CATCH: New pharmacological treatment options for crack-cocaine dependence. Results from three randomised controlled trials

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CATCH

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CATCH

New pharmacological treatment options for crack-cocaine dependence

Results from three randomised controlled trials

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Chapter 1

General introduction*

* This general introduction is an updated and extended version of the study protocol published as: Mascha Nuijten, Peter Blanken, Wim van den Brink, & Vincent Hendriks (2011). Cocaine Addiction Treatments to improve Control and reduce Harm (CATCH): New Pharmacological Treatment Options for Crack-Cocaine Dependence in the Netherlands. *BMC Psychiatry, 11*: 135.

Introduction

Compulsive cocaine use, particularly crack-cocaine (i.e. smoking or 'basing' cocaine), is associated with serious negative consequences, including physical, mental and social problems, and is a great burden for both the user and society (Degenhardt et al., 2014; Degenhardt and Hall, 2012; European Monitoring Centre for Drugs and Drug Addiction, 2014; Karila et al., 2012; Oteo Perez et al., 2015; Pomara et al., 2012).

The number of estimated cocaine users worldwide in 2013 was 16 million, corresponding to 0.4% of the global adult population (United Nations Office on Drugs and Crime, 2015). Overall in Europe, cocaine is the most commonly used illicit stimulant drug and approximately 3.4 million Europeans aged 15-64 years (1.0% on average) are estimated to have used cocaine in the last year (European Monitoring Centre for Drugs and Drug Addiction, 2015). Compared with this European average, in the Netherlands, this percentage was slightly higher with 1.6%, corresponding to an estimated 170,000 cocaine users in 2014 (Trimbos-instituut, 2015).

Cocaine users can be roughly divided into recreational, integrated users, who generally snort their cocaine and often use other (semi)legal substances (e.g. alcohol, cannabis), and socially marginalised compulsive users, who mostly inject cocaine or smoke crack-cocaine and often use other illegal drugs (e.g. opioids) (European Monitoring Centre for Drugs and Drug Addiction, 2012). Nearly 6% of first users are estimated to become cocaine dependent within the first two years (O'Brien and Anthony, 2005; Wagner and Anthony, 2002) and about 20% of first time users are estimated to ultimately become cocaine dependent (Lopez-Quintero et al., 2011), with a higher risk to become cocaine dependent when cocaine is smoked (crack) or injected than when it is snorted (Chen and Anthony, 2004; O'Brien and Anthony, 2005; Reboussin and Anthony, 2006). In the Netherlands, the prevalence of crack-cocaine dependence between 2009 and 2011 in the three largest cities (i.e. Amsterdam, The Hague and Rotterdam) was estimated to be 0.51%, corresponding with 6,660 persons in the age of 15-64 years (Oteo Perez et al., 2013).

With respect to annual cocaine-related treatment demand in Dutch addiction care, the number of patients increased from approximately 9,300 in 1995 to nearly 17,000 in 2008, subsequently declined to 14,500 in 2012, and stabilised

around 14,000 between 2012 and 2014 (Trimbos-instituut, 2015). Most of these cocaine dependent patients have a history of multiple and extensive treatment episodes (Wisselink et al., 2015), and for 45% of these cocaine-related treatment-seekers smoking or basing cocaine was the predominant route of administration, with the remaining 55% predominantly snorting cocaine (Trimbos-instituut, 2015).

Cocaine treatment

Psychosocial treatment

Almost all treatment-seeking cocaine dependent patients receive psychosocial treatment (Lingford-Hughes et al., 2012), including cognitive behavioural therapy (CBT) and relapse prevention. However, psychosocial treatments for cocaine dependence have generally produced modest results (Dutra et al., 2008; Shearer, 2007), and both study data and practice-based experiences indicate that poor compliance is a major complicating factor in these treatments, with dropout rates up to 42% in cocaine dependent patients in trials (Dutra et al., 2008). Patients with dual cocaine and heroin dependence often participate in methadone maintenance treatment, but in a systematic review and meta-analysis, including 3,029 patients from 37 studies, it was concluded that opiate maintenance therapy alone is not effective in achieving cocaine abstinence and that additional interventions, such as co-prescribed pharmacotherapy or contingency management, are essential (Castells et al., 2009). In addition, case management is offered to this – often chronic – patient population, but there is no convincing evidence that case management reduces drug use (Hesse et al., 2007).

