Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled trial.

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2nd European Conference on Addictive Behaviours and Dependencies
overview of presentation

• good medical practice

• pharmacotherapy for cocaine

• pharmacotherapy trials in the Netherlands – CATCH
  • topiramate
  • modafinil
  • sustained-release dexamphetamine

• conclusions
good medical practice

principles of good medical practice are fundamental in the treatment of all disorders – including substance use disorders. Treatment may not harm the patient: "First, do no harm", and must be directed towards:

- if necessary: crises intervention / life threatening situations
  - treatment acute intoxication and withdrawal
  - treatment acute psychiatric / medical co-morbidity

- if possible:
  - cure: initiate abstinence prevent relapse (frequency and severity), or

- if cure not possible:
  - care: reduce or stabilize substance use reduce physical, psychological, and social harm

Meanwhile as much as possible, feasible and desirable support recovery and improvement in psychosocial functioning

pharmacotherapy for cocaine
effective pharmacotherapy for cocaine

- 6 systematic Cochrane reviews
  - anticonvulsants (Minozzi, 2015)
    20 studies – 2,068 patients
  - antidepressants (Pani, 2011)
    37 studies – 3,551 patients
  - antipsychotics (Indave, 2016)
    14 studies – 719 patients
  - disulfiram (Pani, 2010)
    7 studies – 492 patients
  - dopamine agonists (Minozzi, 2015)
    24 studies – 2,147 patients
  - psychostimulants (Castells 2016)
    26 studies – 2,366 patients
effective pharmacotherapy for cocaine

- 6 systematic Cochrane reviews: > 100 studies; > 10,000 patients
  - "... no current evidence supports the clinical use of anticonvulsant medications in the treatment of patients with cocaine dependence" (2015)
  - "... at the current stage of evidence data do not support the efficacy of antidepressants in the treatment of cocaine abuse/dependence" (2011)
  - "... at present, there is no evidence supporting the clinical use of antipsychotic medications in the treatment of cocaine dependence" (2016)
  - "... there is low evidence, at the present, supporting the clinical use of disulfiram for the treatment of cocaine dependence" (2010)
  - "... current evidence from randomised controlled trials does not support the use of dopamine agonists for treating cocaine misuse" (2015)
  - "... this review found mixed results. Psychostimulants improved cocaine abstinence in some analyses* compared to placebo, but did not improve treatment retention. ( ) ... substitution treatment with psychostimulants appears promising and deserves further investigation" (2016)

* When we included the type of drug as a moderating variable, the proportion of patients achieving sustained cocaine abstinence was higher with bupropion and dexamphetamine than with placebo.
cocaine addiction treatments to improve control and reduce harm
• feasibility pharmacotherapy crack-cocaine dependence
• pre-randomisation, double consent design
• intervention: 12 weeks "treatment as usual" (CBT + MI)
• 4 proposed "add on" pharmacotherapies:
  ● rimonabant ($2 \times n = 36$)
  ● modafinil ($2 \times n = 36$)
  ● dexamfetamine-SR ($2 \times n = 36$)
  ● oral cocaine ($2 \times n = 36$)
  ● topiramate ($2 \times n = 36$)
CATCH

study 1

study 1

topiramate
Brijder, The Hague

modafinil
Jellinek, Amsterdam
          Mentrum, Amsterdam
                  Brijder, The Hague

Treatment of crack-cocaine dependence with topiramate: A randomized controlled feasibility trial in The Netherlands

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Original Paper

Modafinil in the treatment of crack-cocaine dependence in the Netherlands: Results of an open-label randomised controlled feasibility trial

Mascha Nuijten1, Peter Blanken1, Wim van den Brink2 and Vincent Hendriks1

Drug and Alcohol Dependence

Contents lists available at ScienceDirect

Journal homepage: www.elsevier.com/locate/drugalcdep

Psychopharm
Topiramate

- Acceptance
  - Insufficient medication adherence
- Efficacy
  - CBT + topiramate = CBT only
  - Topiramate probably effective in patients with comorbid heroin dependence

Modafinil

- Acceptance
  - Insufficient medication adherence
- Efficacy
  - CBT + modafinil = CBT only
  - Modafinil probably effective in patients with high medication adherence
study 3

dexamfetamine sustained-release

Jellinek, Amsterdam
Antes-Bouman, Rotterdam
Brijder, The Hague
agonist pharmacotherapy rationale
rationale agonist pharmacotherapy for cocaine

- no proven effective pharmacotherapy for cocaine dependence in terms of abstinence and/or relapse-prevention
- uncontrolled and (potentially) harmful use versus controlled, medical, supervised and (relatively) safe use
- stabilising: biology, addiction-related behaviour, daily structure
- motivate patients for additional (recovery-oriented) interventions
- balancing potential positive effects versus potential harms ...
- most promising: dexamfetamine (sustained-release)

Grabowski et al. 2004 Addictive Behaviors; Shearer 2008 Drug Alcohol Review; Herin et al. 2010 Annals NY Academy Sciences; Castells et al. 2016 Cochrane Systematic Reviews
**CATCH** – dexamfetamine-SR treatment and design

