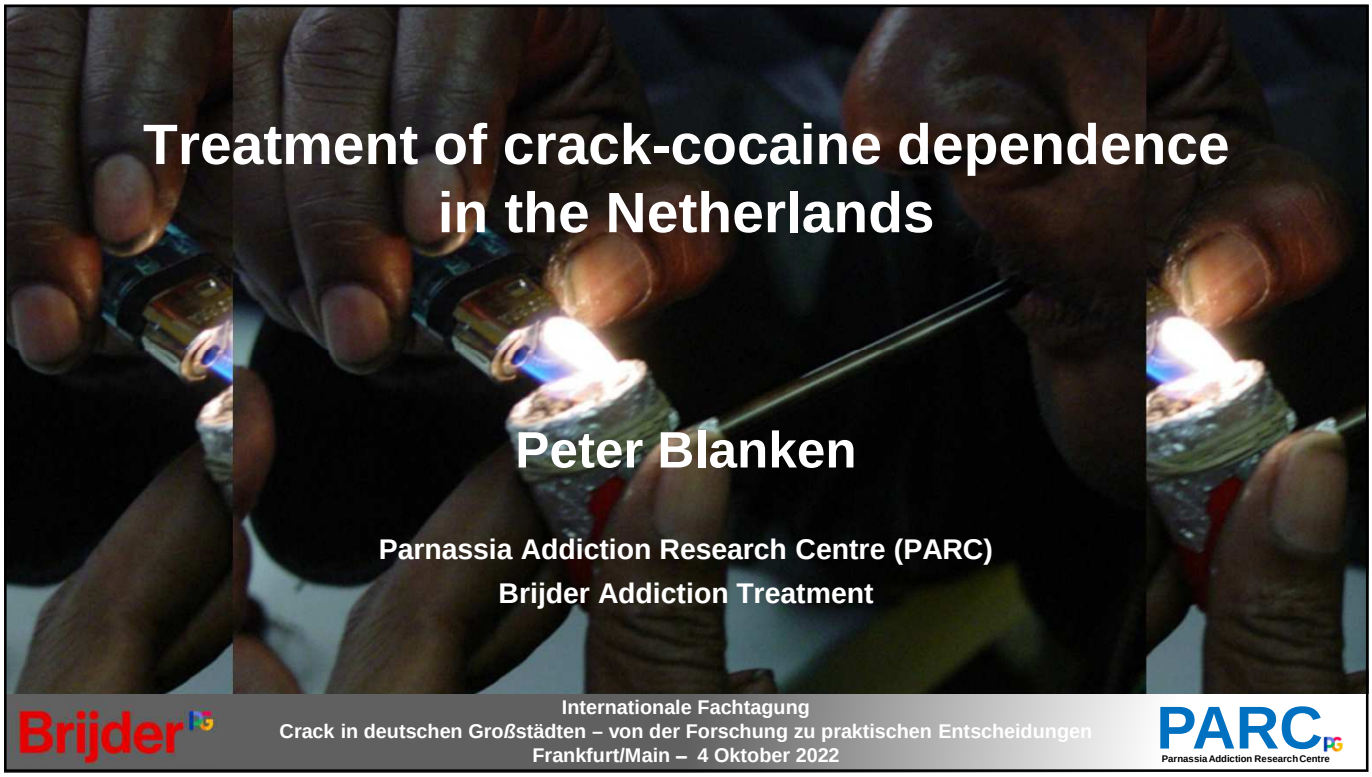


1

conflict of interest
Peter Blanken

Interest	Name of organization
Grants	Ministry of Health, Welfare and Sports (VWS) Netherlands Organisation for Health Research and Development (ZonMw)
Honoraria	Novartis (advise on Contingency Management)
Advisory board/ consultant	n.a.

