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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Summary

Background **Heroin-assisted treatment is effective for methadone treatment-refractory heroin-dependent patients, but continued comorbid cocaine dependence remains problematic. Sustained-release dexamfetamine is a promising agonist pharmacotherapy for cocaine dependence and we aimed to assess its acceptance, efficacy, and safety.**

Methods **In this multicentre, randomised, double-blind, placebo-controlled trial, patients who were treatment-refractory, as indicated by at least two earlier failed treatments aimed at reducing or abstaining from cocaine use, and who regularly (≥8 days/month) used crack-cocaine were enrolled from four heroin-assisted treatment centres in the Netherlands. Eligible patients were randomly assigned (1:1) to receive either 12 weeks of daily, supervised prescription of 60 mg/day oral sustained-release dexamfetamine or placebo in addition to co-prescribed methadone and diacetylmorphine. Randomisation was done by the collaborating pharmacist, using a computer-generated random number sequence with stratification by treatment centre in blocks of four per stratum. Randomisation was masked to patients, staff, and researchers throughout the study. The primary outcome was the number of self-reported days of cocaine use during study treatment, assessed every 4 weeks. Primary and safety analyses were done in the intention-to-treat population. The study was registered with the European Union Drug Regulating Authorities Clinical Trials (EUdraCT 2013-004024-11) and with The Netherlands Trial Register (NTR2576).**

Findings **Between Aug 8, 2014, and Feb 27, 2015, 111 patients were assessed for eligibility, of whom 73 were enrolled and randomised; 38 patients were assigned to the sustained-release dexamfetamine group and 35 to the placebo group. Sustained-release dexamfetamine treatment resulted in significantly fewer days of cocaine use than placebo treatment (mean 44·9 days [SD 29·4] *vs* 60·6 days [24·3], respectively [95% CI of difference 3·1–28·4]; p=0·031; Cohen's standardised effect size d=0·58). One or more adverse events were reported by 28 (74%) patients in the dexamfetamine group and by 16 (46%) patients in the placebo group. Most adverse events were transient and well-tolerated.**

Interpretation **Sustained-release dexamfetamine is a well accepted, effective, and safe agonist pharmacotherapy for comorbid treatment-refractory cocaine dependence in heroin-dependent patients in heroin-assisted treatment. Future research should aim to replicate these findings in chronic cocaine-dependent and other stimulant-dependent patients in more routine treatment settings, including strategies to optimise treatment adherence like medication management interventions and contingency management.**

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Introduction

Heroin-assisted treatment is an effective treatment for methadone treatment-refractory heroin-dependent patients, resulting in reduced illicit heroin use and improvements in mental status, physical health, and social functioning, as has been shown in seven randomised controlled trials[1] and two cohort studies.[2,3] However, many heroin-dependent patients are also cocaine-dependent, which worsens the prognosis of treatment,[4] as is also shown among patients in heroin-assisted treatment, who often show no or only slight reductions in cocaine use.[3] Agonist pharmacotherapy for chronic cocaine dependence among patients in opioid agonist treatment might be a viable strategy. However, a recent randomised placebo-controlled trial with immediate-release methylphenidate (30 mg twice daily) in cocaine-dependent patients currently in heroin-assisted treatment did not show benefits in terms of reduced cocaine use.[5]

Reviews of substitution treatments for cocaine dependence, including psychostimulants and (other) dopamine agonists,[6,7] suggest that sustained-release dexamfetamine is probably the most promising agonist drug with respect to reductions in cocaine use and craving, but previous studies were restricted by low adherence, and cocaine-related outcomes often did not reach statistical significance.[8–10]

We aimed to assess the acceptance, efficacy, and safety of a robust dose of 60 mg/day oral sustained-release dexamfetamine in chronic crack-cocaine-dependent patients with comorbid heroin dependence, currently on heroin-assisted treatment.

Research in context

Evidence before this study

Our reference point was the Cochrane review (Castells et al [2010]), based on 16 randomised parallel group placebo-controlled clinical trials (RCTs) on the efficacy and safety of stimulant medications (bupropion, dexamfetamine, methylphenidate, modafinil, mazindol, methamfetamine, and selegiline) for the treatment of cocaine use disorders until July 24, 2008. As a group, these stimulants did not reduce cocaine use. When type of medication was included in the analysis, the proportion of patients achieving sustained cocaine abstinence was higher with bupropion (three RCTs) and dexamfetamine (three RCTs) than with placebo. The authors concluded that the evidence for stimulants in the treatment of cocaine dependence was inconclusive, but also that promising results existed for dexamfetamine and bupropion.

