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

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39005

Source
ToetsingOnline

Brief title
CATCH-study: Sustained release dexamphetamine

Condition

- Other condition

Synonym
cocaine dependence; cocaine addiction

Health condition

middelen afhankelijkheid

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: cocaine dependence, pharmacotherapy, RCT

Outcome measures

Primary outcome

The primary outcome measure pertains to cocaine use, and is defined as the total number of days of crack-cocaine use during the 12 weeks study period (range: 0 * 84 days).

Secondary outcome

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.

Study description

Background summary

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.

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).

Intervention

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 burden and risks

In both the control and experimental group, study assessments will take place at baseline, and 4, 8, and 12 weeks after baseline. 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. The duration of these study assessments amounts to a maximum of approximately 5 hours in total (during a study period of 12 weeks).
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 (adverse and serious adverse events); weekly check on heart rate and blood pressure; two times/week urine sampling (cocaine metabolites) during the 4 weeks preceding the 12 weeks assessment; monthly pregnancy testing (females).

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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Study participants will be recruited from the population of patients who already receive (ongoing) heroin-assisted treatment in the designated treatment programs in Amsterdam (2 treatment centers), Rotterdam (1 treatment center) and The Hague (1 treatment center). 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. ;To be eligible for the present study, patients must:
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., * 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.

Exclusion criteria

Patients will be excluded in case of:
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 design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-08-2014
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	sustained release dexamphetamine sulphate
Generic name:	sustained release dexamphetamine sulphate

Ethics review

Approved WMO Date:	12-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004024-11-NL
CCMO	NL46415.018.13