- **patients**
  - 73 patients in heroin-assisted treatment with treatment-refractory comorbid cocaine dependence
  - dexamfetamine-SR: n = 38 - 60 mg/day supervised intake
  - placebo: n = 35 - identical placebos

- **medication adherence**
  - 92% medication compliance
  - 61 patients (84%) full medication adherence in final 4 weeks

- **study participation**
  - week 12 interviews: 72 out of 73 (98.6%)
  - urine samples: 516 out of 584 (88.4%)

- **blinding**
  - correct SR dexamfetamine: 54% \( \kappa = 0.14 \)
  - correct placebo: 60%
assessed for eligibility (n=111)

barred by exclusion criteria (n=4)
- ECG abnormalities (n=3)
- renal insufficiency (n=1)

not meeting inclusion criteria (n=34)
- no regular use of crack-cocaine (n=6)
- no treatment demand regarding cocaine use / no motivation to change cocaine use (n=18)
- imprisonment (n=3)
- other (n=7)

randomization (n = 73)

SR dexamphetamine (n=38)
- discontinued treatment (n=4)
  - imprisonment (n=2)
  - adverse events (n=2)

analysed (n=38)

placebo (n=35)
- discontinued treatment (n=4)
  - imprisonment (n=1)
  - adverse events (n=2)
  - no treatment effect (n=1)

analysed (n=35)
CATCH
results: efficacy

outcome
1  days cocaine abstinence *
during 12 week study
39 vs. 23 days; p = 0.03; d = 0.58

2a  days longest consecutive
period cocaine abstinence
18 vs. 7 days; p < 0.01; d = 0.58

2b  ≥ 21 days consecutive
cocaine abstinence
29% vs. 6%; p = 0.02; NNT = 4.3

2c  days cocaine abstinence in
final 4 weeks
15 vs. 8 days; p < 0.01; d = 0.77

3  cocaine-negative urines
11% vs. 4%; p = 0.02; d = 0.31

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CATCH
results: efficacy

# cocaine abstinent days in preceding 4 weeks

![Graph showing the number of cocaine abstinent days for placebo and dexamfetamine SR treatments](image)

**time * treatment:**
\[ F = 8.99; \text{ df } = 1; \ p < 0.01 \]

# cocaine "hits ("basejes") per cocaine use day in preceding 4 weeks

![Graph showing the number of cocaine "hits" for placebo and dexamfetamine SR treatments](image)

**time * treatment:**
\[ F = 5.98; \text{ df } = 1; \ p = 0.02 \]
CATCH results: efficacy - sensitivity analysis

Self-report – urinalysis agreement = 89.2%
Kappa = 0.64
Self-reported "non-use" and urinalysis "positive": 47%

Sensitivity analysis adjusting self-report according to urinalyses in final 4 weeks

# cocaine abstinent days in final 4 weeks

- **Dexamfetamine SR**
- **Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Original</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days</td>
<td>15.2</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>3.9</td>
</tr>
</tbody>
</table>

$d = 0.77$  
$d = 0.71$
ECG

"12 week ECG data were available for 67 patients (dexamfetamine: n=34/36; placebo: n=33/35) with only one abnormality in terms of a repolarisation disturbance in a patient in the placebo group."

| Sustained-release dexamfetamine group (n=36) | | Placebo group (n=35) | | Group x time |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Baseline | Week 12 | Baseline | Week 12 | F=9.58, df=1, p=0.003 | F=0.06, df=1, p=0.809 | F=2.34, df=1, p=0.130 | F=0.21, df=1, p=0.645 |
| Heart rate (beats per min) | 68.2 (11.9) | 76.1 (11.6) | 69.3 (10.0) | 68.7 (12.6) | | | |
| Systolic blood pressure (mm Hg) | 128.1 (15.7) | 127.4 (14.7) | 126.5 (15.8) | 124.9 (14.8) | | | |
| Diastolic blood pressure (mm Hg) | 79.3 (9.3) | 81.2 (9.2) | 80.5 (9.6) | 79.3 (9.7) | | | |
| Bodyweight (kg) | 76.9 (18.7) | 77.2 (18.4) | 74.0 (18.2) | 73.9 (17.9) | | | |

Data are mean (SD), unless otherwise specified.

Table 5: Baseline to week 12 changes in heart rate, blood pressure, and bodyweight.
CATCH results: safety

- medical Adverse Events (AEs)
  - dexamfetamine-SR: 74% *versus* placebo: 46%  *(p = 0.02)*
  - sleep disturbances, agitation, physical arousal
  - mostly mild and transient

- premature/temporal discontinuation medication
  - serious adverse event  *(n = 1; placebo)*
  - severe AE (psychotic symptoms;  *n = 1; SR-dexamfetamine* )
  - other AE-related  *(SR-dexamfetamine:  *n = 1; placebo:  *n = 2)*
  - imprisonment  *(SR-dexamfetamine:  *n = 1; placebo:  *n = 2)*
  - dose reduction  *(n = 2; SR-dexamfetamine)*