We searched MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials for clinical trials—published between July 25, 2008 and Nov 1, 2013—on the efficacy of dexamfetamine in the treatment of cocaine dependence, using the same search terms as Castells et al in 2010. Restricting our results to RCTs on the efficacy of dexamfetamine among treatment seeking cocaine-dependent patients in terms of clinical (cocaine use) outcomes, we retrieved two potentially relevant articles. One study (n=81) tested a combination of mixed amphetamine salts and topiramate (Mariani et al [2012]), making it impossible to know the contribution of dexamfetamine to the effect. The second study (n=73) compared the effects of dexamfetamine, modafinil, and the combination of dexamfetamine plus modafinil with placebo (Schmitz et al [2012]). Modafinil and the combination of modafinil plus dexamfetamine were associated with increased cocaine use and dexamfetamine alone did not clearly separate from placebo in terms of cocaine use.

Added value of this study

Previous studies on the effect of dexamfetamine in cocaine-dependent patients were promising, but often restricted by small sample size, high treatment dropout and, consequently, cocaine use-related outcomes did not reach statistical significance. Our study on sustained-release dexamfetamine in comorbid cocaine- and heroin-dependent patients, participating in heroin-assisted treatment, offered a context in which medication adherence could be optimised, allowing us to assess the real potential of sustained-release dexamfetamine in the treatment of cocaine dependence.

Implications of all the available evidence

Sustained-release dexamfetamine is an effective and safe agonist medication for the treatment of patients with cocaine dependence when medication adherence can be established. Replication of these findings in treatment-refractory cocaine-dependent and other stimulant-dependent patients in routine, optimised treatment settings, with clinical measures to enhance medication adherence, is warranted.

Methods

Study design and participants

This multicentre, randomised, double-blind, placebo-controlled trial was part of a larger project testing three pharmacological drugs (topiramate, modafinil, and sustained-release dexamfetamine) in separate studies in crack-cocaine-dependent patients in the Netherlands.[11]

Study participants were recruited from the population of patients currently receiving oral methadone plus inhalable or injectable diacetylmorphine for their concurrent heroin dependence in supervised heroin-assisted treatment programmes in two treatment centres in Amsterdam, one in Rotterdam, and one in The Hague. Eligible patients: (1) met inclusion criteria for heroin-assisted treatment, including minimum age of 25 years, methadone treatment-refractory heroin dependence, (nearly) daily heroin use, and poor physical, mental or social functioning (for full details, see van den Brink and colleagues);[12] (2) met cocaine dependence criteria according to the Diagnostic and Statistical Manual of Mental Disorders IV edition[13] in the past year and previous 5 years; (3) used cocaine on at least 8 days in the previous month; (4) administered cocaine primarily by means of basing (also known as freebasing and means smoking crack-cocaine); (5) had at least two earlier failed treatments aimed to reduce or abstain from cocaine use (treatment-refractory); (6) were able and willing to participate in the 12-week study; and (7) provided written informed consent.

For the **study protocol** see https://www.brijder.nl/study_protocol_sr_dexamphetamine

Patients were excluded in case of (1) severe medical problems (eg, electrocardiography or blood abnormalities) or severe psychiatric problems (eg, acute psychosis or suicidality); (2) pregnancy or breastfeeding; (3) pharmacotherapy with a potentially effective drug for cocaine dependence (ie, disulfiram, acamprosate, methylphenidate, modafinil, topiramate, immediate-release dexamfetamine, or baclofen); (4) insufficient command of the Dutch language; and (5) current participation in another addiction treatment trial.

The study was approved by the medical ethics committee of the Academic Medical Centre of the University of Amsterdam. The study protocol is available online.

Randomisation and masking

Following screening and baseline assessment, eligibility was determined by the treatment physician, and eligible patients were randomly assigned (1:1) to receive either 12 weeks oral sustained-release dexamfetamine or identical placebo along with continued heroin-assisted treatment. Randomisation was conducted by the collaborating pharmacist, using a computer-generated

random number sequence with stratification by treatment centre (four centres) in blocks of four per stratum. Treatment packs with sufficient study medication or placebo for the 12-week period were numbered sequentially and dispensed by the pharmacist to eligible patients in order of study entry. Randomisation was concealed for patients, staff, and researchers throughout the study.

Procedures

All patients were offered pharmaceutical-grade diacetylmorphine (maximum single dose 400 mg; maximum daily dose 1000 mg) 3 times per day and 7 days per week in designated treatment centres, along with once daily oral methadone (maximum dose 150 mg). Methadone was co-prescribed to achieve a stable base of opioid plasma concentrations and to prevent withdrawal symptoms in case patients missed a visit at the heroin-assisted treatment centre for supervised use of diacetylmorphine.

The study treatment consisted of either ongoing heroin-assisted treatment along with 12 weeks of treatment with sustained-release dexamfetamine, prescribed in a robust, single oral dose of 60 mg/day (2 tablets of 30 mg) in the experimental group or ongoing heroin-assisted treatment along with 12 weeks of identical placebo (2 tablets of 30 mg) in the placebo group. Study medication was dispensed once daily during the patient's morning visit at the heroin-assisted treatment centre, and had to be taken under supervision to allow intensive safety monitoring.

