Project title
New pharmacotherapeutic treatment options for crack-cocaine dependent people in the Netherlands: A double-blind, placebo-controlled randomized feasibility study of sustained release dexamphetamine

Short title
Cocaine Addiction Treatments to improve Control and reduce Harm (CATCH): Sustained release dexamphetamine

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Coordinating investigator

- Prof.dr. Wim van den Brink
  Academic Psychiatric Center AMC-UvA
  Dept. of Addiction PA 1.173
  PO Box 22700
  1100 DE Amsterdam
  Tel. +31 (0)20 8913634
  Mail: w.vandenbrink@amc.uva.nl

Principal investigators

- Prof.dr. Wim van den Brink
  Academic Psychiatric Center AMC-UvA
  Dept. of Addiction PA 1.173
  PO Box 22700
  1100 DE Amsterdam
  Tel. +31 (0)20 8913634
  Mail: w.vandenbrink@amc.uva.nl
- Dr. Vincent Hendriks
  Parnassia Addiction Research Centre (PARC)
  Brijder Verslavingszorg
  Monsterseweg 83
  2553 RJ Den Haag
  Tel. +31 (0)6 51154583
  Mail: vincent.hendriks@brijder.nl

Local investigators
- The Hague: drs. W. Wagenaar, MD
- Rotterdam: drs. J. de Borst, MD
- Amsterdam: drs. I. Eising, MD

Central research group
- prof.dr. Wim van den Brink (AMC-UvA): bestuurlijk verantwoordelijke
- dr. Vincent Hendriks (Brijder Verslavingszorg: PARC): projectleider
- dr. Peter Blanken (Brijder Verslavingszorg: PARC): projectlid
- drs. Mascha Nuijten (Brijder Verslavingszorg: PARC): onderzoeker
- drs. Els Govers (Brijder Verslavingszorg): projectlid
- dr. Ben van de Wetering (BoumanGGZ/Antes): projectlid
- drs. Giel van Brussel (GGD Amsterdam): projectlid

Collaboration
- Brijder Verslavingszorg: Parnassia Addiction Research Centre (PARC)
- Academic Psychiatric Center AMC-UvA, Dept. of Addiction
- Brijder Verslavingszorg (Parnassia Groep)
- BoumanGGZ/Antes
- GGD Amsterdam, Drugsafdeling

Study sponsor
- Academic Psychiatric Center AMC-UvA
  Dept. of Addiction PA 1.173
  PO Box 22700
  1100 DE Amsterdam
  Tel. +31 (0)20 8913634
  Mail: w.vandenbrink@amc.uva.nl

Financer of the study
- Zorgonderzoek Nederland (ZonMw)
  Laan van Nieuw Oost-Indië 334
  2593 CE Den Haag
  Tel. +31 (0)70 3495225

Independent physician
- dr. M. Figee
  Academic Psychiatric Center AMC-UvA
  Dept. of Psychiatry
  Tel. +31 (0)20 8913844 (secretariate, mrs. Esser)
  Mail: k.d.esser@amc.uva.nl

Central pharmacy
- Pharmacy Slotervaart Hospital
  Louwesweg 6
  1066 EC Amsterdam
  Tel. +31 (0)20 5124481

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PREFACE

In November 2007, we received a research grant from ZonMw to conduct a pharmacotherapeutic study, in which we planned to investigate, in three separate randomized controlled feasibility trials, the effectiveness of topiramate, modafinil, and sustained release (SR) dexamphetamine in the treatment of crack-cocaine dependent patients. On February 24, 2010 the Medical Ethical Committee of the AMC approved our study protocol "New pharmacotherapeutic treatment options for crack-cocaine dependent patients in the Netherlands" (MEC 09/197 # 11.17.0029)

At the time of this writing (October 2013), the data pertaining to the studies on topiramate and modafinil have largely been collected. For the feasibility study on dexamphetamine SR, in which we are ready to start patient recruitment, we recently submitted a substantial amendment to the medical ethical committee of the AMC. On September 13, 2013, the MEC informed us that the proposed changes in the study protocol of the dexamphetamine SR study were too substantial to be considered an amendment, and that, instead, this protocol should be submitted to the MEC as a new project. In the present protocol, the dexamphetamine SR study is described as a new project.