One of the more effective psychosocial treatments for cocaine dependence to date is contingency management (CM), an intervention in which positive reinforcement is used to improve medication adherence and/or clinical outcomes (Stitzer and Vandrey, 2008). CM has shown positive results in terms of improved treatment retention (Schierenberg et al., 2012; Van Horn et al., 2011), medication adherence (Lussier et al., 2006; Petry et al., 2012; Schierenberg et al., 2012), and reductions in cocaine use (Blanken et al., 2016; Dutra et al., 2008; Farronato et al., 2013; Lussier et al., 2006; Petitjean et al., 2014; Prendergast et al., 2006; Schierenberg et al., 2012), although evidence supporting the persistence of the effect of CM after treatment termination is equivocal (DeFulio and Silverman,

2012; Farronato et al., 2013). Furthermore, application of CM in clinical practice has been problematic: reasons are both practical obstacles, including cost and time restraints to administer CM, and ideological criticisms on bribery and paying for behaviour that should be exhibited anyway, as well as concerns about negative consequences of external reinforcement, such as replacing internal by external motivation to change and increased risk of relapse when reinforcement stops (Carroll, 2014; Marteau et al., 2009; Petry, 2010). It should be noted, however, that research has demonstrated that CM does not negatively affect motivation to change substance use (Ledgerwood and Petry, 2006; Walter and Petry, 2015) and that it also does not contribute to the use of other substances (Kadden et al., 2009).

Pharmacological treatment

The modest results of psychosocial treatments and the growing knowledge about the neurobiology of cocaine dependence have led to an increasing number of studies searching for effective pharmacological agents to reduce (chronic) cocaine use, including antipsychotics (Alvarez et al., 2013; Amato et al., 2007; Kishi et al., 2013), anticonvulsants (Alvarez et al., 2010; Minozzi et al., 2015b), antidepressants (Pani et al., 2011), indirect dopamine agonists or psychostimulants (Mariani and Levin, 2012; Perez-Mana et al., 2011; Shearer, 2008), direct dopamine agonists (Amato et al., 2011; Minozzi et al., 2015a), cocaine vaccines (Kosten et al., 2013), and cocaine catalysts (Shram et al., 2015). The largest series of studies of pharmacological treatment options for cocaine dependence conducted were the Cocaine Rapid Efficacy Screening Trials (CREST), in which a paradigm was developed to systematically screen a range of drug classes and medications for potential utility in the treatment of cocaine dependence (Leiderman et al., 2005). Within five years, 18 medications were screened of which only four appeared to be worthy of further investigation: tiagabine, reserpine, cabergoline and sertraline (Kampman et al., 2005). However, none of them showed convincing efficacy in subsequent studies (Gonzalez et al., 2007; Winhusen et al., 2007a; Winhusen et al., 2007b), although sertraline showed significant results in terms of delayed relapse in depressed, abstinent cocaine dependent patients, but not on the primary outcome measure, i.e. cocaine use (Mancino et al., 2014; Oliveto et al., 2012). Despite considerable

efforts in the research field, there are still no proven effective medications for cocaine dependence to date.

Basically, pharmacological research has focused on two different strategies (American Psychiatric Association Practice Guidelines, 2007): one directed at cocaine abstinence or substantial reduction, and the other directed at minimising cocaine-related harm by replacing uncontrolled and harmful cocaine use with regulated and safer stimulant use, in terms of dose, route of administration and adverse effects (Grabowski et al., 2004b; Herin et al., 2010; Mariani and Levin, 2012; Shearer, 2008). Concerning the first strategy, from the wide range of medications tested so far, topiramate and modafinil constitute abstinence or stimulant use reduction oriented medications, which are registered for indications other than cocaine dependence and have shown promise in several studies in cocaine dependent populations in terms of cocaine abstinence or cocaine use reduction (Ballon and Feifel, 2006; Kim and Lawrence, 2014; Martinez-Raga et al., 2008; Shinn and Greenfield, 2010). With respect to the second strategy, harm reduction treatment with an agonist medication, a growing number of pre-clinical and human studies have suggested that the indirect dopamine agonist dexamfetamine, more specifically sustained-release (SR) dexamfetamine with a slower onset and limited peak effect, is an important candidate for replacement therapy in cocaine dependence (Castells et al., 2010; Castells et al., 2007; Kim and Lawrence, 2014; Rush and Stoops, 2012; Stoops and Rush, 2013). The basic rationale for this substitution treatment for cocaine dependence is similar to that for other addictions, such as nicotine replacement therapy in tobacco smokers and methadone or buprenorphine in opioid dependent patients. In addition to harm reduction, replacement therapy also facilitates engagement with health care services by attracting and retaining addicted individuals in treatment (Shearer, 2008; Shearer and Gowing, 2004), and the regular supervised prescription regimen may by itself help patients structure their daily life.