2

overview of presentation

- background
- psychosocial treatment for stimulant use disorders – contingency management
  - recommendations from Dutch Multidisciplinary Guideline
- pharmacological treatment for stimulant use disorders – sustained-release dexamphetamine: CATCH & CATCH 2.0
  - recommendations from Dutch Multidisciplinary Guideline
- conclusions

3

background

- cocaine use and cocaine treatment demand in the Netherlands
- good medical practice: "primum non nocere" – cure ⇒ care
- modest efficacy of psychosocial treatment – contingency management as an exception
- no proven effective medications
  agonist medications most promising:
  uncontrolled, potentially harmful use ⇔
  controlled, medical, supervised, relatively safe use

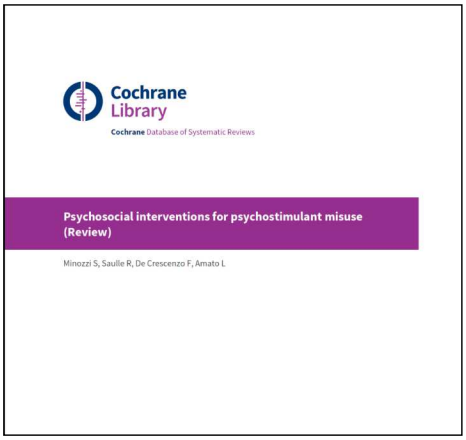
4

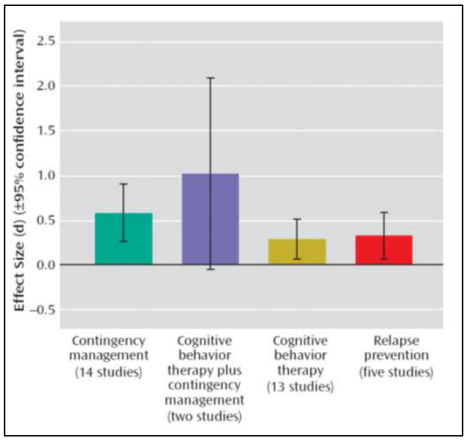
psychosocial interventions for cocaine

5

rationale

- ***add on*** **intervention(s) to reduce cocaine use?**
- **effective pharmacotherapy ~ dexamfetamine-SR**
- **psychosocial interventions ?**





Minozzi et al. 2016 Cochrane; Dutra et al. 2008 American Journal Psychiatry

6

rationale

- ***add on*** **intervention(s) to reduce cocaine use?**
- **effective pharmacotherapy ~ dexamfetamine-SR**
- **psychosocial interventions ?**

results in favour of treatments with some form of contingency management in respect to both reducing drop outs and lowering cocaine use

cognitive behavior therapy and relapse prevention evidence low-moderate effect sizes (d = 0.28 and d = 0.32, resp.)

treatments using contingency management produced moderate-high effect sizes (d = 0.58)

➡ ***contingency management***

Minozzi et al. 2016 Cochrane; Dutra et al. 2008 American Journal Psychiatry

7

cocaine contingency management objectives & design


Drug and Alcohol Dependence 164 (2016) 55–63

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

ELSEVIER

Full length article

Efficacy of cocaine contingency management in heroin-assisted treatment: Results of a randomized controlled trial

CrossMark

Peter Blanken[a,b,*], Vincent M. Hendriks[a,b,c], Ineke A. Huijsman[a], Jan M. van Ree[a,d], Wim van den Brink[a,e]

8

cocaine contingency management within HAT design

- effectiveness of six months ongoing heroin-assisted treatment *plus* cocaine contingency management

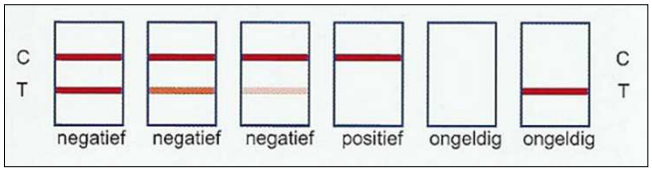
  compared to

  six months ongoing heroin-assisted treatment alone
- among chronic treatment-refractory heroin dependent patients with substantial cocaine use
- in terms of changes in
  - cocaine consumption
  - physical, mental and social health
  - treatment retention
- effect of terminating contingency management (while continuing heroin-assisted treatment)

9

cocaine contingency management within HAT treatment intervention

- supervised collection of urine samples: 1-3 samples per week
- rapid test: cocaine metabolites
  - cocaine-negative urines will be reinforced
  - cocaine-positive urines will be ignored
- outcome entered into web-based computer program