BACKGROUND AND RATIONALE OF THE STUDY

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. Despite this status as one of the most problematic addictions, available treatment options for cocaine dependent patients are limited at best. To date, there are no proven effective pharmacotherapies for cocaine dependence (De Lima et al., 2002; O'Brien, 2005; Kampman et al., 2005; Dürsteler-MacFarland et al., 2013), despite the wide range of medications tested for this specific type of dependence, including: direct and indirect agonists (Amato et al., 2011; Pérez-Maná et al., 2011), antidepressants (Pani et al., 2011), antipsychotics (Amato et al., 2007), anticonvulsants (Minozzie et al., 2008; Alvarez et al., 2010), psychostimulants (Castells et al, 2010), and disulfiram (Pani et al., 2010). In addition, psychosocial interventions for cocaine dependence have generally produced modest results (Knapp et al., 2007; Shearer, 2007). From these, one of the more promising interventions – contingency management – has recently been investigated in the Netherlands by our research group in the context of the medical prescription of heroin to chronic heroin dependent patients with concurrent cocaine use. In this study (the results of which are yet to be published), we found that contingency management resulted in significant but small reductions in cocaine use (Blanken et al., in preparation).

Given the limited success of psychosocial interventions and lack of proven effective pharmacological treatment options, the testing of new medications for cocaine dependence should be high on the research agenda. In this testing program, two basic pharmacological strategies can be distinguished, one directed at substantial reduction or total abstinence from all stimulants and the other directed at the replacement of illegal, short-acting stimulants that are smoked (i.e. crack-cocaine) or injected by medically prescribed, long-acting stimulants that can be taken orally. Concerning the first strategy, the anticonvulsant topiramate and the alpha-adrenergic/glutamate agonist modafinil are currently under investigation in the context of the wider pharmacotherapeutic study of our research group (see Preface). Concerning the second strategy, a growing number of pre-clinical and human studies suggest that the monoamine releaser dexamphetamine should be the prime candidate for replacement therapy (Grabowski et al., 2004a; Castells et al., 2010; Van den Brink 2012). Several controlled studies have shown significant improvements in treatment retention and reduced cocaine use in cocaine addicts receiving sustained release dexamphetamine (Grabowski et al., 2001; Grabowski et al., 2004b; Shearer et al., 2003), without serious adverse events (including no serious cardiovascular complications).

Hence, the pharmacotherapy proposed in the present study will consist of sustained release dexamphetamine. The basic rationale for substitution treatment for cocaine dependence is similar to that for other addictions: it aims to replace uncontrolled and harmful drug use with regulated and safer use, in terms of dose, route of administration and adverse effects, and it facilitates engagement with health care services by attracting and retaining addicted individuals in treatment (Shearer & Gowing,

2004). In addition, the regular supervised prescription regimen may by itself help the patient to structure his daily life. Oral application of sustained release dexamphetamine, with a much slower onset and limited peak effect than crack-cocaine, clearly meets the rationale for substitution treatment. As in any medication study, the primary focus of our study will be on the balance between (potential) benefit and harm produced by the medication, taking into consideration the personal and societal damage associated with continued illicit use of cocaine, in a situation without effective pharmacological treatment options.

STUDY OBJECTIVE

The overall objective of this feasibility study is to investigate the usefulness of sustained release dexamphetamine in the treatment of cocaine dependence, and – dependent upon the results of both this study and the parallel studies of topiramate and modafinil (see Preface) – to yield one or more candidate medications for future investigation in a large-scale confirmatory controlled trial. Specifically, the study aims to evaluate, in crack dependent patients with comorbid heroin dependence, the response to medically prescribed oral dexamphetamine SR (60 mg/day) as an add-on to heroin-assisted treatment, in terms of potential efficacy, acceptance, compliance, safety, and patient satisfaction.

GENERAL STUDY DESIGN

The study will be conducted using a multicenter, double-blind, placebo-controlled, randomized treatment design. Following screening and baseline assessment, eligible patients in a heroin-assisted maintenance treatment program will be randomly allocated (ratio: 1:1) by the collaborating pharmacist to (continued) heroin-assisted treatment plus 12 weeks treatment with placebo (control group; n=36) or to (continued) heroin-assisted treatment plus 12 weeks treatment with sustained release dexamphetamine 60 mg/day (experimental group; n=36). Randomization will be concealed, using a computer-generated randomization list, and will be prestratified by treatment center (4 treatment centers). Study assessments will take place at baseline, and 4, 8, and 12 weeks after baseline. The primary time point at which treatment outcome will be determined is 12 weeks after baseline.