Hence, numerous pharmacological agents have been tested for their efficacy in cocaine dependence, but generally with disappointing or, at best, equivocal results. Topiramate, modafinil and SR dexamfetamine still constitute promising medications, covering both abstinence-oriented and harm reduction treatment strategies. Investigating these agents as potentially new treatment options will contribute to opening up new lines of research and – dependent upon the results

– new lines of treatment for the most problematic group of cocaine users, i.e. crack-cocaine dependent patients.

Topiramate

Topiramate was originally registered as an anticonvulsant and is also approved in Europe for the treatment of migraine, but through its different mechanisms of action, topiramate was also investigated for its efficacy in the treatment of substance use disorders (Shinn and Greenfield, 2010). Topiramate indirectly suppresses dopamine release in the corticomesolimbic system, a brain region involved in reward and reinforcement, by enhancing the gamma-aminobutyric acid (GABA) system and antagonising the glutamatergic system, and, therefore, topiramate is likely to attenuate the reinforcing and rewarding properties of addictive substances and to alleviate withdrawal symptoms (Johnson, 2005; Shinn and Greenfield, 2010).

Topiramate has shown efficacy in the treatment of alcohol dependence by promoting abstinence, reduced alcohol intake, and reduced craving (Arbaizar et al., 2010; Blodgett et al., 2014; De Sousa, 2010; Guglielmo et al., 2015; Hammond et al., 2015; Kenna et al., 2009). In methamphetamine dependent patients, topiramate did not promote abstinence, but it did contribute to reductions in methamphetamine use and relapse rates (Elkashef et al., 2012; Rezaei et al., 2016). In cocaine dependence, prior to the start of our study, two trials with topiramate showed positive effects on cocaine abstinence (Kampman et al., 2004) and cocaine craving (Reis et al., 2008).

Modafinil

Modafinil is currently registered to promote wakefulness in adult patients with excessive sleepiness associated with narcolepsy with or without cataplexy. Modafinil has a diverse mechanism of action, but is primarily a selective dopamine reuptake inhibitor that increases extracellular levels of dopamine (Federici et al., 2013; Wisor, 2013; Zolkowska et al., 2009). Modafinil interacts differently with the dopamine transporter compared with other conventional stimulants, which is suggested to underlie the low abuse potential (Minzenberg and Carter, 2008; Wisor, 2013). As with all dopamine enhancing medications, however, there is a risk for addiction and this should not be disregarded (Volkow et al., 2009).

The various neurobiological actions make modafinil an interesting agent for several clinical conditions that are characterised by reduced wakefulness, energy, cognition or attention, such as in chronic fatigue syndrome, attention-deficit/hyperactivity disorder (ADHD), depression, Parkinson's disease and schizophrenia (Ballon and Feifel, 2006; Kumar, 2008; Minzenberg and Carter, 2008; Wisor, 2013). Moreover, modafinil has shown promise in the treatment of stimulant dependence. For example, in methamphetamine dependent patients, modafinil showed improved treatment retention and reduced methamphetamine use (De La Garza et al., 2010; Heinzerling et al., 2010; McElhiney et al., 2009; Shearer et al., 2009), but modafinil had no effect on abstinence (Anderson et al., 2012) or withdrawal (Lee et al., 2013). Prior to the start of our study, the efficacy of modafinil in the treatment of cocaine dependence was suggested in two studies: modafinil contributed to cocaine abstinence and protracted abstinence (Dackis et al., 2005), particularly in cocaine dependent patients without a comorbid alcohol use disorder (Anderson et al., 2009).

