

# Added Value of Cocaine Contingency Management in Heroin-Assisted Treatment Results from a Randomized Controlled Trial



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ADDICTION  RESEARCH

THS11 - Les Rencontres de Biarritz  
Biarritz, 10 October 2013

# Content



- HAT for treatment resistant patients
- Adding Cocaine Contingency Management
- Conclusions and Recommendations



# Heroin-Assisted Treatment



# HAT in the Netherlands

Supplement European Neuropsychopharmacology, 2010



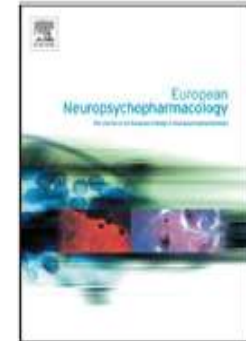
European Neuropsychopharmacology (2010) 20 (Supplement 2), S105–S158

(50 pages overview)



ELSEVIER

[www.elsevier.com/locate/euroneuro](http://www.elsevier.com/locate/euroneuro)



## Heroin-assisted treatment in the Netherlands: History, findings, and international context ☆

Peter Blanken<sup>a,b,+</sup>, Wim van den Brink<sup>a,c,+,\*</sup>, Vincent M. Hendriks<sup>a,b</sup>,  
Ineke A. Huijsman<sup>a</sup>, Marjolein G. Klous<sup>d</sup>, Elisabeth J. Rook<sup>d,e</sup>,  
Jennifer S. Wakelin<sup>f</sup>, Cas Barendrecht<sup>g</sup>, Jos H. Beijnen<sup>d</sup>, Jan M. van Ree<sup>a,h</sup>

<sup>+</sup> Both authors contributed equally.

# HAT in the Netherlands

Two RCTs 1998-2002



Test HAT in chronic, treatment-refractory heroin dependent patients recruited from methadone maintenance treatments

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## Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials

Wim van den Brink, Vincent M Hendriks, Peter Blanken, Maarten W J Koeter, Barbara J van Zwieten, Jan M van Ree

BMJ

2003

(August 2013: cited 125 times)

# Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials

Wim van den Brink, Vincent M Hendriks, Peter Blanken, Maarten W J Koeter,  
Barbara J van Zwieten, Jan M van Ree

2003



BMJ

Age (mean)	39 years	
Gender (% males)	19%	
Ethnicity (% Dutch/Western)	86%	
Duration heroin use (mean)	16 years	26 days/month
Duration cocaine use (mean) – 92%	10 years	18 days/month
Duration poly drug use (mean)	17 years	29 days/month
Duration methadone treatment (mean)	12 years	29 days/month
Physical problems (MAP-HSS >8)	66%	
Mental problems (SCL-90 > 41/60)	60%	
Social problems (> 6 days crime/no contact)	72%	

# Primary Outcome: Responder



At least 40% improvement in mental health

AND/OR

At least 40% improvement in physical health

AND/OR

At least 40% improvement in social function (incl. criminality)

AND

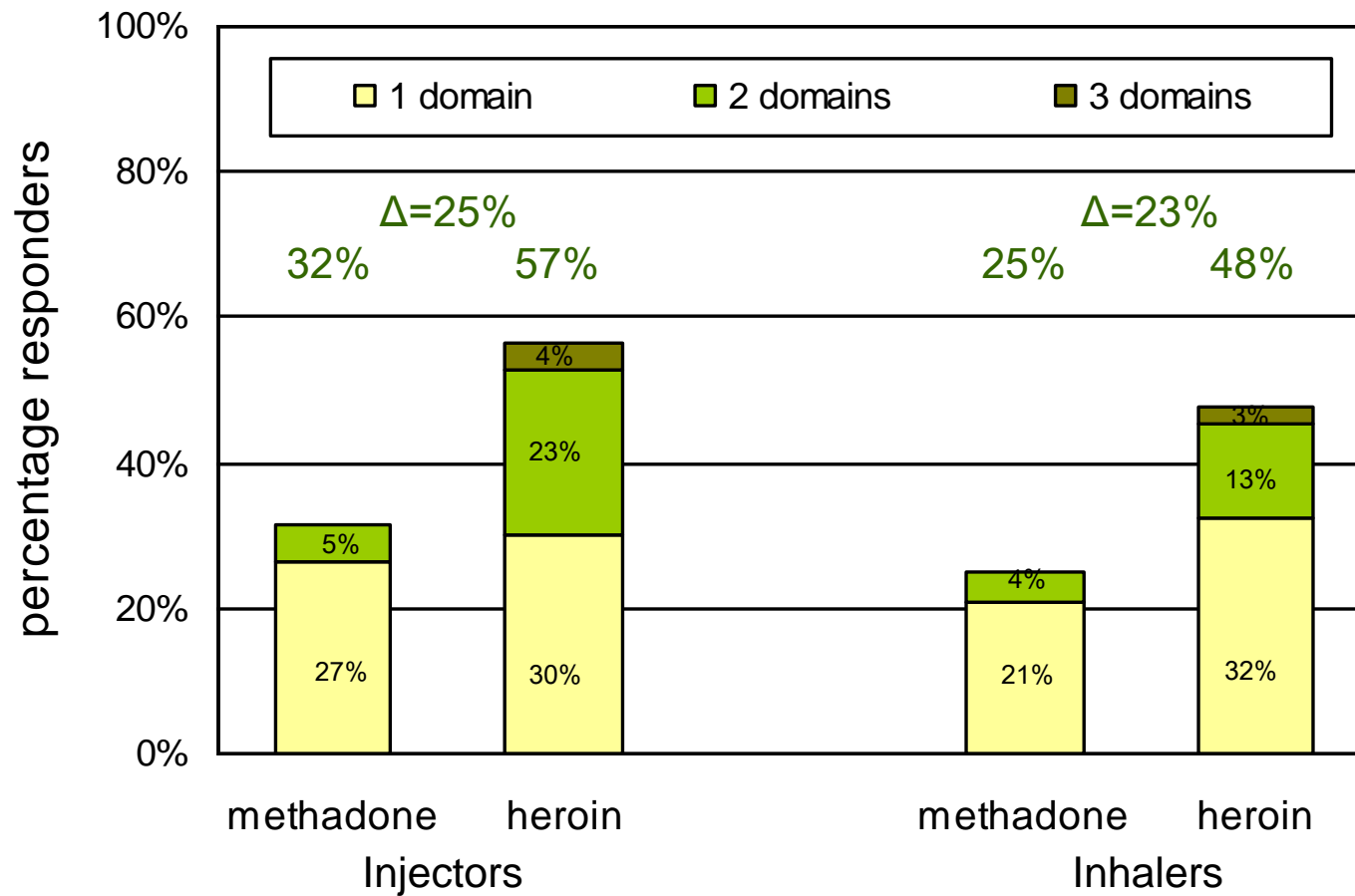
No substantial (>40%) deterioration in any of previous domains