A placebo-controlled design is deemed feasible, given that cocaine dependent patients in an earlier study using sustained release dexamphetamine 60 mg/day were not able to distinguish placebo from dexamphetamine (Grabowski, personal communication). Hence, selection bias due to drop-out resulting from recognition of placebo is not expected.

The addiction treatment organizations that participate in the present study are: Brijder Verslavingszorg (The Hague: 1 study site), BoumanGGZ/Antes (Rotterdam: 1 study site), and GGD Amsterdam (Amsterdam: 2 study sites).

STUDY POPULATION

Target population

The study will be conducted in crack-cocaine dependent patients who already participate in a maintenance treatment program in which they receive pharmaceutical grade heroin (diacetylmorphine) on medical prescription for their concurrent heroin dependence (‘heroin-assisted treatment’). This choice is based on the following line of reasoning:

1. The far majority of chronic, crack-cocaine dependent patients in the Netherlands – both inside and outside the addiction treatment system – have a concurrent chronic heroin dependency (Oteo Pérez et al., 2012).
2. From those in treatment for combined crack-cocaine and heroin dependence, the far majority participates in an opioid substitution program, predominantly methadone maintenance treatment. Studies have consistently shown that the effect of methadone maintenance on cocaine use in heroin dependent patients is limited at best (Kosten et al., 1992; Shearer, 2003; Sees et al., 2000; Castells et al., 2009; Van den Brink, 2012).

3. Approximately 500-600 patients in the Netherlands with both crack-cocaine and heroin dependence currently participate in an opioid substitution program with medically prescribed heroin. Studies of our research group have indicated that this 'heroin-assisted treatment' results in substantial reductions in illegal heroin use, and large improvements in physical and mental health and social functioning in chronic, treatment-resistant heroin dependent patients (Van den Brink et al., 2003; Blanken et al., 2010). However, among patients who concurrently used crack cocaine – 84-90% of the patients in heroin-assisted treatment – no substantial reduction in crack-cocaine use was observed (Blanken et al., 2010).
4. For reasons of both medical and public order safety, and given that sustained release dexamphetamine is not (yet) a registered medication in the Netherlands and is subject to the Dutch Opium Act, it is important that the present study will be conducted in a treatment setting with ample – treatment and research – experience in using strict safety procedures with respect to the storage, staff-supervised prescription, and prevention of diversion of a controlled study medication, monitoring of adverse and serious adverse events, and drug accountability. Given their extensive experience with prescribing diacetylmorphine to heroin dependent patients, heroin-assisted treatment programs are fully equipped to meet these requirements.

Against this background, we propose to evaluate the effectiveness of sustained release dexamphetamine in heroin dependent patients with comorbid crack-cocaine dependence in a heroin-assisted treatment program.

Study participants

Study participants will be recruited from the population of patients who already receive (ongoing) heroin-assisted treatment in the designated treatment programs in The Hague, Rotterdam and Amsterdam. To qualify for heroin-assisted treatment, patients must meet a set of well-defined selection criteria pertaining to the situation prior to the start of heroin-assisted treatment, which include that the patient must be at least 25 years old, and have a treatment-resistant heroin dependency, as indicated by (a) a history of heroin dependence (DSM-IV) of at least five years, (b) a minimum dose of 50 mg/day (patients who inhale their heroin) or 60 mg/day (patients who inject their heroin) of methadone for an uninterrupted period of at least 4 weeks in the previous 5 years, (c) a history of regular treatment contacts with the methadone program in the previous 6 months, (d) a history of unsuccessful methadone maintenance treatments, (e) daily or nearly daily use of illicit heroin, and (f) poor physical, mental or social functioning (Van den Brink et al., 2003). It is important to note that these selection criteria for participation in heroin-assisted treatment pertain to the situation prior to the start of heroin-assisted treatment, which for most patients is (far) more than a year ago.

<u>To be eligible for the present study, patients must</u>:

1. be at least 25 years old;
2. be cocaine dependent (DSM-IV) during at least the previous 5 years;
3. use cocaine on a regular basis (i.e., $\geq$ 8 days) in the previous month;
4. administer their cocaine primarily by means of basing ('crack');
5. have a history of earlier failed treatments aimed at reducing, or abstaining from, cocaine use ('treatment-refractory'). In order to qualify as 'treatment-refractory', the patient must have had at least two earlier treatment episodes targeted at reduction of cocaine use, yet still be cocaine dependent in the previous year, and use cocaine on a regular basis in the previous month;
6. be able and willing to participate in the study treatment and assessments;
7. have provided written informed consent.