In addition to the positive clinical outcomes of modafinil in patients with a stimulant use disorder, there is evidence suggesting that modafinil also improves cognitive functioning in patients with substance use disorders (Mereu et al., 2013). For instance, in alcohol dependent patients, modafinil improved cognitive control (Schmaal et al., 2013a) and impulsive decision making (Schmaal et al., 2014), whereas in patients with methamphetamine dependence verbal memory recall (Hester et al., 2010) and learning performance (Ghahremani et al., 2011) improved. Furthermore, in patients with cocaine dependence, modafinil reduced risk-taking (Canavan et al., 2014), improved working memory and attention (Kalechstein et al., 2013), and attenuated neural reactivity to cocaine-related cues and self-reported craving (Goudriaan et al., 2013). Finally, modafinil-related improvements were found in subgroups with poor baseline cognitive performance, including response inhibition (Schmaal et al., 2013b) and memory (Joos et al., 2013b) in alcohol dependent patients and working memory in methamphetamine dependent volunteers (Kalechstein et al., 2010), or in inhibitory control and processing speed in methamphetamine dependent patients with low baseline methamphetamine use (Dean et al., 2011).

Hence, modafinil is a promising agent for the improvement of both clinical outcomes and cognitive performance in substance use disorders. Still, to date,

there has only been one study relating modafinil administration to both cognitive performance and clinical outcomes: in a randomised, placebo-controlled trial in alcohol dependent patients, 300 mg/day modafinil was investigated for its effects in reducing alcohol use and impulsivity (Joos et al., 2013a). Although modafinil did not increase abstinence or reduce heavy drinking in the total sample, modafinil prolonged the time to alcohol relapse in patients with poor baseline response inhibition, whereas it increased heavy drinking and reduced abstinence in those patients with good baseline response inhibition (Joos et al., 2013a). These findings suggest that the effect of modafinil on reduced substance use and abstinence may be mediated by improvements in cognitive functions of patients with impaired baseline cognitive control.

Dexamfetamine

Dexamfetamine is an indirect dopamine agonist or psychostimulant that is registered and prescribed for the treatment of patients with attention deficit hyperactivity disorder (ADHD) or adult patients with excessive sleepiness in the context of narcolepsy. Through increases in extracellular concentrations of dopamine, norepinephrine and serotonine, dexamfetamine shares pharmacological mechanisms with cocaine and is therefore considered a potential replacement therapy for stimulant dependence (Grabowski et al., 2004b; Herin et al., 2010), particularly in sustained-release (SR) preparations, which are used to maintain steady blood levels and have lower abuse potential compared with immediate-release preparations (Mariani and Levin, 2012).

Agonist replacement therapy with SR dexamfetamine has been investigated among stimulant dependent patients in several studies. Results are equivocal for problematic (meth)amphetamine use (Perez-Mana et al., 2013) with one study showing dexamfetamine to be associated with amphetamine use reduction and higher treatment adherence (Longo et al., 2010) and other studies failing to show superiority of dexamfetamine (Galloway et al., 2011; Shearer et al., 2001). In studies among cocaine dependent patients that were conducted prior to our study, dexamfetamine prescription was generally associated with reduced cocaine use (Grabowski et al., 2001; Grabowski et al., 2004a; Shearer et al., 2003), but small sample sizes in all trials, as well as administration of the immediate-release

preparation in the study of Shearer and colleagues (2003) are likely to be responsible for the lack of a robust effect of dexamfetamine so far.

The CATCH project

Given the burden that is associated with compulsive crack-cocaine use, the high prevalence of cocaine dependence and cocaine-related treatment demand, as well as the limited treatment options to date, the search for new pharmacological treatment options should be high on the research agenda. Against this background, in January 2007 we submitted a study proposal on "Prevalence, treatment needs and new pharmacotherapeutic treatment options for crack-cocaine dependent people in the Netherlands" to The Netherlands Organisation for Health Research and Development (ZonMw), which consisted of two sub-studies: (1) an epidemiological sub-study to determine the prevalence of crack-cocaine use in the three largest cities in the Netherlands, and (2) a pharmacotherapeutic sub-study. The results of the first sub-study have been described elsewhere (Oteo Perez et al., 2015; Oteo Perez et al., 2012; Oteo Perez et al., 2013) and the results of the second sub-study are the subject of the present thesis.

It is noteworthy that the study protocol concerning the pharmacotherapeutic sub-study originally consisted of four separate feasibility trials, with modafinil and rimonabant directed at abstinence or drug use reduction as the treatment goal, and SR dexamfetamine and – if acceptable in medical-ethical and legal terms – medically prescribed inhalable cocaine directed at harm reduction or drug use reduction as the treatment goal. At that time, pre-clinical studies on the cannabinoid CB1 receptor antagonist rimonabant had shown potential efficacy in attenuating reinforcement and relapse across different classes of drugs, including cocaine (Carai et al., 2005; Le Foll and Goldberg, 2005). In humans, rimonabant was found to be effective in reducing food intake (Black, 2004; Boyd and Fremming, 2005) and was approved as an anorectic anti-obesity drug in Europe in 2006. Moreover, rimonabant had shown promise in treating nicotine dependence (Cohen et al., 2005; Steinberg and Foulds, 2007). However, in 2008 rimonabant was withdrawn from the market due to potentially serious side effects, including depression and suicide (Christensen et al., 2007; Topol et al., 2010). Therefore,

the proposed trial with rimonabant was cancelled and replaced by a trial with topiramate.