10

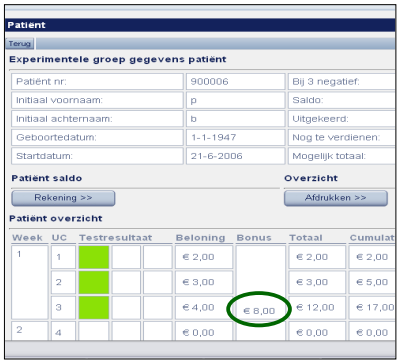
cocaine contingency management within HAT treatment intervention

escalating reward schedule

- first cocaine-negative urine: € 2
- escalating reward for each consecutive cocaine-negative urine: plus € 1
- three consecutive cocaine-negative urines: € 8 bonus

maximum earnings

- per sample: € 16
  (after 15 consecutive cocaine-free urines)
- per week: € 56
- during trial: € 1,111
  (after 65 consecutive cocaine-free urines)



11

cocaine contingency management within HAT treatment intervention

escalating reward schedule

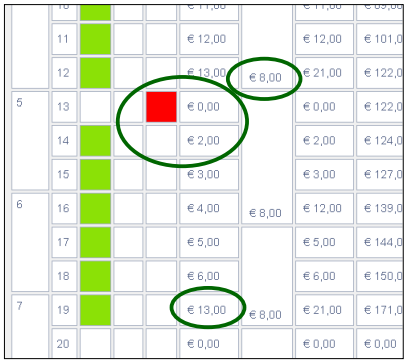
- € 2, € 3, € 4 --- € 16 maximum
- three consecutive cocaine-negative urines: € 8 bonus

but ...

- after cocaine-positive urine reward will be reset to € 2

... and ...

- after five consecutive cocaine-negative urines the reward will return to the highest value achieved before submitting cocaine-positive urine



12

cocaine contingency management results

13

cocaine contingency management within HAT results – cocaine use (ITT sample)

	HAT only (n = 107)		HAT + CM (n = 107)			
primary outcome measure	**mean**	**sd**	**mean**	**sd**	**p-value**	**Cohen's d**
# weeks longest duration cocaine abstinence	1.59	2.17	3.72	5.84	< 0.001	0.48 (0.21 – 0.76)
secondary cocaine-related outcome measures	**mean**	**sd**	**mean**	**sd**	**p-value**	**Cohen's d**
# weeks cocaine negative urine-samples	3.62	4.57	6.25	8.24	0.008	0.47 (0.20 – 0.75)
secondary cocaine-related outcome measures	**n**	**%**	**n**	**%**	**p-value**	**NNT**
at least 8 weeks uninterrupted cocaine abstinence	3	2.8	17	15.9	0.003	7.6 (4.8 – 18.2)
at least 12 weeks uninterrupted cocaine abstinence	1	0.9	11	10.3	0.018	10.7 (6.5 – 30.2)
at least 16 weeks uninterrupted cocaine abstinence	0	0.0	7	6.5	0.014	15.3 (8.7 – 63.3)
final four weeks cocaine abstinence	1	0.9	13	12.1	0.010	8.9 (5.7 – 21.0)