<u>Patients will be excluded in case of</u>:

1. severe medical (e.g., severe renal or kidney insufficiency/failure, hypertension, glaucoma) or psychiatric problems (e.g., acute psychosis or history of drug-induced psychotic disorder, acute suicidality), which constitute a contraindication for participation;

2. cardiovascular problems (ECG);
3. (desired) pregnancy or continued lactation;
4. anticipated necessity of inpatient treatment (clinical judgement);
5. insufficient command of the Dutch language;
6. current participation in another addiction treatment trial.

STUDY TREATMENTS

As described before, study participants will be recruited from the population of patients who already receive (ongoing) heroin-assisted treatment for their concurrent heroin dependency. Hence, heroin-assisted treatment will be the underlying treatment ("treatment as usual") for all patients, in both the control and experimental group. In heroin-assisted treatment, patients have the possibility to receive – dependent upon their usual route of heroin administration – oral or injectable heroin (pharmaceutical grade diacetylmorphine; max. single dose 400 mg; max. daily dose 1000 mg) three times a day (morning, afternoon, evening), during seven days a week in designated treatment centers, and oral methadone once a day (max. daily dose 150 mg). Both heroin and methadone have to be taken under supervision at the treatment site. On a yearly basis, the treating physician and other treatment staff evaluate whether continuation of heroin-assisted treatment is indicated, based on the patient's health and social functioning. Diacetylmorphine was registered in the Netherlands for the treatment of chronic, treatment-resistant heroin dependence in December 2006, and has since then been prescribed for this indication in 17 designated treatment programs throughout the Netherlands.

Control treatment consists of ongoing heroin-assisted treatment (as described above) plus 12 weeks treatment with placebo. Placebo (2 tablets/day) will be matched to sustained release dexamphetamine tablets, and will be dispensed once daily during the patient's morning visit at the treatment center. For the purpose of the present study, the placebo tablets were manufactured by the Slotervaart pharmacist (group of prof.dr. Jos Beijnen), in compliance with the principles and guidelines of good manufacturing practice (see appendix: IMP-dossier, July 2013).

Experimental treatment consists of ongoing heroin-assisted treatment (as described above) plus 12 weeks treatment with sustained release dexamphetamine sulfate, prescribed in a fixed, single oral dose of 60 mg/day (2 tablets of 30 mg each). Oral sustained release dexamphetamine dose-levels of 30-60 up to 110 mg/day have been used in several studies in methamphetamine (Galloway et al., 2011; Longo et al. 2010) and cocaine dependent (Grabowski et al., 2001, 2004b) patients. In addition, oral dexamphetamine is prescribed to amphetamine users with heavy, problematic use in the United Kingdom at doses ranging from 5-200 mg/day (Bradbeer et al., 1998). Sustained release dexamphetamine has an average elimination half-life of approx. 12 hours, will be dispensed once daily during the patient's morning visit at the treatment centre, and – to allow intensive safety monitoring – must be taken under supervision at the treatment site. In addition, weekly assessments of heart rate and blood pressure will be conducted during the entire study period of 12 weeks. For the purpose of the present study, sustained release dexamphetamine sulfate tablets of 30 mg each were manufactured by the Slotervaart pharmacist (group of prof.dr. Jos Beijnen), in compliance with the principles and guidelines of good manufacturing practice (see appendix: IMP-dossier, July 2013).

In case a patient terminates his/her study treatment before week 12, or is withdrawn from the study for medical reasons, he/she will not be replaced by another patient. Following the end of the 12 weeks trial period, patients will continue their heroin-assisted treatment, but the study medication (either placebo or sustained release dexamphetamine; due to blinding unknown to both the treatment physician and research staff) will be terminated in all patients, and all usual treatment options in Dutch addiction care will be available to the patients, if indicated.

STUDY MEDICATIONS

Safety profile

Sustained release dexamphetamine sulfate

For the purpose of the present study, sustained release dexamphetamine sulfate tablets of 30 mg each were manufactured by the Slotervaart pharmacist (group of prof.dr. Jos Beijnen), in compliance with the principles and guidelines of good manufacturing practice (see appendix: IMP-dossier, July 2013).