Nuijten et al. 2016 The Lancet
conclusions
### dexamphetamine for cocaine

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosing Details</th>
<th>Retention</th>
<th>Primary Outcome</th>
<th>Secondary Outcome or Subgroup / Post hoc</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grabowski et al. 2001</td>
<td>dexamphetamine-SR: 15/30 mg (n = ?)</td>
<td>9 %</td>
<td>cocaine use did not differ during weeks 1-4 stabilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(22% crack or freebase)</td>
<td>30/60 mg (n = ?)</td>
<td>40 %</td>
<td>during double-dose phase the 30/60 mg group showed fewer positive urine screens</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- placebo (n = ?)</td>
<td>23 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 4 weeks + 8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- once weekly CBT</td>
<td></td>
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</tr>
<tr>
<td>Shearer et al. 2003</td>
<td>dexamphetamine-IR 60 mg (n = 16)</td>
<td>38 %</td>
<td>improvements did not differ between groups</td>
<td>reduced self-reported cocaine use, criminal activity, craving and dependence severity</td>
<td></td>
</tr>
<tr>
<td>(100% injecting)</td>
<td>- placebo (n = 14)</td>
<td>36 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 14 weeks</td>
<td></td>
<td></td>
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<tr>
<td>Grabowski et al. 2004</td>
<td>dexamphetamine-SR: 15/30 mg (n = 26)</td>
<td>50 %</td>
<td>the 30/60 mg group significantly reduced cocaine use from stabilization to double-dose phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>opioid dependent methadone pts.</td>
<td>30/60 mg (n = 28)</td>
<td>39 %</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>- placebo (n = 28)</td>
<td>25 %</td>
<td>the 30/60 mg group had fewer cocaine positive screens at month 2, 3 and 4</td>
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<tr>
<td></td>
<td>- 4 weeks + 20 weeks</td>
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<td></td>
<td>- once weekly CBT</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mariani et al. 2012</td>
<td>mixed amphetamine salts - ER 60 mg +</td>
<td>74 %</td>
<td>higher proportion of ≥ 3 weeks uninterrupted abstinence</td>
<td>high frequency baseline cocaine use</td>
<td></td>
</tr>
<tr>
<td>(±50% crack)</td>
<td>topiramate 150 mg (n = 39)</td>
<td>83 %</td>
<td>however, significance not reported and unlikely</td>
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<td></td>
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<tr>
<td></td>
<td>- placebo (n = 42)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>- 12 weeks (incl. 2 and 6 weeks titration)</td>
<td></td>
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<tr>
<td></td>
<td>- weekly compliance enhancement Tx</td>
<td></td>
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<tr>
<td>Schmitz et al. 2012</td>
<td>modafinil 400 mg (n = 20)</td>
<td>week 12:</td>
<td>relative better cocaine outcomes in placebo and d-amphetamine only groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>'majority' crack</td>
<td>d-amp-SR 60 mg (n = 22)</td>
<td>40 %</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>d-amphetamine-SR 30 mg +</td>
<td>week 16:</td>
<td></td>
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<tr>
<td></td>
<td>modafinil 200 mg (n = 15)</td>
<td>20 %</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>- placebo (n = 16)</td>
<td>no group</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- 16 weeks + once weekly CBT</td>
<td>difference</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mooney et al. 2015</td>
<td>lisdexamfetamine 70 mg (n = 22)</td>
<td>64%</td>
<td>no difference in cocaine use between lisdexamfetamine and placebo</td>
<td>significantly less craving in lisdexamfetamine than placebo</td>
<td></td>
</tr>
<tr>
<td>route unknown</td>
<td>- placebo (n = 21)</td>
<td>no group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(±50% crack)</td>
<td>- 14 weeks + once weekly CBT</td>
<td>difference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levin et al. 2015</td>
<td>mixed amphetamine salts - ER 60 mg (n = 40)</td>
<td>79 %</td>
<td>higher odds of negative cocaine week and higher proportion of ≥ 3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±50% crack</td>
<td>- 80 mg (n = 43)</td>
<td>75 %</td>
<td>uninterrupted abstinence</td>
<td>higher odds of ≥ 30% reduction in ADHD symptoms</td>
<td></td>
</tr>
<tr>
<td>comorbid ADHD</td>
<td>- placebo (n = 43)</td>
<td>67 %</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>- 13 weeks + once weekly CBT</td>
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</tr>
</tbody>
</table>
conclusions

- robust dosage dexamfetamine-SR (≥ 60 mg/day) is: → feasible
  → safe
  → efficacious

  in the treatment of *this specific group of* chronic, treatment refractory cocaine dependence *in this specific treatment setting* of heroin-assisted treatment

- and also in patients with cocaine use disorder + comorbid ADHD
  (Levin et al. 2015 JAMA Psychiatry)

- future studies
  - comorbid cocaine-/heroin dependent patients in methadone maintenance Tx
  - cocaine dependent patients in pyschosocial outpatient treatment
  - long-term/ongoing treatment dexamfetamine-SR

- balancing: effectiveness - harmfulness
  taking into account:
  consequences of unsuccessful interventions, or not intervening

Nuijten et al. 2016 The Lancet
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  - Ben van de Wetering, PhD
  - Manja van der Toorn

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