AND

No substantial (> 6days/mnth) increase in cocaine/amphetamines

# Results

## Percentage responders

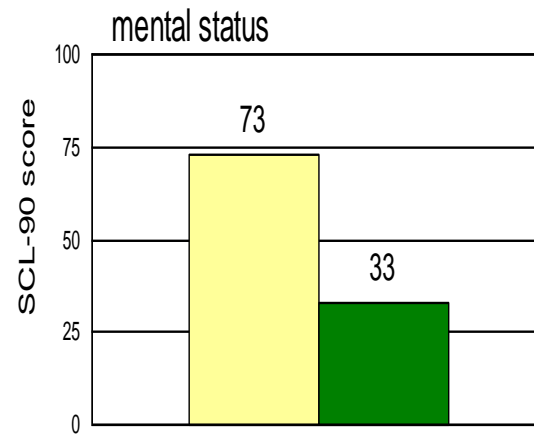
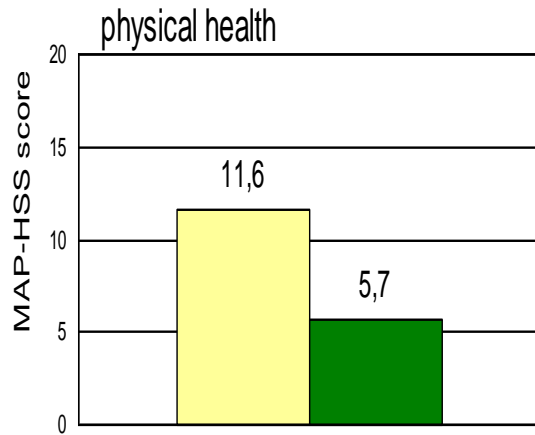


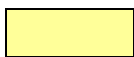

**NNT = 4**

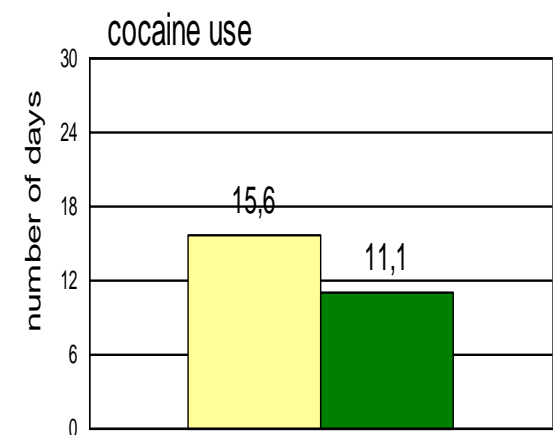
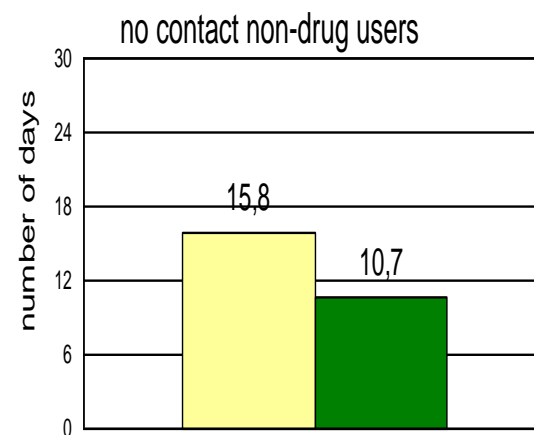
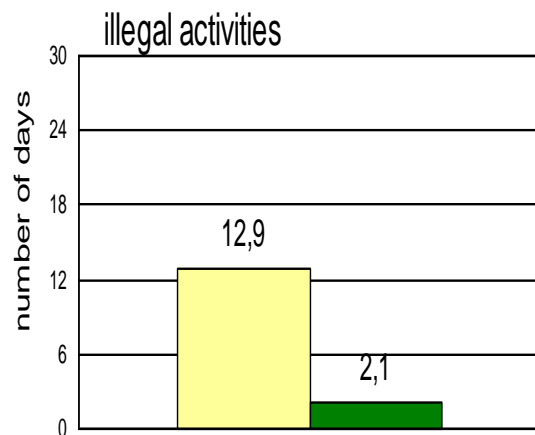


# Results

## Improvement in Responders



 = baseline  
 = 12 months



## Matching of treatment-resistant heroin-dependent patients to medical prescription of heroin or oral methadone treatment: results from two randomized controlled trials

Peter Blanken<sup>1</sup>, Vincent M. Hendriks<sup>1,2</sup>, Maarten W. J. Koeter<sup>3</sup>, Jan M. van Ree<sup>1,4</sup> & Wim van den Brink<sup>1,3</sup>

Central Committee on the Treatment of Heroin Addicts, Utrecht, the Netherlands; <sup>1</sup>Parnassia Addiction Research Centre, The Hague, the Netherlands; <sup>2</sup>Amsterdam Institute for Addiction Research, Amsterdam, the Netherlands; <sup>3</sup>and Rudolf Magnus Institute of Neuroscience, Utrecht University, Utrecht, the Netherlands<sup>4</sup>



### ABSTRACT

**Aims** To investigate which baseline patient characteristics of treatment-resistant heroin addicts differentially predicted treatment response to medical heroin prescription compared to standard methadone maintenance treatment. **Design** Two open-label randomized controlled trials; pooled data.

**Setting** Methadone maintenance programmes and heroin treatment centres in six cities in the Netherlands.

**Participants** Four hundred and thirty heroin addicts.

**Intervention** Methadone plus injectable heroin or methadone plus inhalable heroin compared to methadone alone prescribed over 12 months: heroin maximum 1000 mg per day, methadone maximum 150 mg per day.

**Main outcome measure** Dichotomous, multi-domain response index, including validated indicators of physical health, mental status and social functioning.

**Findings** Data of the inhalable and injectable heroin trials were pooled. Intention-to-treat analysis showed that treatment with medically prescribed heroin plus methadone was significantly more effective (51.8% response) than standard methadone maintenance treatment (28.7%) (95% CI of response difference: 14.1–32.2%). Multivariate logistic regression analyses showed that only one of all baseline characteristics was predictive of a differential treatment effect: patients who had previously participated in abstinence-orientated treatment responded significantly better to heroin-assisted treatment than to methadone treatment (61% versus 24%), while patients without experience in abstinence-orientated treatment did equally well in heroin-assisted or methadone maintenance treatment (39% and 38%, respectively).

**Conclusions** The effect of heroin-assisted treatment is not dependent on clinical characteristics, with the exception of previous abstinence-orientated treatment: medical prescription of heroin is most effective for those patients who have previously participated in abstinence-orientated treatment.

Level of baseline cocaine use predicts Tx retention but not Tx response

No clinical treatment outcome predictors with one exception:

Previous experiences with abstinence oriented treatments (also in German trials)

# Efficacy and Safety of HAT



## Heroin maintenance for chronic heroin-dependent individuals (Review)

Ferri M, Davoli M, Perucci CA



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This is a report of a Cochrane review, prepared and maintained by The Cochrane Collaboration.  
2011, Issue 12

<http://www.thecochranelibrary.com>



Heroin maintenance for chronic heroin-dependent individuals (Review)  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## AUTHORS' CONCLUSIONS:

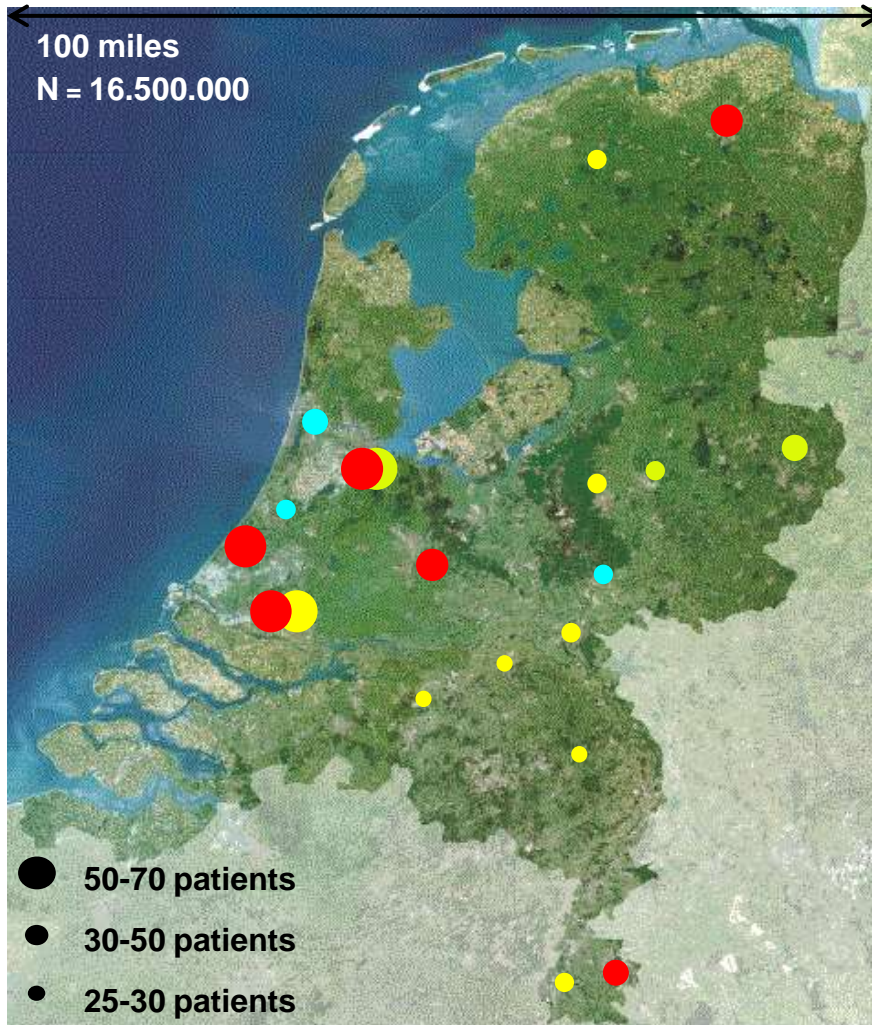
The available evidence suggests an added value of heroin, prescribed alongside flexible doses of methadone for long-term, treatment refractory, opioid users to reach:

- \* a decrease in the use of illicit substances, involvement in criminal activity/incarceration,
- \* a possible reduction in mortality, and
- \* an increase in retention in treatment.

Due to the higher rate of serious adverse events, heroin pre-scription should remain a treatment for people who are currently or have in the past failed maintenance treatment, and it should be provided in clinical settings where proper follow-up is ensured.

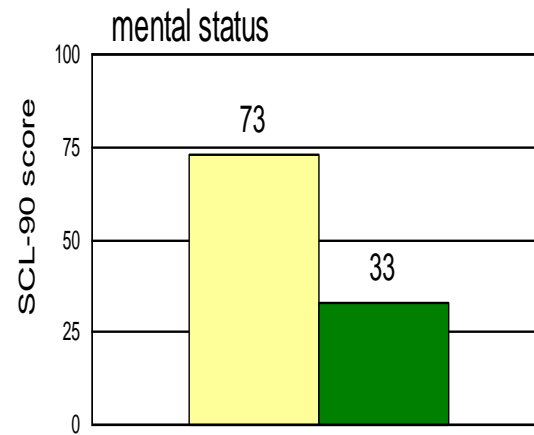
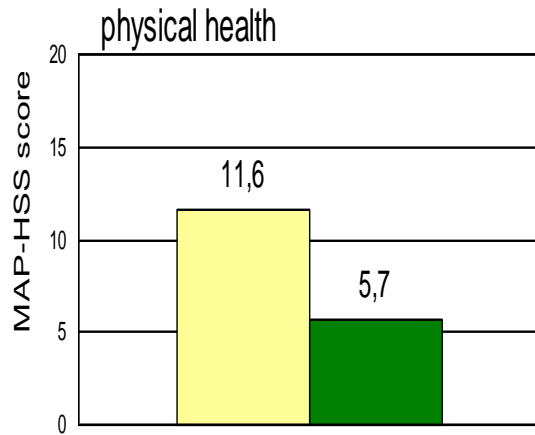


# Current situation

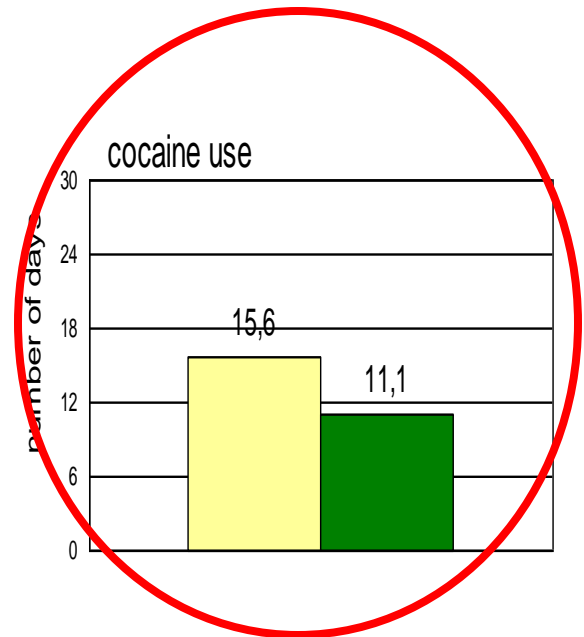
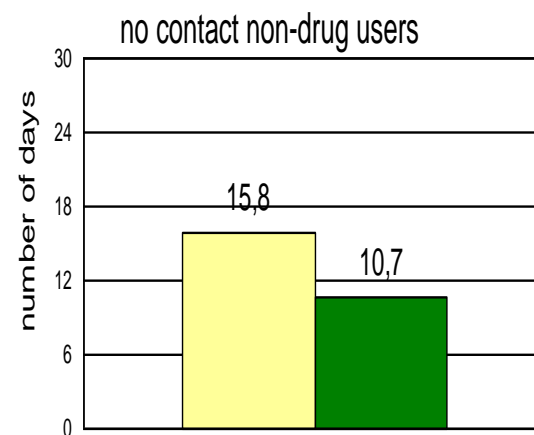
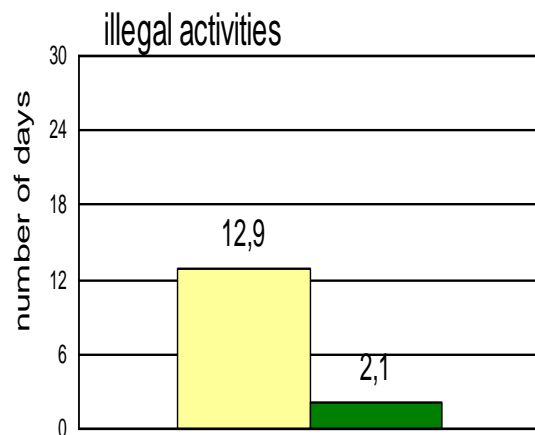


<b>units:</b>	<b>6</b>	<b>→</b>	<b>15</b>	<b>→</b>	<b>20</b>
<b>slots:</b>	<b>300</b>	<b>→</b>	<b>800</b>	<b>→</b>	<b>1.000</b>

# HOWEVER.....



 = baseline  
 = 12 months



# *Add-On Cocaine* Contingency Management



# Rationale



- Heroin-assisted treatment is effective,  
HOWEVER
- Modest reductions cocaine use:
  - at baseline: 84% cocaine use 16 days/month
  - after 12 months: 79% cocaine use 11 days/month
- predictor of (early) treatment discontinuation
- *no* predictor of treatment response