In the United States, sustained release dexamphetamine sulfate is marketed under the brand name Dexedrine® (Spansule capsules), for the treatment of ADHD and narcolepsy. The study medication in the present trial contains the same active ingredient – dexamphetamine sulfate, prescribed in sustained release form – and has a similar dissolution profile as Dexedrine® (see appendix: IMP-dossier, July 2013). The Medication Guide for Dexedrine® (see link below) summarizes the following possible side effects (adverse reactions) for sustained release dexamfetamine sulfate:

Cardiovascular:	Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.
Central nervous system:	Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia , dysphoria, tremor, headache, exacerbation of motor and phonic tics, and Tourette's syndrome.
Gastrointestinal:	Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.
Allergic:	Urticaria.
Endocrine:	Impotence, changes in libido.

Source: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=18b7c145-3e8f-4e7e-c6b5-080d4139a008, accessed at 2013-09-25.

In five double-blind, placebo-controlled randomized trials, Dexedrine® or comparable sustained release dexamphetamine sulfate preparations have been prescribed to cocaine (three studies) and methamphetamine (two studies) dependent patients, at dosages ranging from 15/30 and 30/60 mg/day to individually titrated dosages of max. 110 mg/day. In the three RCTs in cocaine dependent patients (Grabowski et al. 2001, 2004; Shearer et al. 2003), three serious adverse events were reported among patients treated with dexamphetamine. Two SAEs were not related to study participation or medications. The third SAE was related to a patient with an undisclosed history of drug-induced psychotic episodes, who was admitted for 24-hour observation for psychotic symptoms, and was discharged with no evidence of psychotic symptoms. The patient was, nevertheless, withdrawn from treatment (Shearer et al. 2003). In the two RCTs in methamphetamine dependent patients (Longo et al. 2010; Galloway et al. 2011), no SAEs were reported. The following adverse events were reported in these studies:

- one case of hypertension among methamphetamine dependent patients, requiring a dose reduction from 70 to 60 mg (Longo et al. 2010);
- one case of significant abnormalities in ECG in a methamphetamine dependent patient in the sustained release dexamphetamine sulfate group - compared with two abnormalities in ECG in the placebo control condition (Galloway et al. 2011).

In addition, the studies by Longo et al. (2010) and Galloway et al. (2011) reported that heart rate and blood pressure were not significantly affected by the prescribed sustained release dexamphetamine sulfate. In the two studies in which sustained release dexamphetamine (15-30 mg/day and 30-60 mg/day) was prescribed in cocaine dependent patients, Grabowski et al. (2001, 2004b) observed cardiovascular effects that were neither statistically nor clinically significant.

Given the described safety profile of sustained release dexamphetamine sulfate preparations, the few (serious) adverse events and mild and often transient adverse reactions observed in studies in stimulant dependent patients, and since the patients in the present study will be thoroughly screened (medical screening, including blood pallet and ECG at baseline and 12 weeks follow-up) and monitored ((S)AEs weekly; heart rate and blood pressure weekly), with medication intake under direct supervision of the treatment centers' medical staff, safety risks are expected to be small and manageable.

Placebo

For the purpose of the present study, the placebo tablets were manufactured by the Slotervaart pharmacist (group of prof.dr. Jos Beijnen), in compliance with the principles and guidelines of good manufacturing practice (see appendix: IMP-dossier, July 2013). The placebo tablets are identical in shape, color, and content to the sustained release dexamphetamine tablets, with the exception of the active ingredient – dexamphetamine sulfate – which is replaced by an equal amount of lactose monohydrate in the placebo tablets.

Drug accountability

Study medication will be supplied by the central pharmacy to the local treatment centers. Upon receipt, the local treatment center will store the study medication in a safe. Each study center will keep full record per patient of the study medication dispensed on a daily basis. These records will be periodically checked by independent monitors from the AMC hospital pharmacy. The study medication has to be taken under supervision of the treatment staff at the treatment site. Any unused study medication must be accounted for, and documented, by the local treatment center, and will be desctructed according to the procedures developed by the AMC hospital pharmacy.

ASSESSMENTS

In both the control and experimental group, study assessments will take place at baseline, and 4, 8, and 12 weeks after baseline (see Table 1. Overview of assessments and instruments). The assessments will be conducted by trained research-assistants who are independent from the treatment staff, using standardized instruments to minimize information bias. At baseline, the treating physician will conduct a thorough medical examination to determine whether the patient should be excluded from the study due to the presence of contraindications.