Study assessments were done at baseline, and at weeks 4, 8, and 12. At baseline, the Composite International Diagnostic Interview Substance Abuse Module (cocaine and alcohol dependence)[14] and the Mini-International Neuropsychiatric Interview on suicide risk[15] were undertaken. At all assessments we administered the substance use section of the Addiction Severity Index, supplemented with questions about illegal activities;[12,16] the Time Line Follow-Back on self-reported cocaine use;[17] the Obsessive Compulsive Drug Use Scale on past week cocaine craving;[18] the Maudsley Addiction Profile Health Symptoms Scale (MAP-HSS) on physical health;[19] and the Brief Symptom Inventory (BSI) on mental health.[20] In the final 4 study weeks, urine samples were collected (non-supervised) twice weekly, on Mondays and Thursdays. Samples were analysed for the presence of the cocaine-metabolite benzoylecgonine (>300 ng/mL), using qualitative rapid tests (nal von minden GmbH, Moers, Germany). The urine tests had a sensitivity of 95% and a specificity of 90%, and had no cross-reactivity with dexamfetamine sulphate. Additional assessments included blood sampling and electrocardiography (screening and week 12 assessment); weekly medical monitoring of heart rate, blood pressure, and bodyweight; weekly standardised registration of (serious) adverse events and co-medication; monthly pregnancy testing; daily registration of supervised medication adherence; and at week 12 the Client Satisfaction Questionnaire, supplemented with a question to rate the study medication on a scale ranging from 0 (very bad) to 10 (excellent).[21] Participants received a maximum remuneration of €85 for participating in the study assessments.

Outcomes

The primary outcome was the number of self-reported days of cocaine use during the 12-week study (range 0–84 days) and was centrally assessed. Secondary cocaine use-related outcomes were number of cocaine-negative urine samples in the last 4 study weeks, and the following TimeLine FollowBack-based outcomes: longest period of consecutive cocaine abstinence; percentage of patients with at least 21 consecutive days of cocaine abstinence; days of cocaine abstinence during the last 4 study weeks; and changes in so-called cocaine hits (ie, cocaine self-administrations on days patients used cocaine) and changes in days of cocaine abstinence comparing the 4 weeks preceding the baseline and week 12 assessment.

Other secondary outcomes were changes in cocaine craving, (self-reported) use of other substances, physical and mental health, criminality, as well as medication adherence, and safety (ie, [serious] adverse events) during the 12-week study. Safety was assessed in terms of the number of patients that reported at least one (serious) adverse event, the number of (serious) adverse events, and by electrocardiography and monitoring of heart rate, blood pressure, and bodyweight.

Statistical analysis

For the power analysis, the mean difference between the sustained-release dexamfetamine group and the placebo group in number of days of cocaine use during the 12-week treatment period was estimated to be 10, with a pooled SD of 17 days (d=0·59; ie, moderate effect size). For this proof-of-principle study, a lenient alpha of 0·10 was chosen to minimise the risk of a false negative outcome (type 2 error).[11] With a two-sided alpha of 0·10 and power of 0·80, 36 patients were required per study group.

An intention-to-treat approach, including all randomised patients, was used to test group differences in all primary, secondary, and safety analyses. This definition is more strict than the one in the study protocol, which additionally required that patients took at least one dose of the study drug.

The primary outcome—ie, number of self-reported days of cocaine use during the 12-week study—was analysed with negative binomial regression analyses with treatment group as the only independent variable and the interaction of treatment group with treatment centre as the only effect modifier. To fit the negative binomial regression model, a reflection transformation was done on the negatively skewed data of the primary outcome (ie, 84 days minus cocaine use days).

Concerning the secondary cocaine use-related outcomes, different statistical analysis strategies were used based on the nature and distribution of the outcome. Negative binomial regression analyses with treatment group as the only independent variable were used for the longest period of consecutive cocaine abstinence and the mean number of cocaine metabolite-free urine samples in the 4 weeks preceding the week 12 assessment. Achievement of cocaine abstinence for at least 21 consecutive days was analysed by logistic regression analysis, using treatment group as the only independent variable. Group differences in changes in number of days of cocaine abstinence and cocaine hits in the 4 weeks preceding baseline and week 12 were analysed by multilevel analyses (generalised linear mixed models) with a random intercept, and with the two assessments and treatment group as fixed effects. Multilevel analyses were used, instead of repeated measures analyses of variance mentioned in the study protocol, to fit the non-normal distribution of the data. Cohen's d effect sizes were calculated for continuous outcomes and numbers needed to treat (NNT) for dichotomous outcomes.