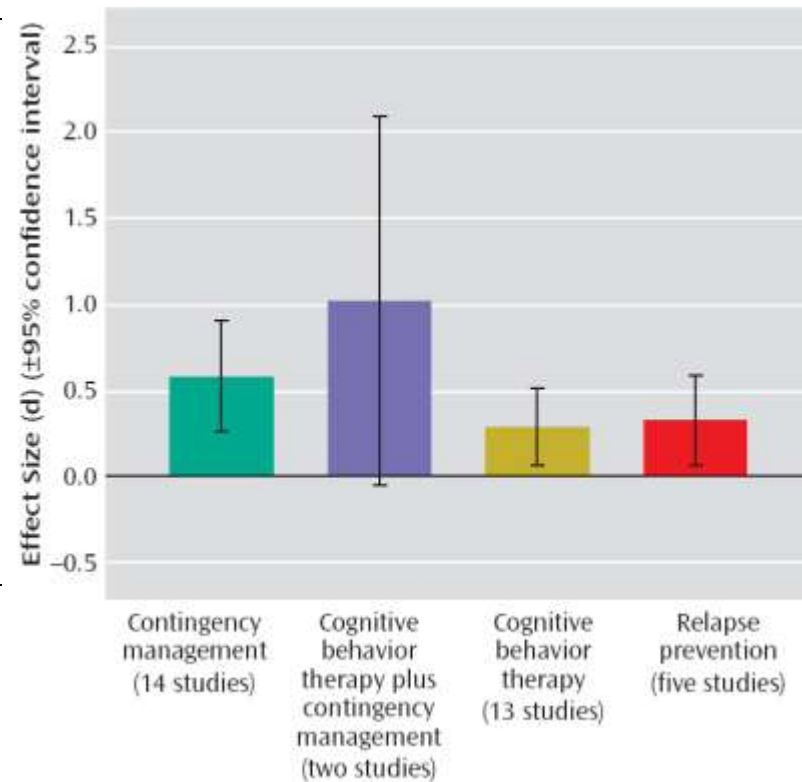
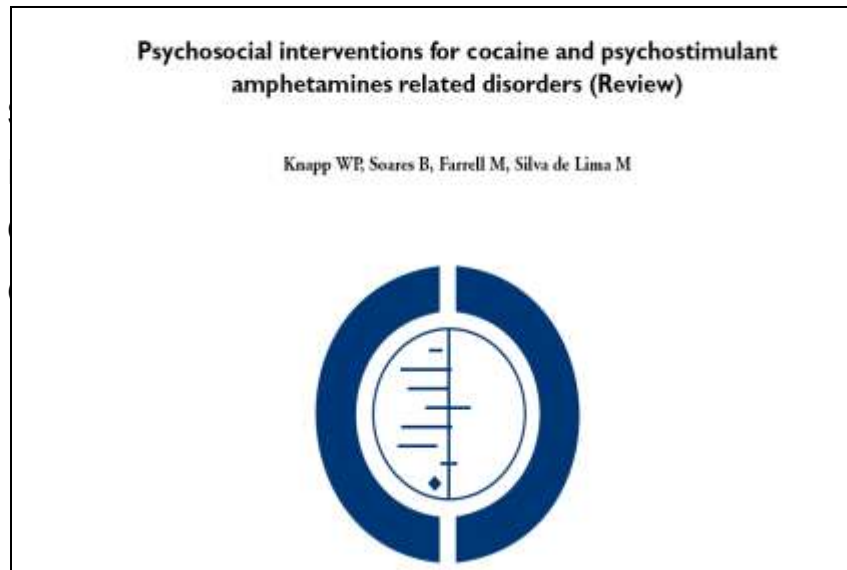
## ***Solutions:***

- *add on* intervention(s) to reduce cocaine use?
  - \* effective pharmacotherapy - not yet !
  - \* psychosocial interventions ?

# Rationale



- \* *add on* intervention(s) to reduce cocaine use?
- \* psychosocial interventions?



 ***contingency***



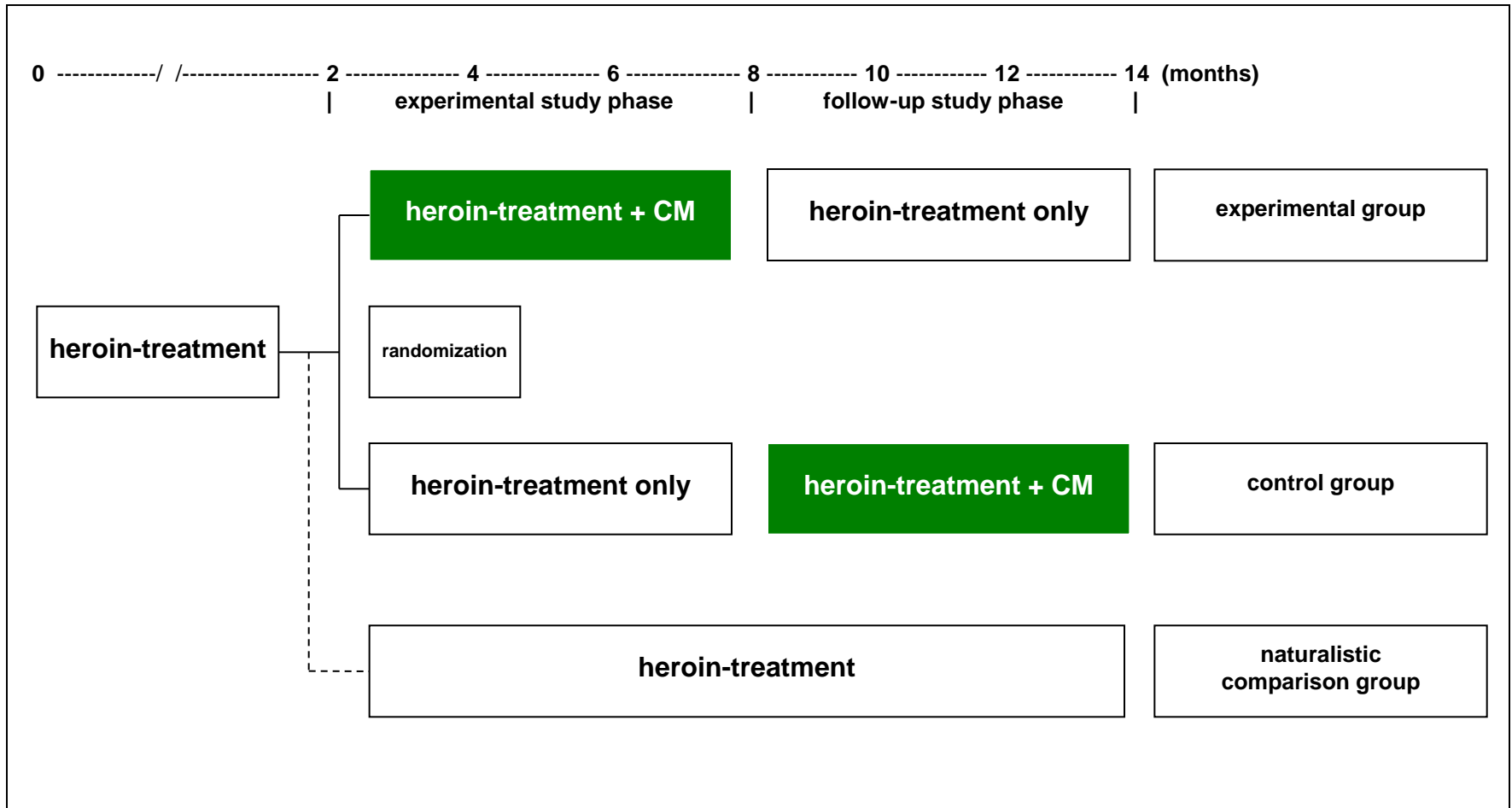
# Study objectives



- Efficacy of 6 months ongoing HAT *plus* cocaine CM vs. 6 months ongoing HAT alone
- In chronic treatment-refractory heroin dependent patients with substantial cocaine use
- Outcomes
  - \* Changes in
    - cocaine consumption
    - physical, mental and social health
    - treatment retention
  - \* Effect of terminating CM while continuing HAT