At baseline, the following self-report instruments will be administered: the Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM; cocaine and alcohol dependence; Cottler, 2000), as well as questions on suicidal risk from the MINI International Neuropsychiatric Interview (MINI; Sheehan et al., 1998); the short version of the Addiction Severity Index (ASI; McLellan et al., 1980, 1992; Hendriks et al., 1989), supplemented with questions about current illegal activities, income, and living arrangements (similar to the ASI-version used in the CRF of the Dutch RCT on medically prescribed heroin); the Time Line Follow-Back (TLFB, pertaining to cocaine use in the previous month; Sobell & Sobell, 1992); the Maudsley Addiction Profile-Health Symptoms Scale (MAP-HSS; Marsden et al., 1998); the Symptoms Check List-90 (SCL-90; Derogatis et al., 1993; Arrindel & Ettema, 1996); the Obsessive Compulsive Drug use Scale (OCDS; Anton et al., 1996; De Wildt et al., 2005), the EuroQol (EQ-5D; Brooks, 1996), and the Readiness to Change Questionnaire (RCQ; Defuentes-Merillas et al., 2002).

At the 12 weeks assessment, (follow-up versions of) each of these instruments will be administered again, with the exception of the CIDI, MINI and RCQ. In addition, patient satisfaction (Client Satisfaction Questionnaire; CSQ-8; De Wilde & Hendriks, 2005), supplemented with questions pertaining to the received medication (placebo or sustained release dexamphetamine) will be assessed.

At the 4 and 8 weeks assessment, the TLFB (pertaining to cocaine use in the previous month) and the ASI-items pertaining to other substance use will be administered, as well as the MAP-HSS, SCL-90, OCDS, and EQ-5D.

Additional assessments include blood sampling (laboratory screen: BSE, MCH, MCV, MCHC, GGT, ALAT, ASAT, alkalase phospate, leucocytes, thrombocytes) (screening/baseline assessment and 12 weeks assessment; 2 x 16 ml), ECG (screening/baseline assessment and 12 weeks assessment), weekly medical screening; weekly check on heart rate and blood pressure during the entire study period; two times/week urine sampling (cocaine metabolites) during the 4 weeks preceding the 12 weeks assessment; monthly pregnancy testing (females); weekly registration of adverse events, serious adverse events (see: Safety reporting), and co-medication; study drug accountability (placebo and sustained release dexamphetamine); treatment compliance.

OUTCOME MEASURES AND DATA ANALYSIS

The study data will be analyzed following an intent-to-treat (ITT) approach. The ITT-population consists of all randomized patients who received at least one dose of the prescribed medication. The end of the trial is defined as the last visit of the last patient undergoing the trial. Effect of the intervention will be evaluated in terms of potential efficacy – cocaine use (self-report; urinalyses) and craving for cocaine, use of other substances, physical and mental health, social functioning (including criminality) – as well as in terms of acceptance, medication compliance, safety, and patient satisfaction.

The primary outcome measure pertains to cocaine use, defined as the total number of days of crack-cocaine use during the 12 weeks study period (range: 0 – 84 days), and will be analyzed in a multivariate regression analysis, controlling for study group and treatment site interactions. Secondary effects of the interventions will be evaluated in terms of additional cocaine use related outcome measures (e.g., longest duration of cocaine abstinence, and the number of days cocaine abstinence as well as the mean proportion of cocaine metabolite-free urine samples in the four weeks preceding the week 12 assessment), cocaine craving, use of other substances (self-report), physical and mental health, social functioning (including criminality), and patient satisfaction. Depending on the measurement level of the secondary outcome measure, differences between the two study groups will be analyzed using 2 (time) x 2 (group) repeated measures ANOVA, multivariate (logistic) regression analyses, and GEE-modelling.

Concerning missing data, multiple imputation will be applied for missing interview data. Missing urine samples (two samples/week in weeks 9 to 12) will be considered cocaine-positive.

Since the medication will be dispensed on a daily basis and medication intake will be supervised, compliance with the study medication can be registered reliably on a daily basis. Differences between the study groups (dexamphetamine *versus* placebo) will be described and analyzed in terms of the total number of days in which the medication was taken during the 12 weeks study period, the number of consecutive weeks in which patients were fully compliant (i.e., daily medication intake), and medication intake in the four weeks preceding the week 12 assessment.

