

**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.

C

cocaine

A

addiction

T

treatments to improve

C

control and reduce

H

harm



CATCH

ZonMW: Risk behaviour and dependence

- 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 × n = 36)~~
 - modafinil (2 × n = 36)
 - dexamfetamine-SR (2 × n = 36)
 - ~~oral cocaine (2 × n = 36)~~
 - topiramate (2 × n = 36)

Nuijten *et al.* *BMC Psychiatry* 2011, **11**:135
<http://www.biomedcentral.com/1471-244X/11/135>



STUDY PROTOCOL

Open Access

Cocaine Addiction Treatments to improve Control and reduce Harm (CATCH): New Pharmacological Treatment Options for Crack-Cocaine Dependence in the Netherlands

Mascha Nuijten^{1*}, Peter Blanken¹, Wim van den Brink² and Vincent Hendriks¹

CATCH

study 1

topiramate

Brijder, The Hague

study 1

modafinil

Jellinek, Amsterdam
Mentrum, Amsterdam
Brijder, The Hague

Drug and Alcohol Dependence 138 (2014) 177–184

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdp

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

Psychopharm

Journal of Psychopharmacology
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DOI: 10.1177/0269881115582151
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CATCH

topiramate

- acceptance
 - insufficient medication adherence
 - acceptable safety profile; few adverse events
- efficacy
 - CBT + topiramate = CBT only
 - topiramate probably effective in patients with comorbid heroin dependence

modafinil

- acceptance
 - insufficient medication adherence
 - 20% treatment discontinuation related to adverse events
- efficacy
 - CBT + modafinil = CBT only
 - modafinil probably effective in patients with high medication adherence

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CATCH

study 3

dexamfetamine sustained-release

Jellinek, Amsterdam
Antes-Bouman, Rotterdam
Brijder, The Hague

Articles



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

Mascha Nuijten, Peter Blanken, Ben van de Wetering, Bastiaan Nuijen, Wim van den Brink, Vincent M Hendriks

www.thelancet.com Vol 387 May 28, 2016

agonist pharmacotherapy rationale

rationale agonist pharmacotherapy for cocaine

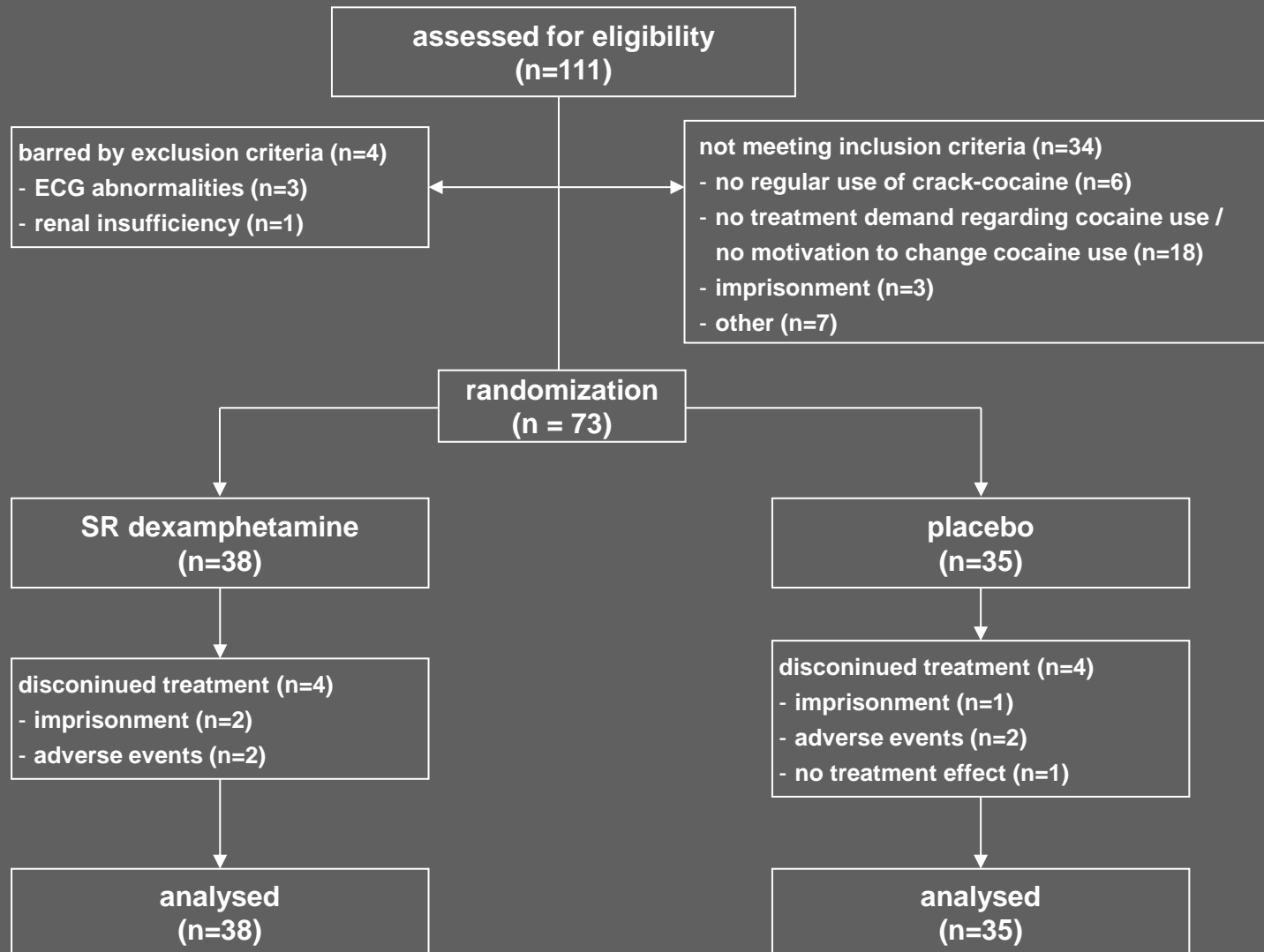
- no proven effective pharmacotherapy for cocaine dependence in terms of abstinence and/or relapse-prevention
- uncontrolled and (potentially) harmful use
versus
controlled, medical, supervised and (relatively) safe use
- stabilising: biology, addiction-related behaviour, daily structure
- motivate patients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