The other secondary outcomes—ie, changes in craving, use of other substances, health status, and criminality—were analysed by generalised estimating equation models with treatment group, assessment (baseline, weeks 4, 8, and 12) and the interaction between treatment group and assessment as independent variables, and using an unstructured correlation matrix. Except craving, all secondary outcomes were non-normally distributed and, therefore, dichotomised based on the presence or absence of past month illicit heroin use, or cannabis use, or heavy (≥5 units per day) alcohol use (all ≥1 day); poor physical health (MAP-HSS total score ≥8); poor mental health (BSI total score ≥0·56 for men and ≥0·71 for women); and past month criminality (≥1 day).[3]

Because the medication was dispensed daily and intake was supervised, adherence with the study medication was registered on a daily basis. Differences between the study groups and treatment centres were described and analysed by means of negative binomial regression analyses in terms of the number of days of medication intake during the 12-week study, the number of consecutive weeks in which patients were fully compliant, and days of medication intake in the final 4 weeks.

Data for one patient in the dexamfetamine group was missing from week 4 onward due to imprisonment, and, following the most conservative strategy, all missing TimeLine FollowBack-days were considered as cocaine use days. Furthermore, 516 (88%) of the 584 scheduled urine samples were submitted, and the remaining 68 missing urine samples were considered cocaine-positive. Agreement between self-reported crack-cocaine use in the 3 days before the last urine sample (week 12) and a cocaine-positive urine was 89·2% with a Kappa-value of 0·64 in both study groups; almost 50% of the patients with no self-reported crack-cocaine use (n=15) did have a cocaine-positive urine.

Data monitoring was conducted by the investigators and the independent supervisory pharmacist (Amsterdam Academic Medical Centre); there was no independent data monitoring committee.

Data were analysed with SSPS (version 23).

The study was registered with the European Union Drug Regulating Authorities Clinical Trials (EUdraCT

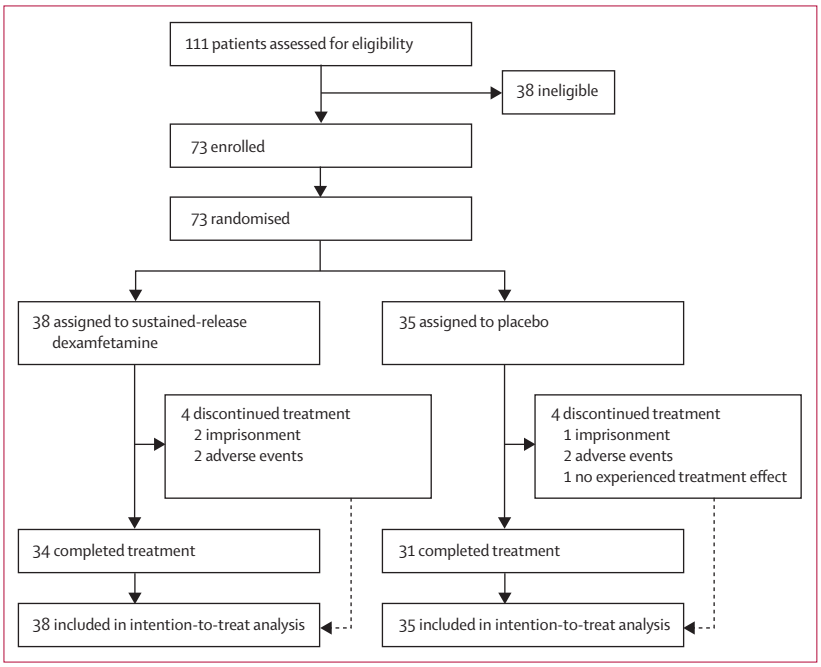

Figure: **Trial profile**

	Sustained-release dexamfetamine group (n=38)	Placebo group (n=35)
Demographic background		
Age (years)	48·4 (6·6)	49·0 (5·3)
Men	35 (92%)	31 (89%)
European descent	26 (68%)	23 (66%)
Substance use		
Lifetime regular crack-cocaine use (years)	19·1 (7·7)	19·9 (7·1)
Cocaine-positive baseline urine	38 (100%)	34 (97%)
Cocaine use days (past month)	23·5 (7·6)	23·7 (7·6)
Lifetime regular heroin use (years)	21·1 (8·4)	23·0 (8·5)
Heavy (≥5 units per day) alcohol use (≥1 day, past month)	13 (34%)	12 (34%)
Cannabis use (≥1 day, past month)	21 (55%)	13 (37%)
Treatment status and treatment history		
Time in heroin-assisted treatment (months)	46·2 (34·3)	57·5 (35·1)
Medical heroin dose (mg)	582·2 (200·8)	635·0 (188·3)
Methadone dose (mg)	67·6 (28·1)	70·1 (24·3)
Previous addiction treatments	6·2 (3·2)	8·4 (7·2)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics**

2013-004024-11) and with The Netherlands Trial Register (NTR2576).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between Aug 8, 2014, and Feb 27, 2015, 111 patients were assessed for eligibility, of whom 73 were enrolled; 38 patients were randomly assigned to sustained-release dexamfetamine and 35 to placebo (figure). Patient recruitment was terminated when the aimed number of patients according to the power calculation was achieved.