The feasibility trial with inhalable cocaine had to be cancelled as well. Although administering medically prescribed inhalable cocaine under strict medical conditions as agonist replacement therapy for chronic, treatment-refractory cocaine dependent patients (Grabowski et al., 2004b) would be an analogue to medically prescribed heroin to opiate dependent patients (Blanken et al., 2010b), the proposed feasibility trial with inhalable cocaine was rejected for ethical and safety reasons. Thus, an adapted study proposal on new pharmacotherapeutic treatments for crack-cocaine dependence was proposed, incorporating three medications: topiramate, modafinil and SR dexamfetamine. In November 2007, this proposal was approved and funded by The Netherlands Organisation for Health Research and Development (ZonMw).

The overall objective of the pharmacotherapeutic sub-study was to evaluate the acceptability, efficacy and safety of 200 mg/day topiramate, 400 mg/day modafinil, and 60 mg/day SR dexamfetamine in the treatment of crack-cocaine dependent patients in the Netherlands, in three separate randomised controlled feasibility trials, and – dependent on the results – to yield one or more candidate medications for future investigation in a large-scale confirmatory trial. As in any medication study, our primary focus was on the balance between (potential) benefit and harm associated with the medications, taking into consideration the personal and societal damage linked to continued illicit use of cocaine, in a situation without effective pharmacological treatment options.
Given the aim of the study – investigating treatment effectiveness with both abstinence and harm reduction as treatment strategies for cocaine dependent patients – the study's acronym is CATCH: Cocaine Addiction Treatments to improve Control and reduce Harm.

Methods

Design & setting

All three pharmacological trials of the CATCH project were parallel-group, randomised controlled, feasibility studies of 12 weeks duration, conducted at different addiction treatment centres.

Topiramate and modafinil trials

In the topiramate and the modafinil trials, the originally proposed pre-randomisation, double-consent ('Zelen'-) design (Zelen, 1979) was used to assign patients to the experimental group (12 weeks cognitive behavioural therapy (CBT) plus study medication: 200 mg/day topiramate [trial 1] or 400 mg/day modafinil [trial 2]) or the control group (12 weeks CBT only; no placebo). According to the Zelen-design, randomisation takes place prior to seeking (final) informed consent: in our study, a first informed consent (to participate in a study evaluating CBT) was obtained from all patients before randomisation, and a second informed consent (to participate in add-on pharmacotherapy) was obtained after randomisation, but only in patients allocated to the experimental group (Figure 1).

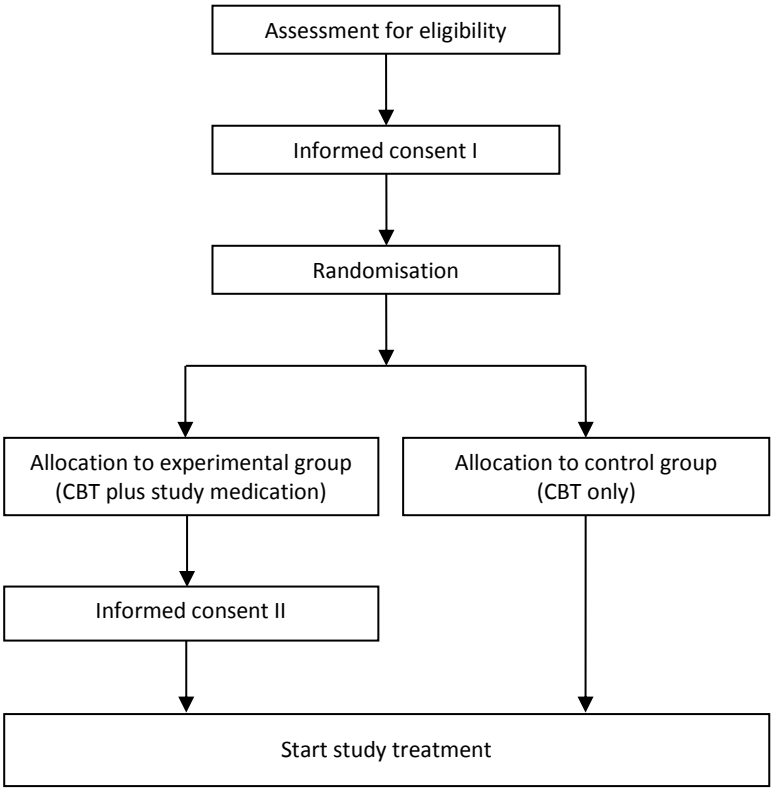
In this pre-randomisation, double-consent design, patients in the control condition receive standard care and are unaware of the experimental condition that they are compared with. This design is considered to be particularly useful when the experimental intervention is expected to be highly attractive to the participants, which is likely to result in recruitment difficulties, non-compliance and selective dropout among control subjects in a traditional randomised design when expectations, raised by the possible prescription of the active medication, are not met (Schellings et al., 1999; Torgerson and Roland, 1998).