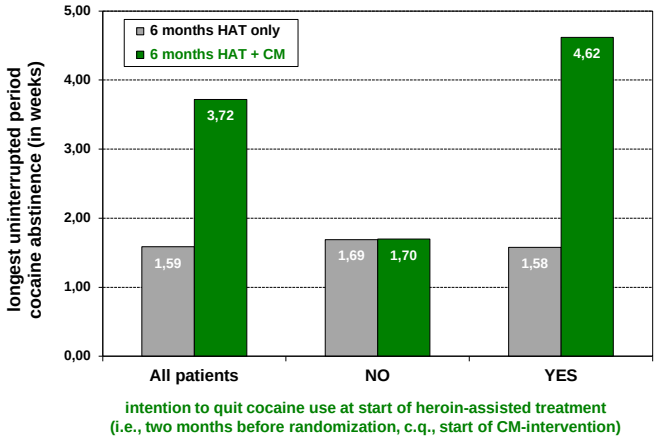
14

cocaine contingency management effect moderators

15

cocaine contingency management within HAT secondary analysis – effect moderation

- cocaine use
- treatment history
- intention



treatment ∗ intention

p = 0.001

$d_{\text{INTENTION-NO}}$ = 0.00

$d_{\text{INTENTION-YES}}$ = 0.61

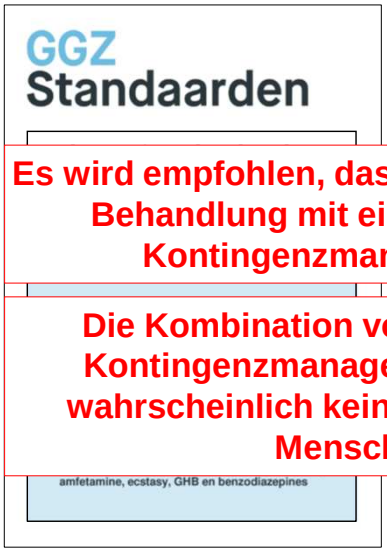
16

Dutch guideline: Treatment non-opioid drug use disorders

https://www.ggzstandaarden.nl/richtlijnen/stoornissen-in-het-gebruik-van-cannabis-cocaine-amfetamine-ecstasy-ghb-en-benzodiazepines/introductie
accessed: Thursday, 29 September 2022

17

Dutch guideline: Treatment non-opioid drug use disorders



- **major recommendations: psychological treatment cocaine**
  - **1st choice: contingency management**

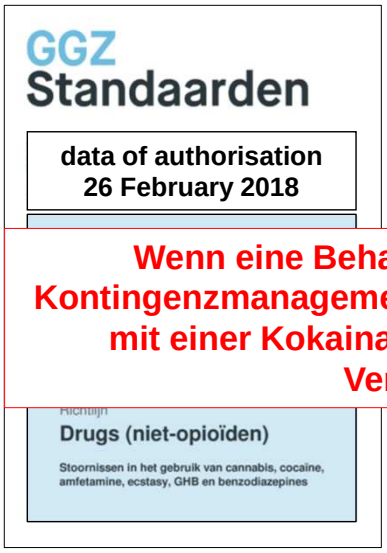
Es wird empfohlen, dass bei Personen mit einer Kokainabhänigkeit eine Behandlung mit einem auf den Drogenkonsum ausgerichteten Kontingenzmanagement als erste Wahl angeboten wird.

Die Kombination von auf den Substanzkonsum ausgerichtetem Kontingenzmanagement und kognitiven Verhaltenstherapie hat wahrscheinlich kein zusätzlichen Nutzen bei der Behandlung von Menschen mit einer Kokainabhänigkeit.

https://www.ggzstandaarden.nl/richtlijnen/stoornissen-in-het-gebruik-van-cannabis-cocaine-amfetamine-ecstasy-ghb-en-benzodiazepines/introductie
accessed: Thursday, 29 September 2022

18

Dutch guideline: Treatment non-opioid drug use disorders



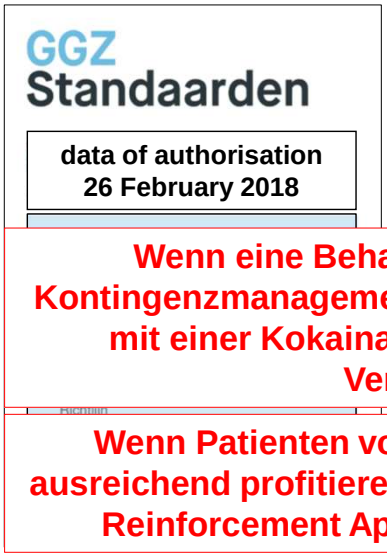
- **major recommendations: psychological treatment cocaine**
  - **1st choice: contingency management**
  - **2nd choice: cognitive behaviour therapy**

Wenn eine Behandlung mit substanzkonsumorientiertem Kontingenzmanagement nicht möglich ist, wird empfohlen, Personen mit einer Kokainabhängigkeit eine Behandlung mit kognitiver Verhaltenstherapie anzubieten.

https://www.ggzstandaarden.nl/richtlijnen/stoornissen-in-het-gebruik-van-cannabis-cocaine-amfetamine-ecstasy-ghb-en-benzodiazepines/introductie
accessed: Thursday, 29 September 2022

19

Dutch guideline: Treatment non-opioid drug use disorders



- **major recommendations: psychological treatment cocaine**
  - **1st choice: contingency management**
  - **2nd choice: cognitive behaviour therapy**
  - **3rd choice: community reinforcement approach**

Wenn eine Behandlung mit substanzkonsumorientiertem Kontingenzmanagement nicht möglich ist, wird empfohlen, Personen mit einer Kokainabhängigkeit eine Behandlung mit kognitiver Verhaltenstherapie anzubieten.