# Study design

Randomized waiting list design (multi-centre)



# Target population



- **chronic treatment-refractory heroin addicts**
- **heroin-assisted treatment for two months**
- **clinically relevant cocaine use**
  - in month before heroin assisted treatment:
    - ≥ 1 cocaine positive urine (out of 4), and
    - ≥ 4 days self-reported cocaine use; and
  - in second month of heroin assisted treatment:
    - ≥ 2 cocaine positive urines (out of 12), and
    - ≥ 4 days self-reported cocaine use

# Assessments



- urinalysis: 1-3 times per week
  - rapid test + laboratory verification
- interviews: bi-monthly
  - European Addiction Severity Index + supplements
    - physical health (MAP-HSS; EuroQoL)
    - mental health (SCL-90)
    - social health (EuropASI - supplement)
    - cocaine use (OTI - cocaine use questions)
    - OCDUS - cocaine version

# Outcome measures

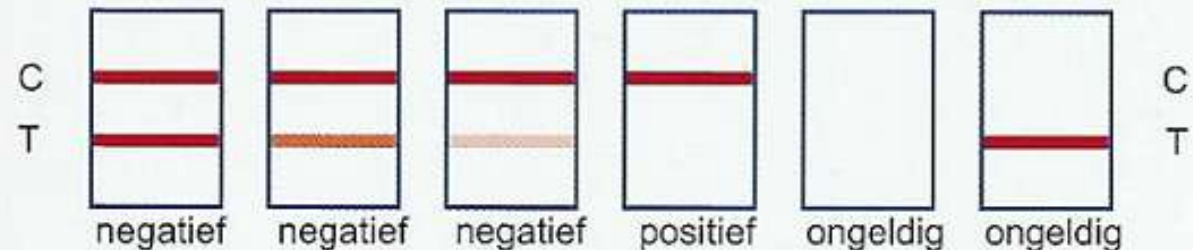


- **primary outcome measure: urinalysis**
  - longest period cocaine metabolite free urines
- **secondary outcome measures:**
  - total number of cocaine metabolite free urines
  - percentage of patients with cocaine metabolite free urines for at least 8, 12, and 16 consecutive weeks
  - cocaine use patterns and craving
  - treatment retention
  - multi-domain response index: physical, mental and social health

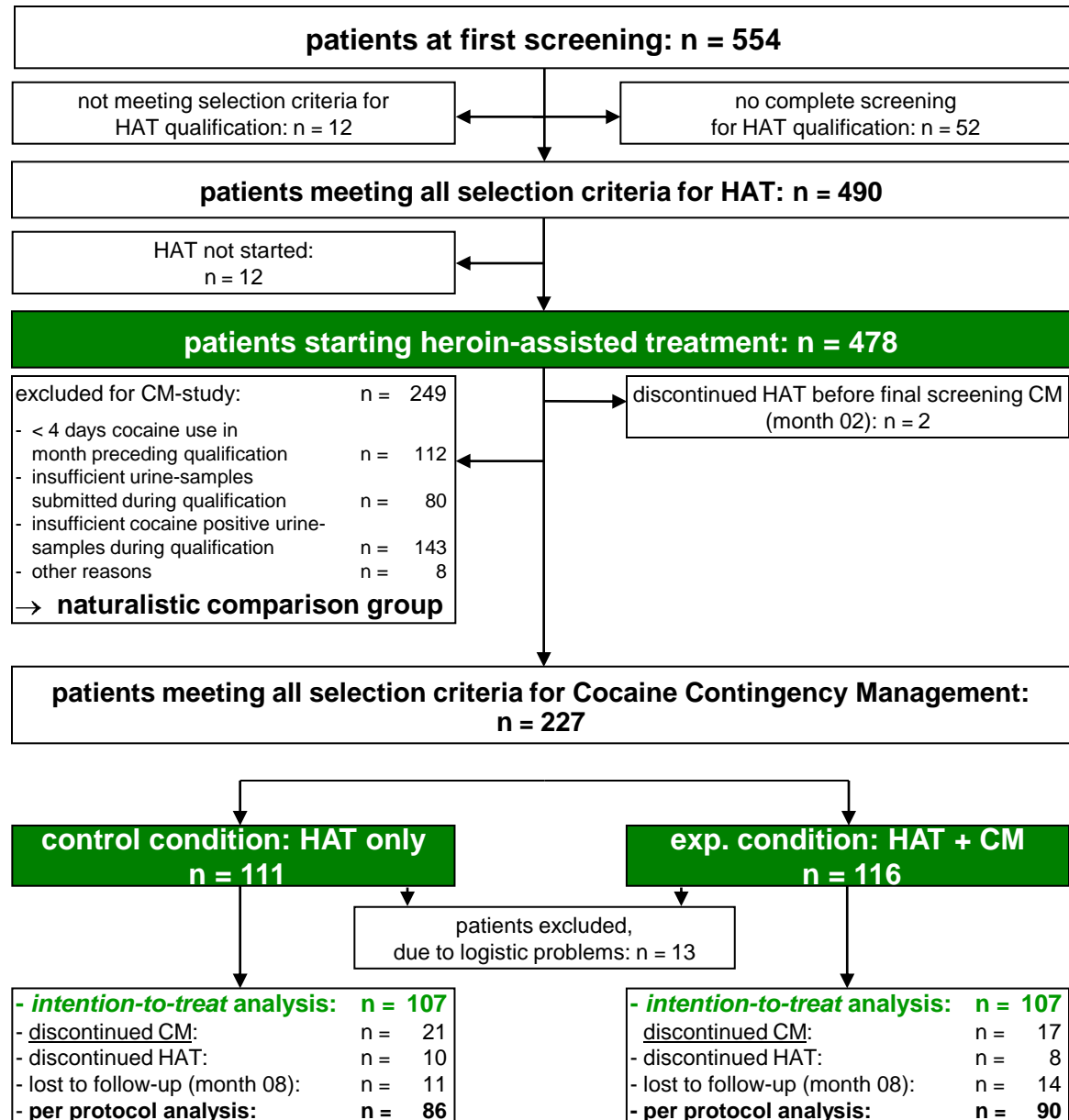
# Intervention



- supervised collection urine samples: 1-3 samples per week
- rapid test: cocaine metabolites
  - cocaine-negative urines are reinforced: vouchers
  - cocaine-positive urines are ignored
- Positive test sent for confirmation
- outcome entered into web-based computer program