Patients were mainly men from European descent, on average 49 years old (SD 6), with a long history of regular illicit heroin and cocaine use, who had multiple previous treatments, and who had used cocaine on an average of 24 days (SD 8) in the past month (table 1). Patients participated in heroin-assisted treatment for on average 4 years (SD 3). One patient injected cocaine; all others smoked crack-cocaine. Baseline characteristics were balanced between the two treatment groups.

Analysis of the primary outcome showed that the mean number of self-reported days of cocaine use in the 84 days treatment period was significantly lower in the dexamfetamine group than in the placebo group (44·9 days [SD 29·4]) *vs* 60·6 days [24·3], respectively [95% CI of difference 3·1–28·4 days]; Wald χ^2=4·66, df=1; p=0·031) (table 2). There was no significant interaction between treatment centre and treatment group (Wald χ^2=2·02, df=3, p=0·569).

With regards to secondary cocaine use-related outcomes, the longest consecutive period of self-reported cocaine abstinence was significantly higher in the dexamfetamine group than in the placebo group (Wald χ^2=16·17, df=1, p<0·0001; table 2). Similarly, patients in the dexamfetamine group were more often abstinent from cocaine for at least 3 consecutive weeks than those in the placebo group (Wald χ^2=5·52, df=1, p=0·019), and reported more days of cocaine abstinence in the final 4 weeks of the study (Wald χ^2=8·45, df=1, p=0·004; table 2). Eight patients (21%) in the dexamfetamine group had at least one cocaine-negative urine in the last 4 weeks compared with two patients (6%) in the placebo group, with a significantly higher proportion of cocaine-negative urine samples in the dexamfetamine group (Wald χ^2=5·11, df=1, p=0·024). Additionally, the average number of days of cocaine abstinence in the 4 weeks preceding baseline compared with the 4 weeks preceding week 12 increased significantly more in the dexamfetamine than in the placebo group (6·5 days [SD 6·9] to 15·2 days [10·8] days *vs* 5·4 days [7·2] to 7·5 [9·1], respectively [treatment by time interaction: F=4·70; df=1; p=0·032; d=0·94]). Moreover, patients in the dexamfetamine group showed higher reductions in the mean number of cocaine hits than did patients in the placebo group on days they used cocaine (8·9 cocaine hits per day [SD 5·9] to 5·1 [4·4] *vs* 8·3 cocaine hits per day [4·4] to 7·7 [5·9], respectively [treatment by time interaction: F=7·45; df=1; p=0·007; d=0·59]).

With respect to the other secondary outcomes—cocaine craving, use of other substances, health, and criminality—we noted significant changes from baseline to week 12 for cocaine craving, heavy alcohol use, and physical health problems, but no significant group differences over time on any of these variables (all p≥0·098; table 3). Finally, patients in the dexamfetamine group rated the study medication at week 12 on average more positively than patients in the placebo group (7·6 [SD 1·4] *vs* 5·7 [2·3], respectively; t=4·27, df=55·1, p<0·0001).

At the week-12 assessment, the study blind was tested. In the dexamfetamine group, 54% of the patients correctly identified their group allocation compared with 60% in the placebo group (Kappa=0·14), indicating that blinding was successful until the end of the study and that patients were not able to discern beyond chance what they had been prescribed. Study medication was taken on a mean of 77 (SD 15·2) of the 84 study days (92%), with no difference between the study groups (75 days [SD 16·9] in

	Sustained-release dexamfetamine group (n=38)	Placebo group (n=35)	Exp(B) (95% CI)	Wald χ^2 (df=1)	p value	Effect size
Primary outcome						
Days of cocaine use during 12-week study	44·9 (29·4)	60·6 (24·3)	1·67 (1·05–2·67)	4·66	0·031	d=0·58
Secondary cocaine use-related outcomes						
Longest period of consecutive cocaine abstinence (days)	17·9 (24·9)	6·7 (11·7)	2·69 (1·66–4·36)	16·17	<0·0001	d=0·58
Consecutive cocaine abstinence for ≥21 days	11 (29%)	2 (6%)	6·72 (1·37–32·97)	5·52	0·019	NNT=4·3
Days of cocaine abstinence in final 4 weeks	15·2 (10·8)	7·5 (9·1)	2·04 (1·26–3·31)	8·45	0·004	d=0·77
Proportion cocaine-negative urine samples in final 4 weeks	10·6 (25·1)	3·9 (17·9)	2·60 (1·14–5·94)	5·11	0·024	d=0·31

Data are mean (SD) or n (%), unless otherwise specified. Exp(B)=exponentiated value of regression coefficient B; odds ratio. df=degrees of freedom. d=Cohen's d, which is a standardised effect size. NNT=number needed to treat.

