Promising Pharmacological Treatment of Stimulant Use Disorder: Time for Translation to Clinical Practice

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International Conference on Drug Prevention, Treatment and Care – Inspiration and Direction, ISUUP, July 2019
Psychostimulant Use Disorder (PSUD)

- Worldwide, 73 million people used illicit (psycho)stimulants: twice as many as those who used opioids
- Some will develop a PSUD, which causes significant health and psychosocial problems
- Only small portion of people with PSUD have access to or receive treatment (large regional disparities)
PSUD: Treatment

- Almost all patients who are in treatment receive only psychosocial interventions
  - In contrast to treatment of opioid use disorder where medications are a standard of care
- Psychosocial interventions (e.g., CBT)
  - limited effectiveness (for frequent users and cognitively impaired individ.)
  - poor treatment engagement
  - expensive to deliver
Current treatment framework for PSUD

Inpatient Treatment
- Medical/psychiatric stabilization - “detox”
- Short-term medication use
- No effect on drug use, high relapse rates

Residential Treatment
- Drug rehab or TC model
- Only psychosocial interventions, high cost
- Large decrease of use, but high relapse rates

Outpatient Treatment
- Psychosocial-only, “abstinence-based”
- Low cost
- Small reductions of use
Addiction: Medical Framework

• Addiction is an acquired bio-behavioral brain disorder
  • It is more likely to develop in people with a genetic predisposition
  • In vulnerable individuals, taking drugs changes the brain
    • There is an abnormal functioning of brain circuits involved in processing of motivation, memory, reward, and decision making
• Abnormal functioning is responsible for symptoms
  • Disturbances of mood, cognition, and decision-making
  • Abnormal reactivity to stress and environmental cues
  • Overwhelming craving and difficulty with controlling behavior
  • Impaired insight and the impaired ability to care for self
• Once developed, addiction has a chronic and relapsing course
  • Abnormal brain responses persist for many months/years
Addiction: Treatment Components

**Pharmacological Treatment**
- Decrease craving, impulsivity and other symptoms of early abstinence

**Self/Mutual Help Groups**
- Social network supportive of recovery

**Recovery-Oriented Activities**
- Develop satisfying lives

**Psychosocial Treatment**
- Skills necessary to cope with cravings and stress to decrease use and maintain abstinence

**Pharmacological Treatment**
- Decrease craving, impulsivity and other symptoms of early abstinence

**Self/Mutual Help Groups**
- Social network supportive of recovery

**Recovery-Oriented Activities**
- Develop satisfying lives
PSUD: Pharmacological Treatments

- Substantial research effort went to finding medications that could improve outcomes of treatment for PSUD
- At present time there is no widely accepted medication to play this role but there are several candidate medications that were found effective when tested in quality controlled clinical trials
- The most effective approach to date is agonist-based treatment
Agonist Approach: Rationale

- Both cocaine and ATSs acutely increase brain levels of dopamine, serotonin, and noradrenaline producing euphoria and other physical effects

- However, chronic users (PSUD) have reduced functioning of DA system

- These changes may be responsible for the continuing use and relapse
  - Low energy, low mood/anhedonia, cognition/decision making, impulsivity

- Correcting those abnormalities can reduce symptoms and help reduce use
  - Agonist-type medication increase DA/NA activity in the brain (pfc)

(Davidson, 2016)
Several agonist medications are used for treatment of other disorders

- Methylphenidate (Ritalin, Concerta), Amphetamines (Adderall), modafinil
- High comorbidity and overlapping neurobiology between PSUD and ADHD

Supervised/medical use of a drug-like substance can stabilize and keep patients in treatment and access other services and medical interventions

- Offering medications may motivate patients for additional treatment
- Patients accept agonist, positive subjective effects promote medication adherence
- Stimulant medication may improve cognitive functioning and improve outcome of psychosocial interventions
Agonist: assuring treatment safety

- Most potent agonists are classified as controlled substances because of the potential for abuse and diversion
  - Treatment must include plan to minimize this risk
  - Similar concerns exist with opioid agonists

- XR preparations have slow onset of action and slower rate of elimination providing stable blood level
  - Less likely to be abused and better adherence

- There is potential for adverse cardiovascular effects and the need to screen out individuals with cardiovascular disease
Agonist Strategy: Meta-analysis 2019 *(Tardelli et al., 2019)*

