</td>
<td>80%</td>
</tr>
<tr>
<td>Females</td>
<td>22.5%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>31%</td>
<td>27.5%</td>
</tr>
<tr>
<td><strong>Total years of education</strong></td>
<td>10.7 (1.6)</td>
<td>10.3 (1.3)</td>
</tr>
<tr>
<td><strong>Daily nicotine users</strong></td>
<td>85%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>Mean days of amphetamine use in the 3 months prior to screening</strong></td>
<td>52.6</td>
<td>37.1</td>
</tr>
<tr>
<td><strong>Lifetime years of amphetamine use</strong></td>
<td>10.42 (7.5)</td>
<td>9.97 (6.1)</td>
</tr>
<tr>
<td><strong>Adult ADHD</strong></td>
<td>47.5%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Effect of NTX on Amphetamine Abstinence (ITT analysis)


Mean 24 samples:
NTX: 65.2 ± 36.1
Placebo: 47.1 ± 33.7
**Effect of NTX Amphetamine Abstinence (completers analysis)**

Mean 24 samples:
- NTX: 79.7 ± 28.8
- Placebo: 64.1 ± 28.0

Effect of Chronic Treatment with NTX on Craving

Effect of NTX on the Rate of Continuous Abstinence

Summary: Clinical trials

- Acute dose of naltrexone (Laboratory study) → Drug naïve healthy subjects
  - Subjective effects
  - Craving

- Acute dose of naltrexone (Laboratory study) → Amphetamine dependent patients
  - Subjective effects
  - Craving

- Daily naltrexone (12 weeks) (Open label trial) → Amphetamine dependent patients
  - Tolerated
  - Drug consumption

- Daily naltrexone (12 weeks) (RCT) → Amphetamine dependent patients
  - Tolerated
  - Relapse
  - Craving
Naltrexone, a novel pharmacotherapy for amphetamine addiction?

Animal models

↓

Human laboratory & clinical trials

↓

Target populations

↓

Mechanistic studies
Acknowledgements

- Jenny Häggkvist
- Nitya Jayaram-Lindström
- Anders Hammarberg
- Sara Lindholm
- Pia Steensland
- Maija Konstenius
- Joar Guterstam
- Camilla Lindblad
- Ingrid Dahlin
- Olof Beck

Dept of Physiology & Pharmacology
- Björn Schilström
- Carl Björkholm
- Torun Malmlöf

Karolinska PET Centre:
- Tomoyuki Saijo
- Anna-Lena Nordström
- Simon Cervenka
- Christer Halldin
- Lars Farde

New York University Dept of Psychiatry
- Malcolm S. Reid

Grants
Swedish Research Council
Swedish National Drug Policy Coordinator
Karolinska Institutet