Wenn Patienten von einer kognitiven Verhaltenstherapie nicht ausreichend profitieren, könnte eine Behandlung mit dem Community Reinforcement Approach (CRA) in Betracht gezogen werden.

https://www.ggzstandaarden.nl/richtlijnen/stoornissen-in-het-gebruik-van-cannabis-cocaine-amfetamine-ecstasy-ghb-en-benzodiazepines/introductie
accessed: Thursday, 29 September 2022

20

Health insurers Nederland

Zorgverzekeraars Nederland (ZN) is the umbrella organization of eleven health insurers in The Netherlands. ( ). ZN supports its members by fulfilling the mission of the Dutch health insurers: to arrange health care of good quality for their insured, that is affordable and accessible at the same time and aimed at promoting the well-being of their insured.

ZN concluded that: "Kontingenzmanagement ist auf dem neuesten Stand von der Wissenschaft und Praxis" ...
and can be offered "Eigenständig im Falle der Kokainsucht"

Teil der Behandlung: bei Opiatabhängigkeit als zusätzliche Maßnahme zur pharmakologischen Behandlung und bei Cannabis- und (Meth)Amphetaminabhängigkeit nur in Kombination mit CBT als begrenzter Teil der Behandlung und wenn die Behandlungsziele im Behandlungsplan enthalten sind.

https://www.zn.nl/336986125/publicaties?DossierIds=339148801
(accessed: Thursday, 29 September 2022)

21

Health insurers Nederland

Zorgverzekeraars N… …brella
organization… …s in The
Nether… …its members by f… …ling
… …health insurers… …
… …od quality for thei…
… …and accessible at… …d at
… …noting the well-bei…

ZN co…luded that: "Ko… …ist auf dem neuesten
Stand von der Wi… …s" …
and can be… …g im Falle der Kokainsucht"

Teil der Behand… …gkeit als zusätzliche Maßnahme zur pharmakologischen Behandlung und
bei Cannabis- u… …aminabhängigkeit nur in Kombination mit CBT als begrenzter Teil der
Behandlung und … Behandlungsziele im Behandlungsplan enthalten sind.

However, the rewards that patients receive, are not yet reimbursed by the insurance companies !!!

The NZa - Dutch Healthcare Authority - is to come with a solution for this dilemma

https://www.zn.nl/336986125/publicaties?DossierIds=339148801
(accessed: Thursday, 29 September 2022)

22

pharmacological treatments for cocaine

23

effective pharmacotherapy – cocaine

- **6 Cochrane reviews: > 100 studies; > 10,000 patients**
  - **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

24

effective pharmacotherapy – cocaine

- 6 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)

  * the proportion of patients achieving sustained cocaine abstinence was higher with bupropion and dexamphetamine than with placebo.

25

Cocaine
Addiction
Treatments to improve
Control and reduce
Harm



26

CATCH

study 1

topiramate

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/drugalcdep

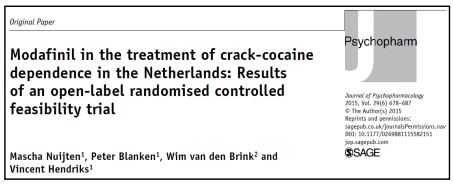
Treatment of crack-cocaine dependence with topiramate: A randomized controlled feasibility trial in The Netherlands

Mascha Nuijten, Peter Blanken, Wim van den Brink, Vincent Hendriks

study 2

modafinil

Jellinek, Amsterdam
Mentrum, Amsterdam
Brijder, The Hague


Original Paper

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

Mascha Nuijten[1], Peter Blanken[1], Wim van den Brink[2] and Vincent Hendriks[1]