- Systematic review and a meta-analysis of RCT that used agonists for the treatment of Cocaine or Amphetamine-type PSUD
- **Medications:** scheduled prescription stimulants: modafinil, methylphenidate, or an amphetamine-type medication (dexamphetamine, mixed amphetamine salts and lisdexamfetamine)
- **Outcome Measure:** sustained abstinence from the drug (2-3 wks)
  - Sustained abstinence, particularly at the end of treatment, is an outcome strongly related to cocaine use during follow-up *(Carroll et al., 2014)*
Sustained Abstinence: Cocaine vs. Amphetamine Use Disorder (Tardelli et al., 2019)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Psychostimulants</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
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<tbody>
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<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
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<td>4</td>
<td>14 5.5%</td>
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<td>54</td>
<td>7</td>
<td>40 8.1%</td>
</tr>
<tr>
<td>Deckers 2006</td>
<td>10</td>
<td>30</td>
<td>4</td>
<td>32 5.2%</td>
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<tr>
<td>Levin 2007</td>
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<td>53</td>
<td>9</td>
<td>63 6.6%</td>
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<td>136</td>
<td>7</td>
<td>72 7.9%</td>
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<tr>
<td>Deckers 2012</td>
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<td>136</td>
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<td>75 4.8%</td>
</tr>
<tr>
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<td>22</td>
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<td>8 14.8%</td>
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<td>13</td>
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<td>7</td>
<td>42 7.2%</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Levin 2015</td>
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<td>18 9.1%</td>
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<tr>
<td>Kampman 2015</td>
<td>11</td>
<td>47</td>
<td>4</td>
<td>47 9.0%</td>
</tr>
<tr>
<td>Nuijten 2016</td>
<td>11</td>
<td>38</td>
<td>2</td>
<td>35 3.2%</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>152</td>
<td>519</td>
<td>72.1%</td>
<td>1.66 [1.26, 2.28]</td>
</tr>
</tbody>
</table>

Total events: 152, 86

Heterogeneity: Tau² = 0.08; Chi² = 17.42, df = 13 (P = 0.18); I² = 25%

Test for overall effect: Z = 3.09 (P = 0.002)

1.1.2 Meth

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Placebo</th>
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<th>Year</th>
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<tbody>
<tr>
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<td>Events</td>
<td>Total</td>
<td>Weight</td>
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<td>Heeringa 2010</td>
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<td>34</td>
<td>10</td>
<td>37 7.7%</td>
</tr>
<tr>
<td>Konstenius, 2010</td>
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<td>12</td>
<td>9</td>
<td>12 11.1%</td>
</tr>
<tr>
<td>Anderson 2012</td>
<td>21</td>
<td>142</td>
<td>12</td>
<td>86 9.2%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>38</td>
<td>317</td>
<td>27.9%</td>
<td>0.89 [0.62, 1.27]</td>
</tr>
</tbody>
</table>

Total events: 38, 31

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = 0.95); I² = 0%

Test for overall effect: Z = 0.83 (P = 0.53)

Total (95% CI): 915, 636, 100.0% | 1.40 [1.05, 1.86]

Total events: 130, 97

Heterogeneity: Tau² = 0.12; Chi² = 25.24, df = 18 (P = 0.07); I² = 57%

Test for overall effect: Z = 2.31 (P = 0.02)

Test for subgroup differences: Chi² = 6.40, df = 1 (P = 0.01); I² = 44.4%

Favours Placebo  Favours Psychostimulants
### Sustained Abstinence: Effect of medication (Tardelli et al., 2019)

#### 1.3.1 Prescription Amphetamines

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Psychostimulants</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Grabowski 2004</td>
<td>24</td>
<td>54</td>
<td>7</td>
<td>40</td>
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<tr>
<td>Levin 2015</td>
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<td>83</td>
<td>3</td>
<td>43</td>
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<tr>
<td>Malanti 2012</td>
<td>13</td>
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<tr>
<td>Hulse 2016</td>
<td>11</td>
<td>38</td>
<td>2</td>
<td>35</td>
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<tr>
<td>Schmitz 2012</td>
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<td>8</td>
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<tr>
<td>Shearer 2003</td>
<td>7</td>
<td>16</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>252</td>
<td>182</td>
<td>30.0%</td>
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<tr>
<td>Total events</td>
<td>77</td>
<td>34</td>
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</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 2.95$ ($P = 0.001$)