Table 2: **Primary and secondary cocaine use-related outcomes**

	Estimated marginal means*				GEE parameters (baseline–week 12)*		
	Baseline	Week 4	Week 8	Week 12	Time	Group	Group×time
Cocaine craving (range 0–20)							
Sustained-release dexamfetamine group (n=38)	8·74	6·00	5·80	5·11	Wald=52·36; p<0·001	Wald=6·52; p=0·011	Wald=4·58; p=0·205
Placebo group (n=35)	9·80	8·13	7·06	7·29	..	..	..
Illicit (non-prescribed) heroin use (≥1 day past month)							
Sustained-release dexamfetamine group (n=38)	0·21	0·24	0·19	0·24	Wald=2·76; p=0·431	Wald=1·44; p=0·230	Wald=0·22; p=0·975
Placebo group (n=35)	0·34	0·34	0·26	0·31	..	..	..
Heavy (≥5 units per day) alcohol use (≥1 day past month)							
Sustained-release dexamfetamine group (n=38)	0·34	0·24	0·24	0·34	Wald=8·58; p=0·035	Wald=0·68; p=0·411	Wald=5·92; p=0·115
Placebo group (n=35)	0·34	0·34	0·40	0·40	..	..	..
Cannabis use (≥1 day past month)							
Sustained-release dexamfetamine group (n=38)	0·55	0·50	0·47	0·49	Wald=2·70; p=0·440	Wald=0·10; p=0·758	Wald=6·30; p=0·098
Placebo group (n=35)	0·37	0·46	0·49	0·57	..	..	..
Physical health problems†							
Sustained-release dexamfetamine group (n=38)	0·76	0·62	0·60	0·52	Wald=15·90; p=0·001	Wald=0·91; p=0·340	Wald=3·88; p=0·275
Placebo group (n=35)	0·57	0·54	0·57	0·46	..	..	..
Mental health problems‡							
Sustained-release dexamfetamine group (n=38)	0·37	0·33	0·30	0·28	Wald=5·14; p=0·162	Wald=0·09; p=0·764	Wald=0·57; p=0·904
Placebo group (n=35)	0·43	0·31	0·34	0·31	..	..	..
Illegal activities (≥1 day past month)							
Sustained-release dexamfetamine group (n=38)	0·13	0·19	0·22	0·13	Wald=4·48; p=0·214	Wald=2·01; p=0·157	Wald=0·69; p=0·875
Placebo group (n=35)	0·20	0·29	0·33	0·29	..	..	..

GEE=generalised estimating equation. *Estimated marginal means were based on generalised estimating equation models, using an unstructured correlation matrix, and assuming missing data (seven of 292 [four × 73] assessments; 2%) were missing completely at random. †Maudsley Addiction Profile ≥8. ‡Brief Symptom Inventory (≥0·71 [women] or ≥0·56 [men]).

Table 3: **Longitudinal changes in secondary outcomes—cocaine craving, substance use, health problems, and criminality (intention-to-treat sample, n=73)**

	Sustained-release dexamfetamine group (n=38)	Placebo group (n=35)
Sleeping problems	13 (34%)	3 (9%)
Agitation/irritability	6 (16%)	2 (6%)
Physical arousal	5 (13%)	2 (6%)
Gastrointestinal problems	5 (13%)	3 (9%)
Changes in appetite	6 (16%)	2 (6%)
Changes in weight	5 (13%)	2 (6%)
Influenza	3 (8%)	3 (9%)
Dizziness	3 (8%)	0 (0%)
Respiratory complaints	0 (0%)	2 (6%)*
Craving	0 (0%)	2 (6%)
Headache	1 (3%)	1 (3%)

Data are n of patients (%). *Including one patient with a serious adverse event (admission to hospital).

Table 4: **Adverse events reported by at least two patients**

the dexamfetamine group *vs* 79 days [12·9] in the placebo group; Wald χ^2=0·05, df=1, p=0·828). Similarly, no group differences were noted between the number of consecutive weeks with full medication adherence (mean 8·7 weeks [SD 3·7] in the dexamfetamine group *vs* 9·3 weeks [3·4] in the placebo group; Wald χ^2=0·09, df=1, p=0·767) and medication acceptance in the final 4 weeks (24·7 days [SD 8·1] in the dexamfetamine group *vs* 25·1 days [7·0] in the placebo group; Wald χ^2=0·01, df=1, p=0·943). Additionally, medication adherence did not differ between the four treatment centres (all p>0·91). Four patients in the dexamfetamine group and four in the placebo group discontinued their medication intake prematurely: three were imprisoned, four due to adverse events, and one had limited treatment effects (figure).