Alternatively, a series of small-scale placebo-controlled randomised trials could have been conducted, corresponding with the previously mentioned Cocaine Rapid Efficacy Screening Trials (Leiderman et al., 2005). However, the occurrence of substantial dropout (i.e. about 30% overall) in the – already small – control groups in these trials limited conclusions with regard to the medication effect (Elkashef et al., 2005; Kampman et al., 2005). This led us to conclude that, given the proposed small sample sizes of the CATCH feasibility trials, and the potentially high risk of premature dropout and biased results, a placebo-controlled randomisation design would not be desirable at this stage.

Instead, the pre-randomisation, double-consent design has the advantage of providing a more naturalistic control condition than a traditional randomised design (e.g. no placebo, less data collection), but without information or selection bias due to patients being aware that they are control subjects, as in a fully naturalistic study in which patients know that they either receive active medication or not. Still, the pre-randomisation, double-consent design maintains

the strength of a randomised design by providing treatment allocation of patients to one of the conditions based on chance (Zelen, 1979). In addition, since acceptance of pharmacotherapy by the target population (i.e. crack-cocaine dependent patients) would be an important aspect of feasibility, the pre-randomisation, double-consent design in which only patients in the experimental condition would be exposed to medication intake, seemed to be the best option.

Figure 1. Overview pre-randomisation, double-consent design.



Nevertheless, the pre-randomisation, double-consent design has some disadvantages as well. Selective dropout can occur when second informed consent has to be provided, which may also result in an extended patient enrolment to achieve the required sample size (Torgerson and Roland, 1998). Moreover, blinding of participants who receive the experimental treatment is not

possible, which may cause an expectation bias in patients, as well as in treatment staff and investigators. This may influence post-randomisation treatment decisions and reported outcomes, and might partly limit the evidence of clinical benefit of the study medication. Comparable problems can also occur when patients in the control condition become aware of the experimental condition, for instance when patients share the same drug scene and talk about study participation. Despite these disadvantages, we believed that this choice was defendable given the feasibility character of the trials, in which – for the first time in the Netherlands – acceptance, safety and efficacy of pharmacotherapy would be explored in crack-cocaine dependent patients, before executing one or more full-scale randomised controlled trials.

The topiramate and modafinil trials were conducted in outpatients of the addiction treatment services in The Hague (Brijder Addiction Care; both trials) and Amsterdam (Jellinek, Mentrum; modafinil trial) among patients who were either new referrals or already received treatment for concurrent substance dependence, including case management or methadone maintenance treatment, but with insufficient results regarding their crack-cocaine use.

SR dexamfetamine trial

In the SR dexamfetamine trial, a standard randomised, placebo-controlled design was used, which was different from the original study protocol and this choice was based on two major arguments. First, the acceptance of pharmacotherapy in terms of providing second informed consent, which was an important outcome variable in all three feasibility trials and was also reason to use the pre-randomisation, double-consent design, had meanwhile been demonstrated in the topiramate and modafinil trials; the vast majority agreed to sign the second informed consent. Thus, a design in which both treatment groups would receive medication was plausible. Second, from correspondence with professor Grabowski, who conducted several trials with 60 mg/day SR dexamfetamine among cocaine dependent patients (Grabowski et al., 2001; Grabowski et al., 2004a), we learned that patients were generally unable to distinguish active medication from placebo. This suggested that dropout would not be different between the patients from the active and inactive medication group, since their

expectations of the study medication were likely to be comparable in terms of both effects and side-effects. Given that the randomised double-blind, placebo-controlled design is the most powerful research design, as well as the fact that the SR dexamfetamine for the current trial was manufactured in the Netherlands and that manufacturing of identical placebo tablets could also be accomplished, it was decided to change the original pre-randomisation, double-consent design to a standard randomised, double-blind, placebo-controlled design.