Psychopharm

Journal of Psychopharmacology 2015, Vol. 29(6) 678–687

© The Author(s) 2015

SAGE

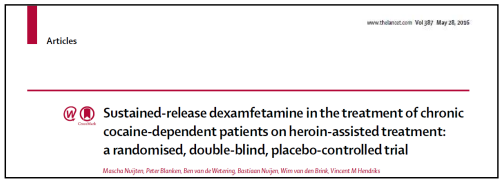
27

CATCH

study 3

dexamfetamine sustained-release

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


www.thelancet.com Vol 387 May 28, 2016

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

28

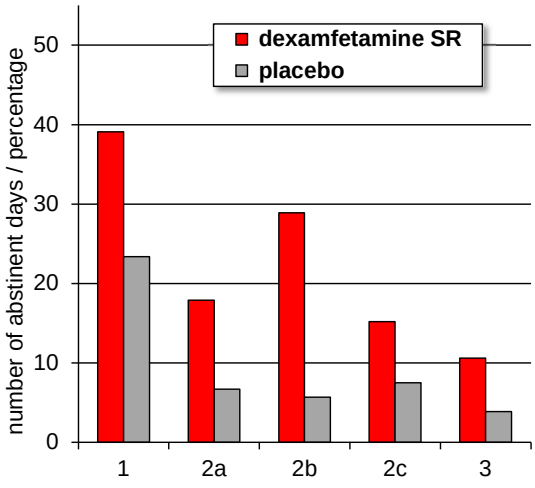
CATCH
results

- **patients**
  - **73 treatment-refractory cocaine dependent patients – participating in heroin-assisted treatment for their comorbid opioid dependence**
- **intervention**
  - **dexamfetamine-SR: n = 38 – 60 mg/day daily supervised intake**
- **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% } **κ = 0.14**

Nuijten et al. 2016 The Lancet

29

CATCH
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

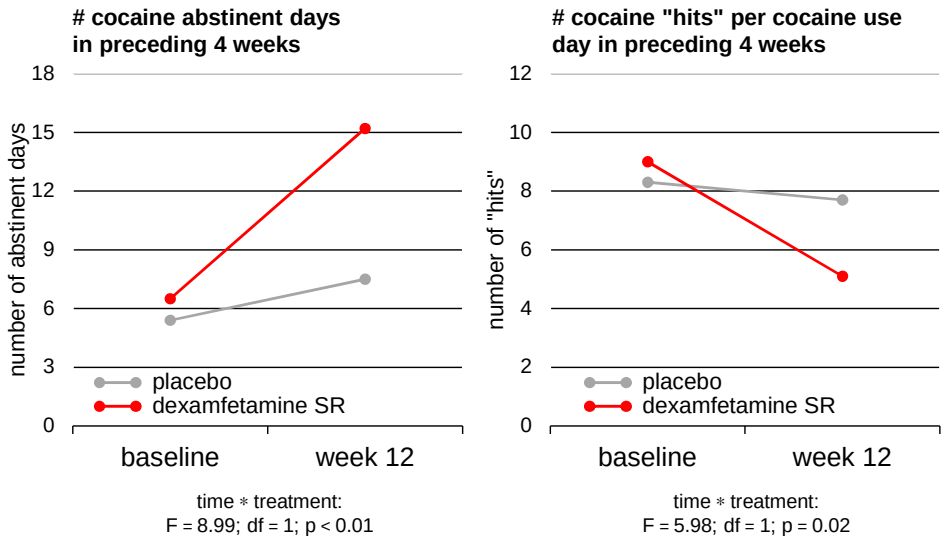
3 cocaine-negative urines
11% *vs.* 4%; p = 0.02; *d* = 0.31

Nuijten et al. 2016 The Lancet

30

CATCH

efficacy



Nuijten et al. 2016 The Lancet

31

CATCH

safety

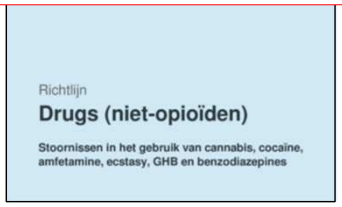
- **medical Adverse Events (AEs)**
  - **dexamfetamine-SR: 74% *versus* placebo: 46% (p = 0.02)**
  - **sleep disturbances, agitation, physical arousal**
  - **mostly mild and transient**
- **premature/temporal discontinuation medication**
  - **serious adverse event (n = 1; placebo; re-started treatment)**
  - **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)**
  - **experienced no medication effect (placebo: n = 1)**
  - **dose reduction (n = 2; SR-dexamfetamine)**

Nuijten et al. 2016 The Lancet

32

Dutch guideline: Treatment non-opioid drug use disorders

GGZ Standaarden



- **major recommendations: pharmacological treatment cocaine**
  - **no proven effective medications**