Emergency unblinding

Unblinding may be necessary in case of a medical emergency in individual study participants. In case of emergency unblinding, unblinding of the treatment allocation code for individual patients and the reason(s) for unblinding will be fully documented in the study data file and statistical report. In order to be able to distinguish between blinded and unblinded subjects and related assessments in the analyses, each patient's Case Report Form (CRF) will include a code which specifies whether emergency unblinding occurred, as well as the date of unblinding.

Following emergency unblinding, the study treatment will be terminated in all unblinded cases, irrespective of their treatment allocation. These unblinded subjects will, however, be asked to continue their participation in the remaining study assessments, and will remain part of the ITT-analysis. In the ITT-analysis, the observed values of the primary outcome measure (days of crack-cocaine use) during these remaining assessments (after unblinding) of these unblinded patients will be replaced by imputed values based on the patient's baseline value on the primary outcome measure. In subsequent exploratory analyses, we will investigate whether the primary outcome of the trial based on these imputed values differs from the outcome based on the observed values in the unblinded assessments.

Following this approach, selective drop-out from the study will not occur. Unblinding will result in early study treatment termination, but this is not essentially different from other cases of early study treatment termination in which unblinding was not deemed necessary or relevant.

As argued before, based on the low incidence of (S)AEs in previous studies with sustained release dexamphetamine sulfate, the safety risks are expected to be small and the need for emergency unblinding is expected to be low, but will nevertheless be closely monitored during the trial.

POWER CONSIDERATIONS

In the primary analysis, treatment effect will be investigated by means of a multivariate regression model with the total number of days of crack-cocaine use during the 12 weeks (84 days) study period as primary outcome measure (see above). The difference between the sustained release dexamphetamine and placebo study groups in total number of days of crack-cocaine use during 12 weeks treatment, is estimated to be 10 days, with a pooled standard deviation of 17 days (i.e., moderate effect size). Given the feasibility character of the study, the sample size should preferably be limited. As in the parallel studies of topiramate and modafinil ("New pharmacotherapeutic treatment options for crack-cocaine dependent people in the Netherlands"; NL22193.018.09; MEC09/197) we, therefore, have chosen for a lenient alpha of 0.10 to minimize loss of statistical power due to small sample size, instead of the usual 5% false-positive rate, which would be more appropriate for a future confirmatory trial. Given the two-sided alpha=0.10, and a 1-beta power of 0.80, n=36 patients are required in each study group (2x36=72 patients for the present study) (Pocock, 1983; Cohen, 1988).

SAFETY MONITORING AND REPORTING

Adverse events and adverse reactions

Adverse events (AEs) are defined as any undesirable medical experience occurring to a study subject during the study. All AEs reported spontaneously by the subject or observed by the treating physician or his staff will be registered on a weekly basis by the treating physician, defining the relationship of each AE with the study medication (definitely not, possibly, probably, certainly, unknown), and its severity. The severity of AEs will be recorded as follows:

- mild: the AE is transient and easily tolerated;
- moderate: the AE causes the subject discomfort and interrupts the subject's usual activities;
- severe: the AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

All AEs will be followed until they have abated, or until a stable situation has been reached.

Adverse reactions (ARs) are defined as all undesirable responses to the study medication related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature or severity is not consistent with the side effects (adverse reactions) of sustained release dexamphetamine sulfate described above.

Serious adverse events and unexpected serious adverse reactions

Serious adverse events (SAEs) are defined as any undesirable medical experience or effect occurring to a study subject during the study that at any dose:

- results in death;
- is life-threatening;
- results in persistent or significant disability or incapacity;
- requires hospitalisation or prolongation of hospitalisation;
- is a congenital anomaly or birth defect.

All SAEs will be registered on a weekly basis – or earlier, when observed – by the treating physician, defining the relationship of each SAE with the study medication (definitely not, possibly, probably,

certainly, unknown). All SAEs will be followed until they have abated, or until a stable situation has been reached.

Suspected unexpected serious adverse reactions (SUSARs) are defined as SAEs that are both unexpected (i.e. not consistent with the side effects (adverse reactions) of sustained release dexamphetamine sulfate described above), and at least possibly related to the study medication.