**Heterogeneity:** $I^2 = 93.03$, $Q = 5$ ($P = 0.12$), $P = 0.01$

#### 1.3.2 Modafinil

<table>
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<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2009</td>
<td>22</td>
<td>138</td>
<td>7</td>
<td>72</td>
<td>7.3%</td>
<td>1.64 [0.74, 3.65]</td>
</tr>
<tr>
<td>Anderson 2012</td>
<td>21</td>
<td>142</td>
<td>12</td>
<td>68</td>
<td>8.2%</td>
<td>0.84 [0.44, 1.60]</td>
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<td>Davis 2015</td>
<td>10</td>
<td>30</td>
<td>4</td>
<td>32</td>
<td>5.2%</td>
<td>2.67 [0.94, 7.00]</td>
</tr>
<tr>
<td>Davis 2012</td>
<td>11</td>
<td>135</td>
<td>4</td>
<td>75</td>
<td>4.9%</td>
<td>1.53 [0.50, 4.63]</td>
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<tr>
<td>Heinzerling 2010</td>
<td>9</td>
<td>34</td>
<td>10</td>
<td>37</td>
<td>7.7%</td>
<td>0.99 [0.45, 2.12]</td>
</tr>
<tr>
<td>Kampman 2015</td>
<td>11</td>
<td>47</td>
<td>4</td>
<td>47</td>
<td>5.0%</td>
<td>2.75 [0.94, 8.02]</td>
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<td>Schmitz 2012</td>
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<td>1</td>
<td>8</td>
<td>1.1%</td>
<td>0.43 [0.03, 5.65]</td>
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<tr>
<td>Schmitz 2014</td>
<td>9</td>
<td>22</td>
<td>10</td>
<td>18</td>
<td>9.1%</td>
<td>0.74 [0.38, 1.41]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>568</td>
<td>357</td>
<td>49.4%</td>
<td></td>
<td></td>
<td>1.22 [0.83, 1.77]</td>
</tr>
<tr>
<td>Total events</td>
<td>84</td>
<td>52</td>
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</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 1.88$ ($P = 0.03$)

**Heterogeneity:** $I^2 = 94.40$, $Q = 7$ ($P = 0.02$), $P = 0.29$

#### 1.3.3 Methylphenidate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Düsterlin-MacFarland 2013</td>
<td>3</td>
<td>30</td>
<td>9</td>
<td>32</td>
<td>2.6%</td>
<td>1.07 [0.2, 4.68]</td>
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<tr>
<td>Konstenius 2010</td>
<td>0</td>
<td>12</td>
<td>9</td>
<td>12</td>
<td>11.1%</td>
<td>0.89 [0.53, 1.49]</td>
</tr>
<tr>
<td>Levin 2007</td>
<td>8</td>
<td>53</td>
<td>9</td>
<td>53</td>
<td>8.8%</td>
<td>0.89 [0.37, 2.13]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td>97</td>
<td>26.0%</td>
<td></td>
<td></td>
<td>0.90 [0.59, 1.38]</td>
</tr>
<tr>
<td>Total events</td>
<td>190</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 0.24$ ($P = 0.62$)

**Heterogeneity:** $I^2 = 46.62$, $Q = 16$ ($P = 0.07$), $P = 0.37$

**Test for subgroup differences:** $Ch^2 = 10.15$, $df = 2$ ($P = 0.006$), $P = 80.3%$
Agonist Strategy: Meta-Analysis 2019

• We found that:
  • Prescription psychostimulants were effective in promoting sustained abstinence in the treatment of PSUD, particularly Cocaine Use Disorder (low-quality evidence)
  • Prescription amphetamines were particularly efficacious on promoting sustained abstinence on patients with Cocaine Use Disorder (high-quality evidence)
... evidence that a higher proportion of participants achieved sustained cocaine abstinence with psychostimulants than with placebo (low quality evidence, small benefit).

In consonance with the efficacy of substitute treatment for heroin use and for nicotine dependence, the findings of this review suggest that psychostimulants are a promising treatment for cocaine dependence.
Implementing medical model to treat patients with PSUD

- **Attract** patients into treatment and keep them engaged
  - Outreach work: offering food, shelter, and welcoming environment
  - Inpatient/residential services if stabilization is needed
- **Offer treatment**
  - Medications to help reduce craving and impulsivity, improve mood and cognition to decrease drug use/prevent relapse
  - Supportive, friendly, and accepting therapeutic environment
  - Therapy to change pathological behaviors and retain patients in treatment
  - Connect with peer-support networks and recovery-oriented services
- **Diagnose and treat co-occurring conditions**
  - Other Substance Use Disorders (alcohol, opioids)
  - Psychiatric problems (depression, anxiety, PTSD, psychosis)
  - Medical problems (e.g., infections, dental, reproductive services)
- **Collect evidence** to test health and economic benefits of this model