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%
 - correct placebo : 60%

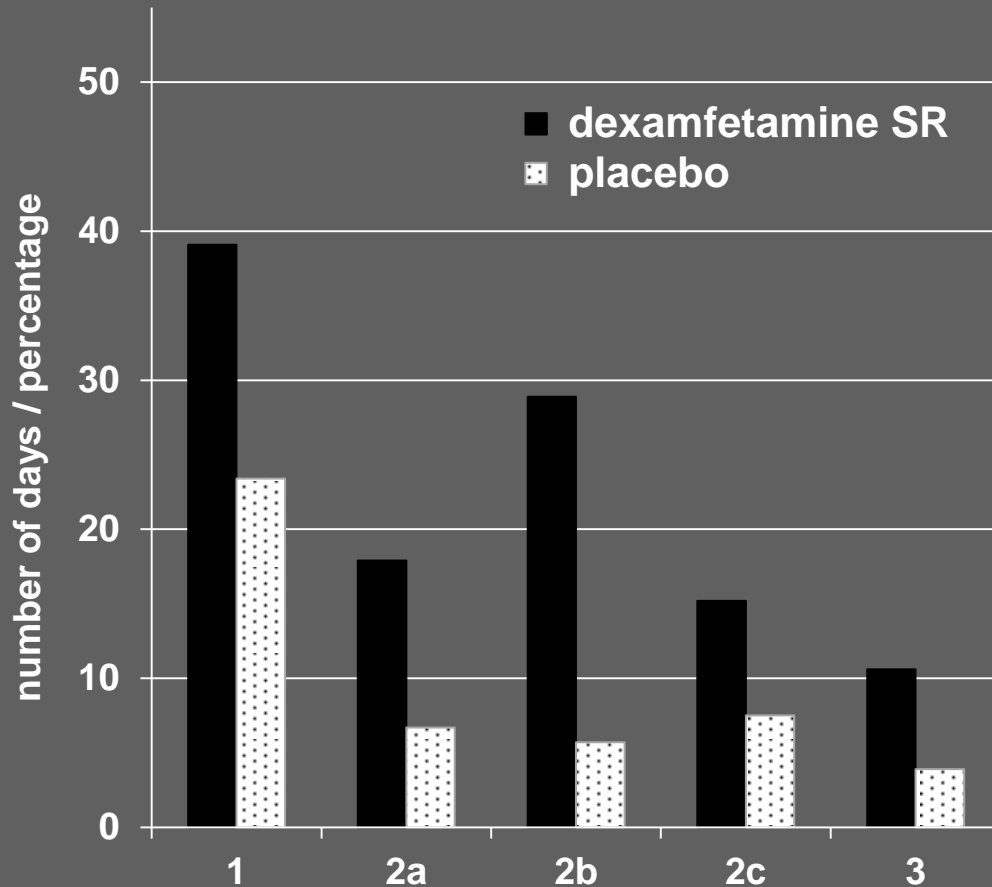
} $\kappa = 0.14$

CATCH – dexamfetamine-SR treatment and design



CATCH

results: efficacy



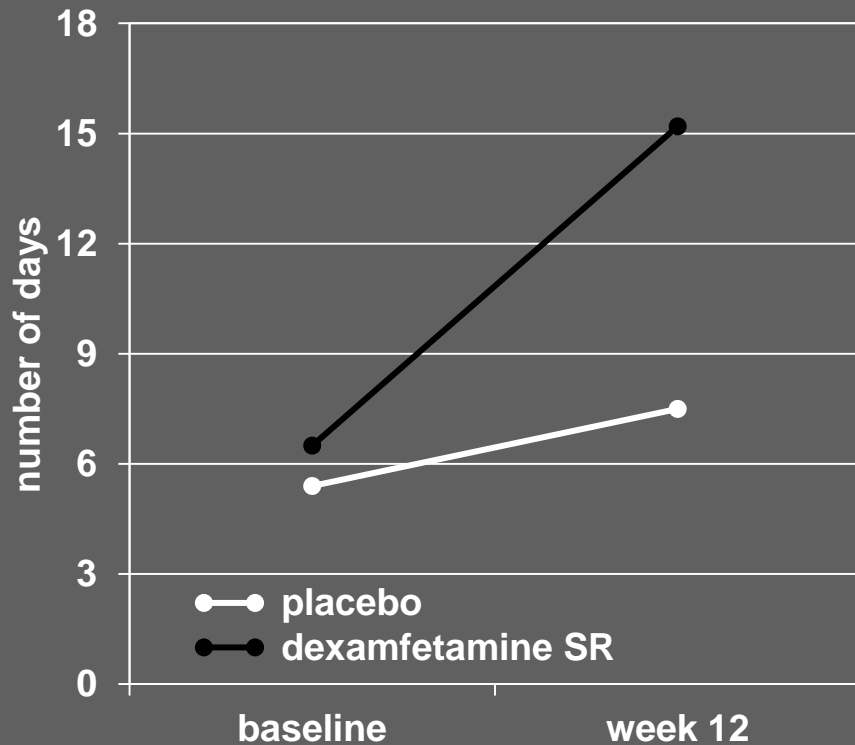
outcome

- 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%; $p = 0.02$; $d = 0.31$

CATCH

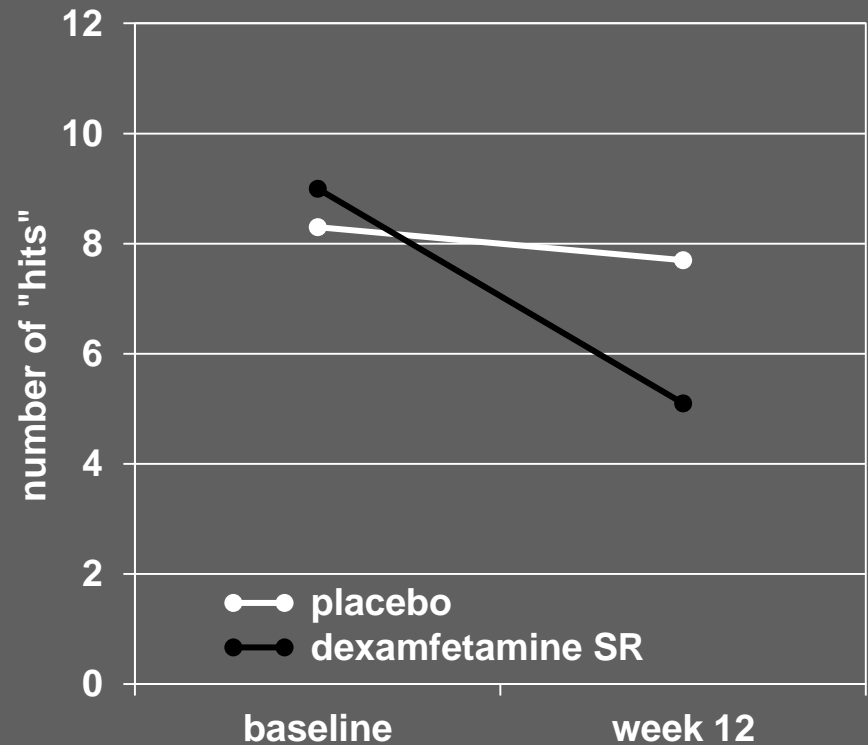
results: efficacy

cocaine abstinent days
in preceding 4 weeks



time * treatment:
 $F = 8.99$; $df = 1$; $p < 0.01$

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

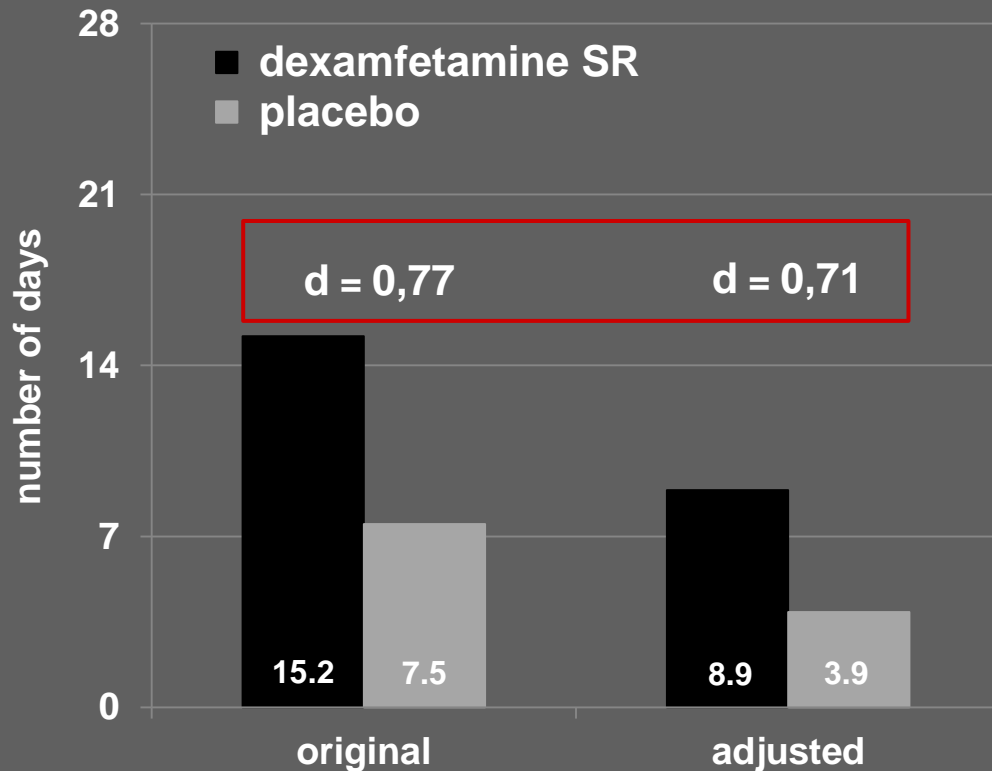


time * treatment:
 $F = 5.98$; $df = 1$; $p = 0.02$

CATCH

results: efficacy - sensitivity analysis

cocaine abstinent days
in final 4 weeks



self-report – urinalysis
agreement = 89.2%

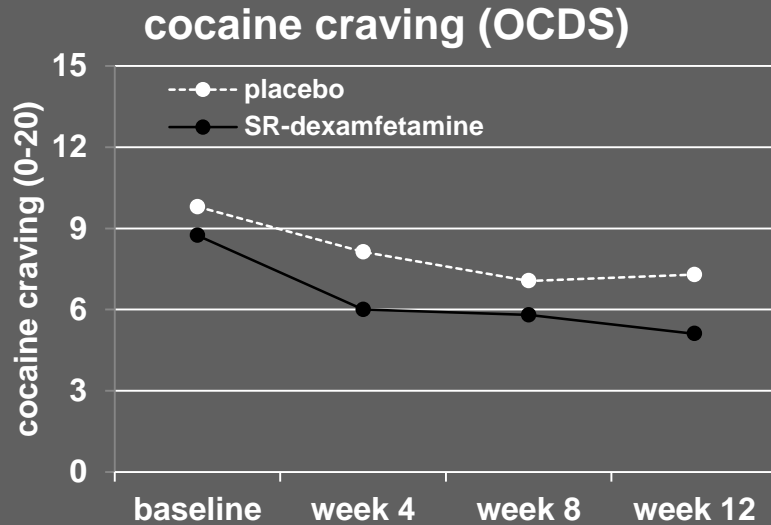
kappa = 0.64

self-reported "non-use" and
urinalysis "positive": 47%

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

CATCH