One or more adverse events were reported by 28 (74%) patients in the dexamfetamine group and by 16 (46%) patients in the placebo group (OR 3·33 [95% CI 1·25–8·87]; p=0·016). Together, 95 adverse events were registered and adverse events that were reported by at least two patients are summarised in table 4. Patients in the dexamfetamine group reported 69 adverse events, of which 58 (84%) events were possibly, probably, or certainly related to the study medication. Most of these adverse events (51 events; 74%)

	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**

were resolved before the end of the study treatment. Sleeping problems was the adverse event reported by most patients (n=13; 34%). In the placebo group, 26 adverse events were reported, of which 18 (69%) were possibly, probably, or certainly related to the study medication.

One serious adverse event occurred: a patient in the placebo group was admitted to hospital during the study period due to an exacerbation of chronic obstructive pulmonary disease, which was not related to the study drug. After admission, this patient resumed treatment. In six other patients, adverse events resulted in (temporary) discontinuation of study treatment: two in the placebo group and four in the dexamfetamine group. Of the latter four patients, two resumed treatment with a dose of 30 mg/day sustained-release dexamfetamine, one patient discontinued medication intake due to psychotic symptoms, and one patient due to concurrent adverse events of mild to moderate severity.

Heart rate significantly increased from baseline to week 12 among patients in the dexamfetamine group compared with those in the placebo group (table 5). No significant group by time interaction effects were noted for blood pressure or bodyweight. Week 12 ECG data were available for 67 patients (dexamfetamine n=34; placebo n=33) with only one abnormality in terms of a repolarisation disturbance in a patient in the placebo group.

Discussion

This multicentre, randomised, double-blind, placebo-controlled trial shows the acceptance, efficacy, and safety of 60 mg/day oral sustained-release dexamfetamine as a substitution drug in the treatment of chronic crack-cocaine dependence in heroin-dependent patients, currently in heroin-assisted treatment. Sustained-release dexamfetamine was superior to placebo in terms of the primary cocaine-related outcome (d=0·58), and all self-reported and urine-based secondary cocaine use-related outcomes (d=0·58–0·94 and d=0·31, respectively). Sustained-release dexamfetamine was generally well-accepted, with high medication adherence. No serious adverse events occurred in the dexamfetamine-treated patients. There were no unexpected adverse events and most adverse events were transient and well-tolerated.

Our findings are an important contribution to the search for effective pharmacotherapies for cocaine dependence: it is the first study that shows the benefits of a robust dose of sustained-release dexamfetamine as a valuable agonist medication in the treatment of cocaine dependence. This is by contrast with previous studies in which strong inferences could not be made because of high rates of premature treatment discontinuation and promising, but often non-significant, indications of cocaine use reductions. In two randomised controlled trials by Grabowski and colleagues,[8,9] reductions in cocaine use were larger in the 60 mg/day sustained-release dexamfetamine group than in the 30 mg/day sustained-release dexamfetamine and placebo groups, but both studies had treatment discontinuation rates of up to 60% and the reported effects were only significant in subgroup analyses. In a small randomised controlled trial of 30 cocaine injectors, significant reductions in cocaine use and cocaine-related improvements were noted in the dexamfetamine group (60 mg/day), but not in the between-group comparison.[10] In a randomised placebo-controlled trial (n=73) on the efficacy of 60 mg/day sustained-release dexamfetamine, 400 mg/day modafinil, and the combination of both compounds, 60% of the patients had discontinued treatment at 12 weeks and no benefits of sustained-release dexamfetamine over placebo were noted.[22] Finally, in a recent pilot randomised placebo-controlled trial, 70 mg/day of the prodrug lisdexamfetamine (containing approximately 30 mg/day dexamfetamine) resulted in reduced craving but not in an increase of cocaine abstinence.[23] Thus, sustained-release dexamfetamine has repeatedly shown to be a promising treatment for cocaine dependence, but no studies so far have shown a convincing benefit in terms of significant and substantial reductions in cocaine use, most likely due to small samples and low treatment adherence. By contrast, our study shows very good medication adherence and superiority of dexamfetamine in reducing self-reported and urine-based cocaine use.

We believe that our high medication adherence resulted from daily supervised intake that enabled the treatment staff to motivate patients and intensively monitor potential side effects of the study medication, which are important strategies to optimise adherence.[24] Additionally, increased

doses of sustained-release dexamfetamine, such as 60 mg/day, are likely to result in more robust findings.[9,23] The observed effect sizes in our study were fair (urine-based cocaine use) to moderate (self-reported cocaine use) and at least comparable to effect sizes in studies on other chronic disorders, including alcohol dependence[25] and many other psychiatric and general medical conditions.[26]

Efficacy of sustained-release dexamfetamine was not shown for our secondary, health-related outcome measures. This could be due to the fact that our study population already participated in heroin-assisted treatment for on average 4 years, whereas much improvement in physical and mental health and reduction in criminality already occurs at an early phase of heroin-assisted treatment, as was shown by Blanken and colleagues.[3] Hence, in this ageing population with a long history of cocaine and heroin dependency in heroin-assisted treatment, there might be little room for further improvements in these areas.