# Results:



# Patient characteristics (N = 214)

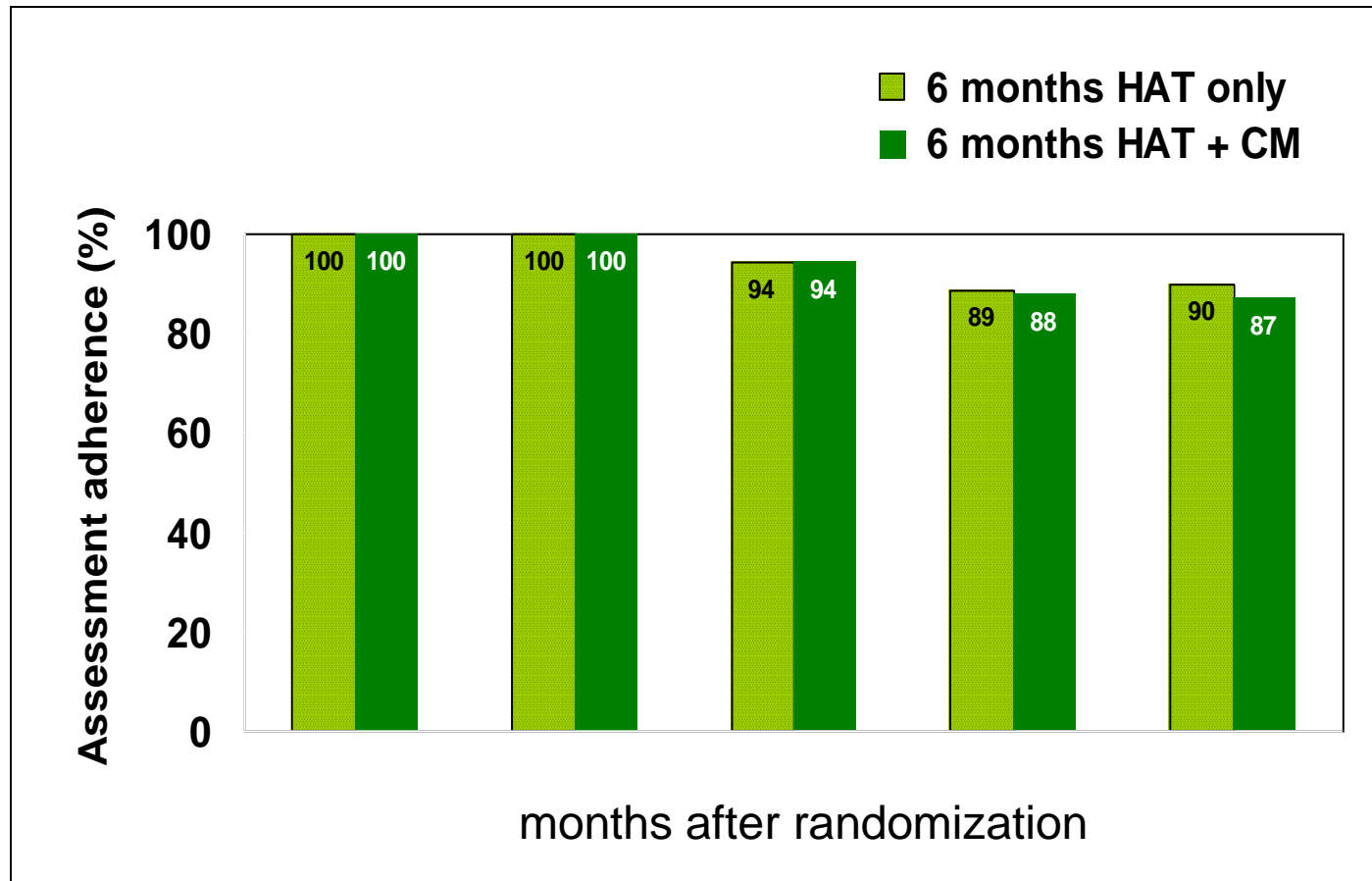


- demographics
  - age 44 years
  - female patients 15 %
  - Dutch/Western 70 %
- substance use
  - heroin 21 years 25 days/month
  - methadone 15 years 30 days/month
  - cocaine 17 years (99%) 19 days/month (100%)
  - poly drug use 22 years 28 days/month
- health status
  - physical problems 76 %
  - psychiatric problems 74 %  $\geq 2$  problem domains: 78%
  - social problems 67 %
- prescribed medication: 86% inhalable heroin



# Assessment Adherence

## ITT Sample



# Primary Outcome (ITT)

## Longest duration cocaine abstinence



primary outcome measure	HAT only (n = 107)		HAT + CM (n = 107)		p-value	Cohen's d
	mean	stddev	mean	stddev		
# weeks longest duration cocaine abstinence	1.79	2.26	3.89	6.03	0.001	0.46 (0.19 – 0.73)

# Cocaine Outcomes

## ITT Sample



	HAT only (n = 107)		HAT + CM (n = 107)			
primary outcome measure	mean stddev		mean stddev		p-value	Cohen's d
# weeks longest duration cocaine abstinence	1.79	2.26	3.89	6.03	0.001	0.46 (0.19 – 0.73)
secondary cocaine-related outcome measures	n	%	n	%		Cohen's d / NNT
# cocaine negative urine-samples	3.86	4.69	6.37	8.37	0.008	0.47 (0.20 – 0.75)
at least 8 weeks uninterrupted cocaine abstinence	3	2.8	19	17.8	< 0.001	6.7 (4.4 – 14.2)
at least 12 weeks uninterrupted cocaine abstinence	1	0.9	12	11.2	0.003	9.7 (6.0 – 24.8)
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	15	14.0	< 0.001	7.6 (5.0 – 16.0)

# Cocaine Outcomes

## ITT vs. Treatment Completers



	ITT-sample (n = 214)	TC-sample (n = 176)
<b>primary outcome measure</b>	<b>Cohen's d</b>	<b>Cohen's d</b>
# weeks longest duration cocaine abstinence	0.46 (0.19 – 0.73)	0.57 (0.27 – 0.87)
<b>secondary cocaine-related outcome measures</b>	<b>Cohen's d / NNT</b>	<b>Cohen's d / NNT</b>
# cocaine negative urine-samples	0.47 (0.20 – 0.75)	0.46 (0.16 – 0.76)
at least 8 weeks uninterrupted cocaine abstinence	6.7 (4.4 – 14.2)	5.0 (3.4 – 9.2)
at least 12 weeks uninterrupted cocaine abstinence	9.7 (6.0 – 24.8)	7.8 (4.9 – 19.2)
at least 16 weeks uninterrupted cocaine abstinence	15.3 (8.7 – 63.3)	12.3 (7.0 – 48.8)
final four weeks cocaine abstinence	7.6 (5.0 – 16.0)	6.1 (4.1 – 12.5)

# Tx Retention & Tx Response

(ITT sample)



secondary (non cocaine-related) outcome measures	HAT only (n = 107)		HAT + CM (n = 107)		p-value	NNT	
	n	%	n	%			
treatment retention (ITT-sample; n = 214)	97	90.7	99	92.5	0.81	53.5	(10.7 – ∞)
treatment response (ITT-sample; n = 214) *	51	47.7	57	53.3	0.49	17.8	(5.3 – ∞)

\* treatment response after two months heroin-assisted treatment, i.e. at start of cocaine contingency management intervention:

HAT only: 43.9 % → 47.7% → ↑ 3.8%

HAT + CM: 37.4 % → 53.3% → ↑ 15.9%

# Tx Retention & Tx Response

(ITT sample)



secondary (non cocaine-related) outcome measures	HAT only (n = 107)		HAT + CM (n = 107)		p-value	NNT	
	n	%	n	%			
treatment retention (ITT-sample; n = 214)	97	90.7	99	92.5	0.81	53.5	(10.7 – ∞)
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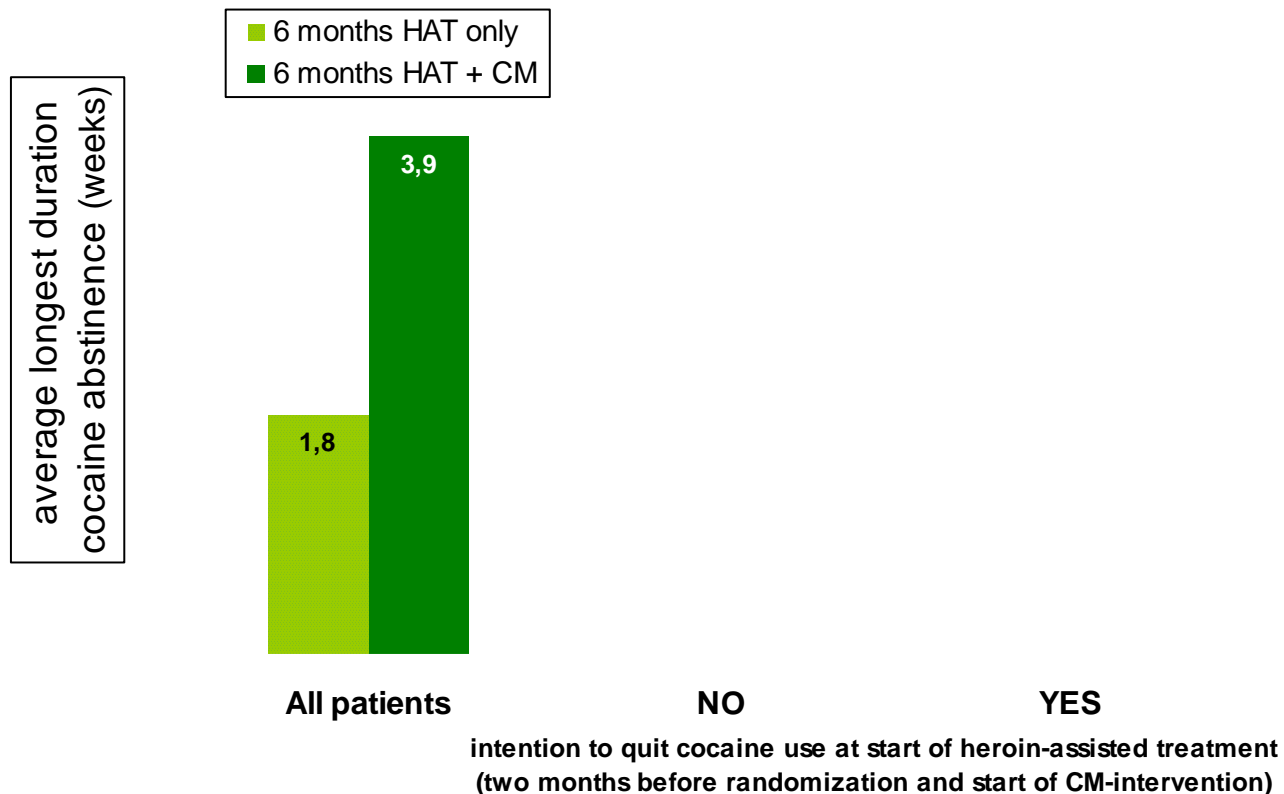
\* treatment response after two months heroin-assisted treatment, i.e. at start of cocaine contingency management intervention:

HAT only:	43.9 %	→	47.7%	→	↑	3.8%
			Δ = 5.6%		Δ = 12.1%	
HAT + CM:	37.4 %	→	53.3%	→	↑	15.9%

# Patient byTx Interaction



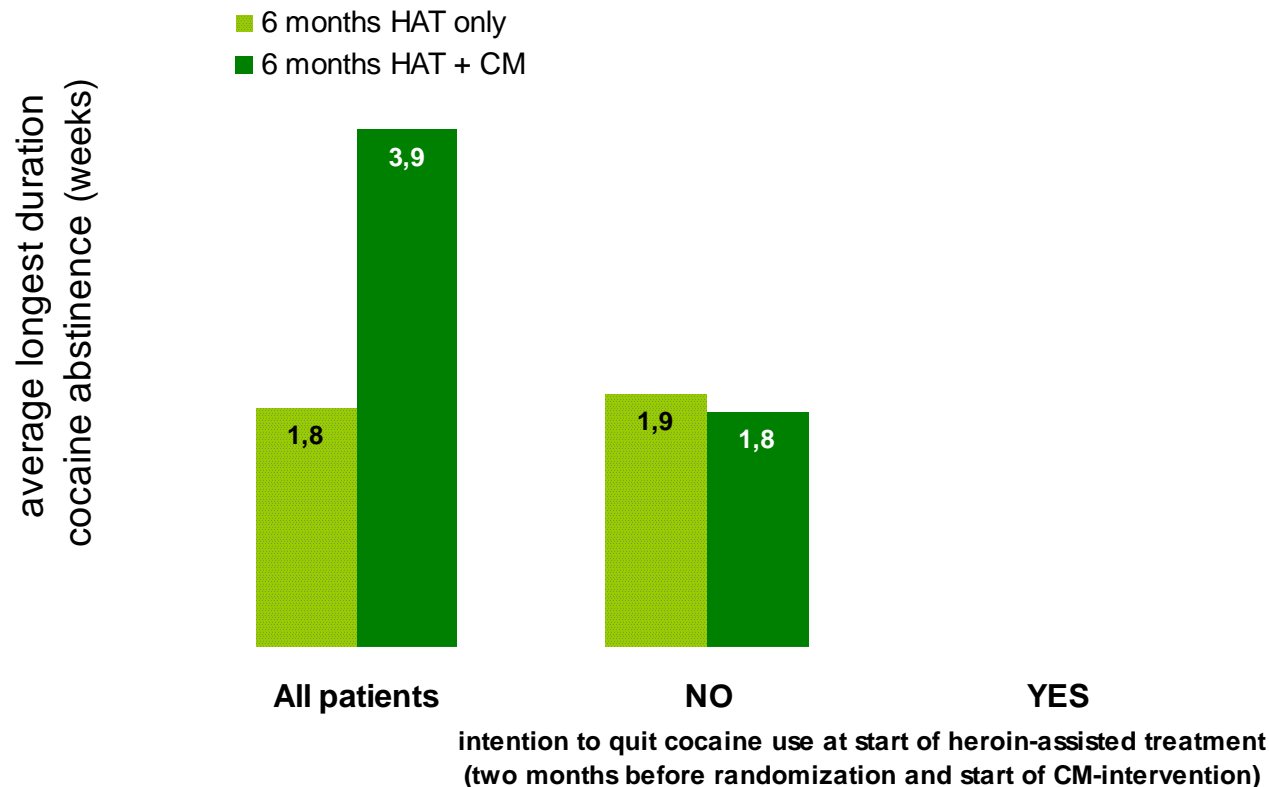
- level of cocaine use at baseline
- treatment history: abstinence Tx
- **intention to stop cocaine use**



# Patient byTx Interaction



- level of cocaine use at baseline
- treatment history: abstinence Tx
- **intention to stop cocaine use**