results: secondary outcomes



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

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)

conclusions

dexamphetamine for cocaine	retention	primary outcome	secondary outcome or subgroup / post hoc	Quality
Grabowski et al. 2001 [22% crack or freebase]	- dexamphetamine-SR: 15/30 mg (n = ??) 30/60 mg (n = ??) - placebo (n = ??) - 4 weeks + 8 weeks - once weekly CBT	9 % 40 % 23 %	- cocaine use did not differ during weeks 1-4 stabilization - during double-dose phase the 30/60 mg group showed fewer positive urine screens	
Shearer et al. 2003 [100% injecting]	- dexamphetamine-IR 60 mg (n = 16) - placebo (n = 14) - 14 weeks	38 % 36 %	- improvements did not differ between groups	- reduced self-reported cocaine use, criminal activity, craving and dependence severity
Grabowski et al. 2004 [47% crack] opioid dependent methadone pts.	- dexamphetamine-SR: 15/30 mg (n = 26) 30/60 mg (n = 28) - placebo(n = 28) - 4 weeks + 20 weeks - once weekly CBT	50 % 39 % 25 %	- the 30/60 mg group significantly reduced cocaine use from stabilization to double-dose phase - the 30/60 mg group had fewer cocaine positive screens at month 2, 3 and 4	
Mariani et al. 2012 [±50% crack]	- mixed amphetamine salts - ER 60 mg + topiramate 150 mg (n = 39) - placebo (n = 42) - 12 weeks (incl. 2 and 6 weeks titration) - weekly compliance enhancement Tx	74 % 83 %	- higher proportion of ≥ 3 weeks uninterrupted abstinence however, significance not reported and unlikely	- high frequency baseline cocaine use
Schmitz et al. 2012 ['majority' crack]	- modafinil 400 mg (n = 20) - d-amp-SR 60 mg (n = 22) - d-amphetamine-SR 30 mg + modafinil 200 mg (n = 15) - placebo (n = 16) - 16 weeks + once weekly CBT	week 12: 40 % week 16: 20 % no group difference	- relative better cocaine outcomes in placebo and d-amphetamine only groups	
Mooney et al. 2015 [route unknown]	- lisdexamfetamine 70 mg (n = 22) - placebo (n = 21) - 14 weeks + once weekly CBT	64% no group difference	- no difference in cocaine use between lisdexamfetamine and placebo	- significantly less craving in lisdexamfetamine than placebo
Levin et al. 2015 [±50% crack] comorbid ADHD	- mixed amphetamine salts - ER - 60 mg (n = 40) - 80 mg (n = 43) - placebo (n = 43) - 13 weeks + once weekly CBT	79 % 75 % 67 %	- higher odds of negative cocaine week and higher proportion of ≥ 3 weeks uninterrupted abstinence	- higher odds of ≥ 30% reduction in ADHD symptomatology

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 psychosocial outpatient treatment
 - long-term/ongoing treatment dexamfetamine-SR
- balancing: effectiveness - harmfulness
taking into account:
consequences of unsuccessful interventions, or
not intervening

I would like to thank

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- Bastiaan Nuijen, PhD
- Ben van de Wetering, PhD
- Manja van der Toorn

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