Reporting

- An annual safety report will be submitted to the MEC of the AMC and the Medicine Evaluation Board via ToetsingOnline, consisting of:
  - a list of all SAEs;
  - a list of all (expected or unexpected) serious adverse reactions, and a summary table of these serious adverse reactions, ordered by organ system;
  - an analysis of the safety of the study subjects, including an evaluation of the balance between the efficacy and the harmfulness of the study medication.
- All SUSARs that have arisen during the study will be reported expedited (i.e. within 15 days after the first knowledge of the SUSAR, or within 7 days [preliminary report] in case of a fatal or life-threatening SUSAR) to the MEC of the AMC and to the Medicine Evaluation Board.

ETHICAL CONSIDERATIONS

The study will be conducted under the provisions of the Declaration of Helsinki, as amended in Seoul (2008). The study protocol will be submitted to the Medical Ethics Committee of the Academic Medical Center in Amsterdam, and will not start before formal approval is obtained.

Patients participating in heroin-assisted treatment, with clinically relevant comorbid cocaine use (see inclusion criteria) will be informed about the study and its procedures by means of a written patient information form, and will receive oral explanation about the study by a trained research assistant. Patients will be asked to provide written informed consent by the treating physician before the baseline screening, and have approximately 2 weeks time to consider their decision. Subjects will be informed that they are free to leave the study at any moment, and that this will have no consequences for their ongoing participation in the underlying heroin-assisted treatment.

The investigators will ensure that the subject's anonymity will be maintained. All study data will be treated confidentially and processed anonymously. Each subject will receive a unique identification number, which does not contain initials or date of birth. The CRF and other study documents will only identify subjects by their unique identification number. These identification numbers will be linked with the name of the subject on only one location. This linked file will be kept in a safe, which can only be accessed by the principal investigators.

Patients will receive remuneration for their participation in the study assessments (baseline assessment: 10 euro; 4 weeks assessment: 10 euro; 8 weeks assessment: 10 euro; 12 weeks assessment: 15 euro). In addition, patients will receive 5 euro for each urine sample provided during the 4 weeks preceding the 12 weeks assessment (max. total remuneration: 85 euro).

All patients will be insured for their participation in the study in accordance with legal requirements of article 7 of the WMO.

STUDY PHASES

The duration of the study is 12 months. Month 1: preparation of the study; month 2-5: recruitment of patients in a prevalent sample of crack-cocaine using patients in daily supervised heroin-assisted treatment; month 2-8: execution of the pharmacotherapeutic treatment intervention and related assessments; month 9-12: analyses, reporting, and dissemination.

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Table 1. Overview of assessments and instruments

Assessments (researchers)	**Baseline**	**Week 4**	**Week 8**	**Week 12**
Checklist inclusion criteria	•			
CIDI - Substance Abuse Module (cocaine, alcohol)	•			
MINI – Suicidal risk	•			
Addiction Severity Index + supplement [1]	•			
Addiction Severity Index (only substance use + supplement)		•	•	•
Time Line Follow-Back (cocaine)	•	•	•	•
Maudsley Addiction Profile (MAP) – HSS	•	•	•	•
Symptom Check List- 90 (SCL-90)	•	•	•	•
Obsessive Compulsive Drug Use Scale (OCDS)	•	•	•	•
EuroQol (EQ-5D)	•	•	•	•
Readiness to Change Questionnaire (RCQ)	•			
Client Satisfaction Questionnaire- 8 (CSQ-8) + supplement [2]				•
Evaluation				•

Medical assessment (physician)	**Baseline**	**Week 4**	**Week 8**	**Week 12**
Checklist exclusion criteria (control and experimental)	•			
Informed consent (control and experimental)	•			
Medical assessment: ECG + blood analysis	•			•
Medical screening: heart rate, blood pressure [3]	•	• • • •	• • • •	• • • •
Pregnancy (only women)	•	•	•	•
(Serious) adverse events	•	• • • •	• • • •	• • • •
Drug accountability		• • • •	• • • •	• • • •
Urinalysis cocaine- metabolites (obtained by research assistant)	•			• • • •
Treatment participation (medication compliance)		• • • •	• • • •	• • • •

[1] The ASI-supplement concerns illegal activities, income, and living arrangements.
[2] Additional questions about the treatment(s).
[3] Blood pressure and heart rate will be assessed weekly during the entire study period of 12 weeks.
• • • • Indicates weekly (instead of monthly) registration.