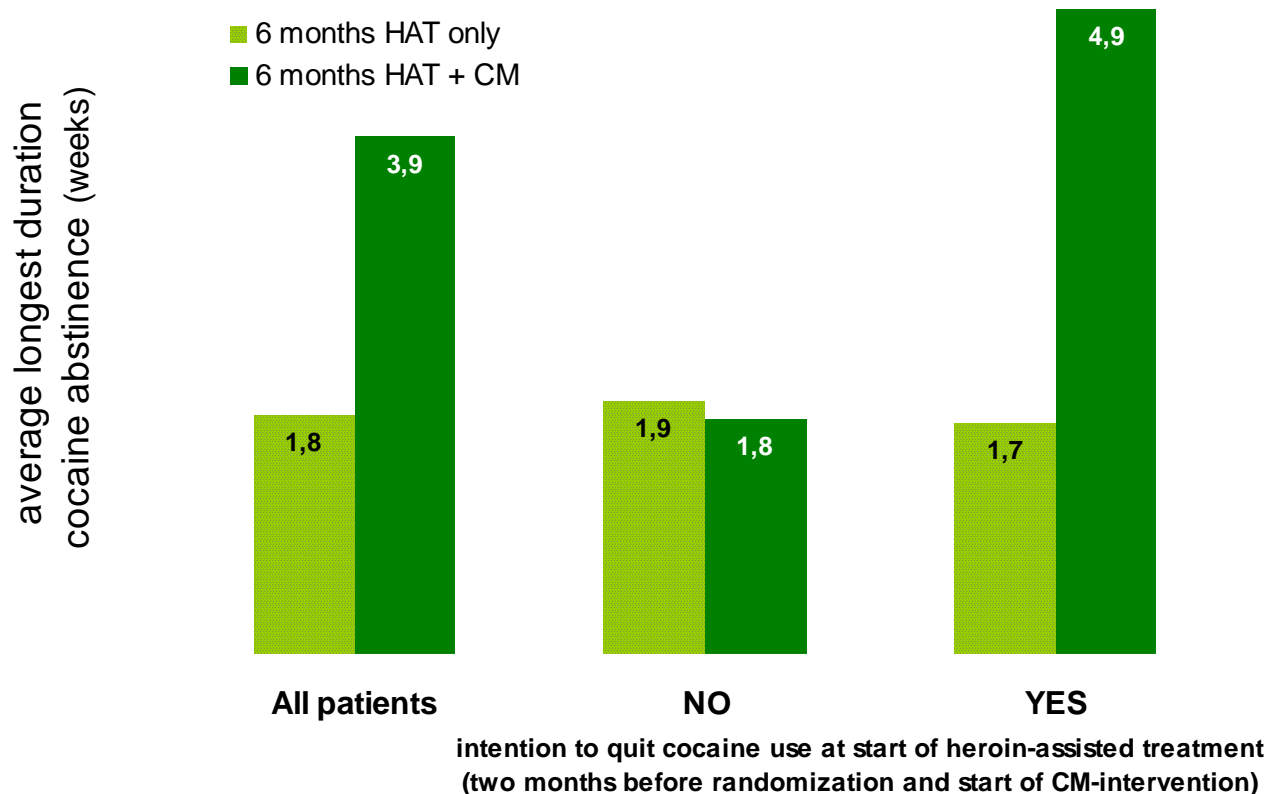




# Patient byTx Interaction



- level of cocaine use at baseline
- treatment history: abstinence Tx
- **intention to stop cocaine use**



# Conclusions CM Trial



- Trial was successfully implemented
- Cocaine CM is effective *add on* psychosocial intervention to HAT in terms of cocaine use
- Motivation is potential effect modifier
- no indication (yet) of effect on Tx retention/Tx response
- consequences of discontinuation CM not yet clear:

# Conclusions



# Conclusions



- HAT is effective Tx option for chronic treatment refractory cases
- HAT is effective, safe and cost effective with positive long-term outcomes.
- Unfortunately about 50% is not responding to HAT →
- Additional Tx and care options are needed, e.g. **improvement of HAT**, **new medications**, **user rooms**, **deep brain stimulation (DBS)**?
- Improvement HAT with Cocaine CM is a feasible and effective option, but ....modest effect size and politically problematic →
- Reduction cocaine use and improvement HAT outcome with dexamphetamine XR?

# Additional Options



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<sup>1\*</sup>, Peter Blanken<sup>1</sup>, Wim van den Brink<sup>2</sup> and Vincent Hendriks<sup>1</sup>

#### Abstract

**Background:** Cocaine, particularly in its base form ('crack'), has become one of the drugs of most concern in the Netherlands, being associated with a wide range of medical, psychiatric and social problems for the individual, and with significant public order consequences for society. Available treatment options for cocaine dependent users are limited, and a substantial part of the cocaine dependent population is not reached by the addiction treatment system. Psychosocial interventions for cocaine dependence generally show modest results, and there are no registered pharmacological treatments to date, despite the wide range of medications tested for this type of dependence.

The present study (Cocaine Addiction Treatments to improve Control and reduce Harm; CATCH) investigates the possibilities and problems associated with new pharmacological treatments for crack dependent patients.

**Methods/Design:** The CATCH-study consists of three separate randomised controlled, open-label, parallel, feasibility trials, conducted at three separate addiction treatment institutes in the Netherlands. Patients are either new referrals or patients already in treatment. A total of 216 eligible outpatients are randomised using a pre-randomisation double-consent design and receive either 12 weeks treatment with oral topiramate (n = 36; Brijder Addiction Treatment, The Hague), oral modafinil (n = 36; Arkin, Amsterdam), or oral dexamphetamine sustained-release (n = 36; Bouman GGZ, Rotterdam) as an add-on to cognitive behavioural therapy (CBT), or receive a 12-week CBT only (controls; n = 3 x 36).

Primary outcome in these feasibility trials is retention in the underlying psychosocial treatment (CBT). Secondary outcomes are acceptance and compliance with the study medication, safety, changes in cocaine (and other drug) use, physical and mental health, social functioning, and patient satisfaction.

**Discussion:** To date, the CATCH-study is the first study in the Netherlands that explores new treatment options for crack-cocaine dependence focusing on both abstinence and harm minimisation. It is expected that the study will contribute to the development of new treatments for one of the most problematic substance use disorders.

**Trial Registration:** The Netherlands National Trial Register NTR2576  
The European Union Drug Regulating Authorities Clinical Trials EudraCT2009-010584-16

We just started RCT on the effect of adding dexamphetamine XR in this population

# Alternatives for HAT



## REVIEW

### Deep brain stimulation in addiction: a review of potential brain targets

J Luigjes<sup>1</sup>, W van den Brink<sup>1</sup>, M Feenstra<sup>2</sup>, P van den Munckhof<sup>3</sup>, PR Schuurman<sup>3</sup>, R Schippers<sup>4</sup>, A Mazaheri<sup>1</sup>, TJ De Vries<sup>4</sup> and D Denys<sup>1,2</sup>



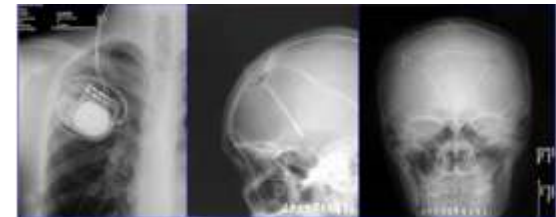
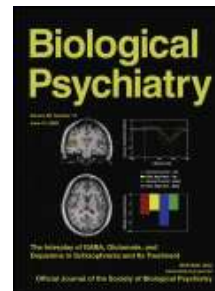
### Effective Deep Brain Stimulation in Heroin Addiction: A Case Report with Complementary Intracranial Electroencephalogram

*Carlos-Eduardo Valencia-Alfonso<sup>a,b</sup>  
Judy Luigjes<sup>b\*</sup>  
Ruud Smolders<sup>b</sup>  
Michael X. Cohen<sup>c</sup>  
Nina Levar<sup>b</sup>  
Ali Mazaheri<sup>b</sup>  
Pepijn van den Munckhof<sup>d</sup>  
P. Richard Schuurman<sup>d</sup>  
Wim van den Brink<sup>b</sup>  
Damiaan Denys<sup>a,b</sup>*



## CORRESPONDENCE

### Deep Brain Stimulation of Nucleus Accumbens on Heroin-Seeking Behaviors: A Case Report



We just finished treating a non-successful HAT patient with DBS

# Thank you for your attention!



[w.vandenbrink@amc.uva.nl](mailto:w.vandenbrink@amc.uva.nl)