Trotz zahlreicher Studien gibt es keine überzeugenden Beweise für die Wirksamkeit einer pharmakologischen Behandlung der Kokainabhängigkeit. Bei der Behandlung einer Kokainabhängigkeit sollte man daher mit der Verschreibung von Medikamenten vorsichtig sein.

https://www.ggzstandaarden.nl/richtlijnen/stoornissen-in-het-gebruik-van-cannabis-cocaine-amfetamine-ecstasy-ghb-en-benzodiazepines/introductie
accessed: Thursday, 29 September 2022

33

Dutch guideline: Treatment non-opioid drug use disorders

GGZ Standaarden

data of authorisation
26 February 2018

- **major recommendations: pharmacological treatment cocaine**
  - **no proven effective medications**
  - **if insufficient effect from psychosocial treatment ⇒ indirect dopamine agonist might be considered: sustained-release dexamphetamine / mixed amphetamine salts / bupropion / modafinil**

Bei Erwachsenen mit Kokainabhängigkeit, die von einer psychologischen Behandlung nicht ausreichend profitieren, kann eine Pharmakotherapie mit indirekten Dopaminagonisten in Betracht gezogen werden.

Insbesondere Dexamphetamin und gemischte Amphetaminsalze mit verzögerter Wirkstofffreisetzung und vielleicht auch - bei ausreichender Adhärenz - Bupropion und Modafinil könnten wirksam sein.

https://www.ggzstandaarden.nl/richtlijnen/stoornissen-in-het-gebruik-van-cannabis-cocaine-amfetamine-ecstasy-ghb-en-benzodiazepines/introductie
accessed: Thursday, 29 Sptember 2022

34

Dutch guideline: Treatment non-opioid drug use disorders

GGZ Standaarden

data of authorisation
26 February 2018

- **major recommendations: pharmacological treatment cocaine**
  - **no proven effective medications**
  - **if insufficient effect from psychosocial treatment ⇒ indirect dopamine agonist might be considered: sustained-release dexamphetamine / mixed amphetamine salts / bupropion / modafinil**
  - **off-label ⇒ informed consent, monitoring**

Wenn die Entscheidung getroffen wird, eine Pharmakotherapie für die Behandlung einer Kokainabhänigkeit zu starten, sollte der Arzt den Patienten deutlich darauf hinweisen, dass es sich um ein "Off-Label" verordnetes Arzneimittel handelt und der Patient sein Einverständnis ("informed consent") dazu geben muss. Es wird empfohlen, dies sorgfältig zu legitimieren und zu dokumentieren und den Fortschritt der Behandlungsfortschritte, einschließlich der Nebenwirkungen regelmäßig zu überwachen.

oductie
accessed: Thursday, 29 September 2022

35

what happened since then ...

36

CBG MEB MEDICINES EVALUATION BOARD

Psychopharmacology
https://doi.org/10.1007/s00213-020-05563-3

REVIEW

Check for updates

Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis

Vitor S. Tardelli[1] · Adam Bisaga[2] · Felipe B. Arcadepani[1] · Gilberto Gerra[3] · Frances R. Levin[2] · Thiago M. Fidalgo[1]

Conclusion Prescription psychostimulants, particularly prescription amphetamines given in robust doses, have a clinically significant beneficial effect to promote abstinence in the treatment of individuals with PSUD, specifically the population with cocaine use disorder.

https://www.unodc.org/documents/drug-prevention-and-treatment/Treatment_of_PSUD_for_website_24.05.19.pdf
accessed: Thursday, 29 September 2022

37

CBG MEB MEDICINES EVALUATION BOARD

ZonMw

The Netherlands Organisation for Health Research and Development

ZonMw

Full application – Rational Pharmacotherapy
5th Rediscovery call

FULL APPLICATION FORM – 5th REDISCOVERY CALL

Rational Pharmacotherapy
(Goed Gebruik Geneesmiddelen)

Deadline for submission: 11th of January, 2022 (14:00h)