The study has several limitations. First, the sample size was limited, but in view of the a priori expected effect size, the study was adequately powered and a larger sample would not be approved by a medical ethics committee for this the proof-of-principle study. Moreover, the study was undertaken in four treatment centres and the effects were not driven by only one specific centre. Second, a study with a duration of 12 weeks can not give a conclusive answer about the best treatment for a chronic relapsing disorder such as cocaine dependence. However, at 12 weeks, 89% of the patients were still in treatment and there are no reasons to expect that drop-out was imminent or that the effect of the treatment was waning. We therefore believe that this study provides a strong indication for the potential long-term effectiveness of sustained-release dexamfetamine as an agonist pharmacotherapy for cocaine dependence. Third, the efficacy of sustained-release dexamfetamine on self-reported cocaine abstinence might be somewhat over-estimated in our study in view of the substantially smaller effect size in urine-based cocaine use and the modest agreement between self-reported and urine-based cocaine use in the final 4 weeks of the study. Therefore, we did a post-hoc sensitivity analysis with days of cocaine abstinence in the last 4 study weeks as dependent variable, in which self-reported days of cocaine abstinence in the 2 days preceding the urinalysis were converted into non-abstinent days in case of a cocaine-positive or missing urine sample (data not shown). This analysis showed that patients in the dexamfetamine group on average still had significantly more cocaine-free days (8·9 days) than did those in the placebo group (3·9 days), with a comparable effect size (adjusted d=0·71 *vs* original d=0·77). However, we also have to consider the possibility that our urine-based efficacy of sustained-release dexamfetamine on cocaine abstinence is an underestimation of the true effect, because qualitative urine tests only provide dichotomous outcomes (cocaine-positive or cocaine-negative) and can not detect reductions in the amount of cocaine that was used, such as those noted in our study. In view of the rationale for agonist substitution treatment with sustained-release dexamfetamine, cocaine use reductions and stabilisation rather than cocaine abstinence are also valid treatment goals. Fourth, the study was undertaken in a quite specific treatment setting, and it is an important question whether the demonstrated efficacy of sustained-release dexamfetamine can be generalised to cocaine-dependent patients outside heroin-assisted treatment. We believe that the results are generalisable to chronic cocaine-dependent patients with comorbid heroin dependence in methadone maintenance treatment with daily visits and supervised methadone intake, because these patients have very similar patterns of cocaine use, largely similar clinical characteristics, and daily supervised intake of sustained-release dexamfetamine can be established in this context. Generalisability is less clear when it comes to cocaine and comorbid heroin-dependent patients in methadone maintenance treatment without daily supervised methadone intake and regular take home doses of methadone. In this context, sustained-release dexamfetamine prescription should be made conditional on regularly supervised intake of the medication and on other measures to improve compliance, such as compliance enhancement therapy[24] or contingency management directed at treatment attendance and cocaine-free urines.[27,28] Similar measures are needed in cocaine-dependent patients without comorbid heroin dependence, and thus not in substitution treatment. In view that in previous studies of dexamfetamine twice weekly visits to the treatment centre were related to high treatment discontinuation rates,[8,9,22] future studies on the efficacy of sustained-release dexamfetamine among more general populations of cocaine-dependent patients in routine addiction treatment services should incorporate medication management interventions, including frequent monitoring of medication adherence and adverse events, frequent dose evaluations and motivational enhancement,[24] combined with providing relevant incentives for both treatment attendance and cocaine abstinence[29] to improve treatment outcomes.

Finally, our findings might not only be relevant for the treatment of patients with cocaine dependence, but possibly also for the many patients with other stimulant addictions, although the efficacy of sustained-release dexamfetamine in these populations still has to be established.[30] Our study has shown that agonist pharmacotherapy with a robust dose of sustained-release dexamfetamine is possible and safe, and shows at least one way to improve medication adherence and treatment outcomes in chronic patients with a stimulant dependence, and our approach and the discussed strategies can be examples for future studies in the field of addiction.

We conclude that sustained-release dexamfetamine is a well-accepted, effective, and safe agonist drug for the

treatment of cocaine-dependent patients currently in heroin-assisted treatment. Replication of these findings in treatment-refractory cocaine-dependent and other stimulant-dependent patients in less specific treatment settings is warranted, using multiple strategies to optimise treatment adherence, such as medication management interventions and contingency management.

Contributors

VH, PB, WB, and BW designed the study and wrote the protocol. BN was involved in the development and manufacturing of the investigational medicinal product, the blinding procedure and randomisation. MN and PB undertook the statistical analysis, and MN wrote the first draft of the manuscript with support of all co-authors. All authors contributed to and have approved the final manuscript.

Declaration of interests

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