Also different from the original study protocol, the SR dexamfetamine trial was conducted in crack-cocaine dependent patients with comorbid heroin dependence, participating in heroin-assisted treatment (HAT), based on the following line of reasoning:

1. The vast 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 Perez et al., 2012).
2. From those in treatment for combined crack-cocaine and heroin dependence, the vast majority of patients participate 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 (Castells et al., 2009; Van den Brink, 2012).
3. Approximately 500-600 patients in the Netherlands with combined crack-cocaine and heroin dependence currently participate in an opioid substitution program with medically prescribed heroin: heroin-assisted treatment (HAT). Studies have indicated that HAT 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 (Blanken et al., 2010b; Van den Brink et al., 2003). However, among patients who concurrently used crack-cocaine – 84-90% of the patients in HAT – only modest reductions in crack-cocaine use were observed (Blanken et al., 2010b).
4. For reasons of both medical and public order safety, and given that SR dexamfetamine is not (yet) a registered medication in the Netherlands and is subject to the Dutch Opium Act, it was important that the present study would be conducted in a treatment setting with sufficient – treatment and research – experience in using strict safety procedures with respect to the storage, staff-supervised prescription, and prevention of diversion of controlled study

medication, monitoring of (serious) adverse events, and drug accountability. Given their extensive experience with prescribing diacetylmorphine to heroin dependent patients, heroin-assisted treatment programs were fully equipped to meet these requirements. Two HAT-settings in Amsterdam (Public Health Care [GGD]), one in Rotterdam (Bouman) and one in The Hague (Brijder Addiction Treatment) were involved. Patients who participated in the SR dexamfetamine study received either 12 weeks 60 mg/day SR dexamfetamine or placebo parallel to their medically prescribed heroin and methadone.

Participants

Participants in the three trials were adult outpatients who were cocaine dependent (American Psychiatric Association, 1994) in the last year and who used their cocaine predominantly by basing ('crack') for at least eight days per month. The most important exclusion criteria were: severe somatic problems (e.g. renal insufficiency or cardiovascular problems), severe psychiatric problems (e.g. acute psychosis, suicidality), need for inpatient treatment, and current pharmacological treatment with a potentially effective agent for cocaine dependence (i.e. naltrexone, baclofen, acamprosate, disulfiram, or methylphenidate). Given the agonistic nature of SR dexamfetamine, eligible patients in the dexamfetamine trial had to be cocaine dependent in the previous five years and had to be treatment-refractory in terms of having a history of at least two failed treatments directed at reduction of or total abstinence from cocaine use.

Outcome measures

Study outcome measures included treatment retention in CBT (topiramate and modafinil trials), self-reported and urine-based crack-cocaine use, cocaine craving, other substance use, and improvements in health and social functioning (all three trials). In addition, acceptance in terms of willingness to participate in pharmacotherapy, medication adherence and patient satisfaction, as well as safety, assessed by the occurrence of (serious) adverse events, were measured.

In the modafinil study, given the potentially cognitive enhancing capacities of modafinil, changes in cognitive performance (i.e. impulsivity and attentional bias) were also assessed.

Additional information on assessments (time points and instruments) and data analyses is described in the following chapters.

Content of the present thesis

This thesis presents the results of the CATCH project, investigating new pharmacological treatment options for crack-cocaine dependence in the Netherlands. In the Chapters 2 and 3, the acceptance, efficacy and safety of 200 mg/day topiramate and 400 mg/day modafinil are evaluated in crack-cocaine dependent outpatients, respectively. The interrelationship between modafinil, impulsivity and attentional bias, and clinical outcomes in this study population is described in Chapter 4. Acceptance, efficacy and safety of 60 mg/day sustained-release dexamfetamine as agonist pharmacotherapy in chronic, treatment-refractory, cocaine dependent patients with comorbid opioid dependence in heroin-assisted treatment are evaluated in Chapter 5. Chapter 6 contains the Summary and general discussion in which the empirical findings of the three trials are summarised and discussed in a broader context, and ends with conclusions and recommendations for future research.