38

Cocaine
Addiction
Treatments to improve 2.0
Control and reduce
Harm



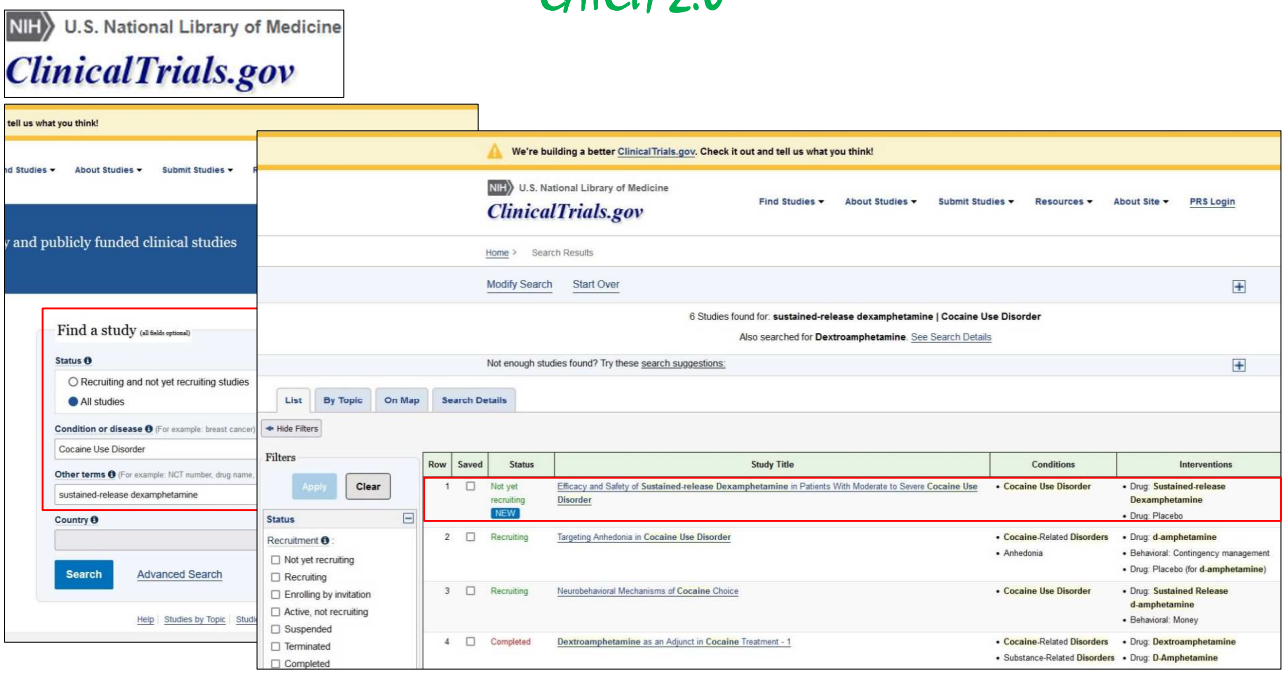
39

CATCH 2.0
objectives and design

- **objectives**
  - efficacy of 24 weeks SR-dexamphetamine treatment in patients with moderate/ severe cocaine use disorder, participating in routine methadone maintenance treatment for their comorbid opioid use disorder
  - consequences of discontinuation of SR-dexamphetamine after 24 weeks
- **design: double-blind, placebo-controlled randomised trial**
- **intervention**
  - individually titrated SR-dexamphetamine: **max. 90 mg/day (3 tablets of 30 mg)**
  - medication (*verum* and placebo): dispensed **twice weekly** + **take-home doses**
- **outcome parameters**
  - primary endpoint: days cocaine abstinence in final 4 weeks of treatment
  - key secondary endpoint: overall health status (physical, mental, social)
  - **safety** (e.g., ECG, vital signs, haematology, (S)AEs) – and testing **study blind**

40

CATCH 2.0



https://www.clinicaltrials.gov/ct2/results?cond=Cocaine+Use+Disorder&term=sustained-release+dexamphetamine&cntry=&state=&city=&dist=
accessed: Thursday, 29 September 2022

41

I would like to thank …

* all the **patients** and **treatment staff** that participated in and contributed to our studies

* my **colleagues**:

- Vincent M Hendriks, PhD. Prof.
- Wim van den Brink, PhD. Prof.
- Mascha Nuijten, PhD.
- Jos H Beijnen, PhD. Prof.
- Bastiaan Nuijen, PhD
- Ben van de Wetering, PhD
- Manja van der Toorn
- Jan M van Ree, PhD. Prof.
- Ineke A Huijsman, LL.M.
- and many others ...

for more information

www.brijder.nl/wetenschappelijk-onderzoek

Brijder

peter.blanken@brijder.nl

PARC
Parnassia Addiction Research Centre

42