Chapter 2

Treatment of crack-cocaine dependence with topiramate:
A randomised controlled feasibility trial in the Netherlands

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Abstract

Background: Crack-cocaine dependence is a complex disorder with limited treatment options. Topiramate is one of the promising medications with reported reductions in cocaine use and craving in former studies. The present study evaluated the acceptance and effectiveness of topiramate as an add-on to cognitive behavioural therapy (CBT) in crack-cocaine dependent patients.
Methods: Seventy-four crack-cocaine dependent outpatients participated in an open-label, randomised feasibility trial. They were randomised to receive either 12-week CBT plus topiramate (200 mg/day) or 12-week CBT only. The primary outcome measure was treatment retention. Secondary outcomes included medication adherence, safety, cocaine and other substance use, health, social functioning, and patient satisfaction.
Results: Adherence to topiramate treatment was low. In the intent-to-treat analyses, topiramate neither improved treatment retention nor reduced cocaine and other substance use. Post hoc, exploratory analyses suggested a moderation effect of comorbid opioid dependence, with a significant effect of topiramate on cocaine use reduction only in crack-cocaine dependent patients with comorbid opioid dependence.
Conclusions: Topiramate was safe and well-tolerated in this sample of crack-cocaine dependent patients, but efficacy was not supported probably due to low acceptance of the treatment. Given the equivocal results of previous studies and the negative findings in our study, the potential of topiramate in the treatment of cocaine dependence seems limited.

Introduction

Crack-cocaine use is associated with a wide range of medical, psychiatric and social problems for the individual and with significant public nuisance (Degenhardt and Hall, 2012; United Nations Office on Drugs and Crime, 2012). In the Netherlands, cocaine-related annual treatment demand increased from 9,300 patients in 1995 to 19,000 in 2008, with a subsequent decline to 17,000 patients in 2010 (Trimbos-instituut, 2012). More than half of these patients are using crack-cocaine (Wisselink et al., 2013).

Given the absence of proven effective medications for the treatment of cocaine dependence, virtually all cocaine dependent patients receive a standard offer of psychosocial treatment (Lingford-Hughes et al., 2012), but – with the exception of contingency management (Lussier et al., 2006; Prendergast et al., 2006) – psychosocial interventions have shown modest results, mainly due to poor compliance (Dutra et al., 2008; Knapp et al., 2007; Shearer, 2007).

The past decade has shown an upsurge in research investigating pharmacological agents for the treatment of cocaine dependence (Kampman et al., 2005; Karila et al., 2008; Preti, 2007; Van den Brink, 2012), including antipsychotics (Amato et al., 2007), anticonvulsants (Alvarez et al., 2010; Minozzi et al., 2008), antidepressants (Pani et al., 2011), psychostimulants (Castells et al., 2010; Shearer, 2008), (other) dopamine agonists (Amato et al., 2011; Herin et al., 2010), and – on an experimental basis – anti-cocaine vaccines (Kosten et al., 2013).

In these studies, two basic strategies can be distinguished: one focused at substantial reduction or abstinence from cocaine use, and the other directed at minimizing cocaine-related harm by replacing the short-acting, illicit stimulant cocaine by a long-acting, legal stimulant that can be taken orally (Grabowski et al., 2004b; Shearer, 2008).

The anticonvulsant topiramate and the alpha-adrenergic/glutamate agonist modafinil are examples of promising medications for the first strategy (Johnson, 2005; Karila et al., 2008; Shearer, 2008; Shinn and Greenfield, 2010; Van den Brink, 2012), whereas the monoamine reuptake inhibitor dexamfetamine, particularly in sustained-release form, is an important candidate for the second strategy (Grabowski et al., 2004b; Shinn and Greenfield, 2010; Van den Brink,

2012). Against this background, topiramate, modafinil and sustained-release dexamfetamine were investigated in three separate feasibility trials in the Netherlands in project CATCH: Cocaine Addiction Treatments to improve Control and reduce Harm (Nuijten et al., 2011). The present paper reports on the results of the first trial, pertaining to topiramate.

Topiramate is approved in Europe for the treatment of migraine and epilepsy. Among its different mechanisms of action, topiramate lowers dopamine levels by enhancing gamma-aminobutyric acid (GABA) and antagonizing the glutamatergic system (Johnson, 2005; Shinn and Greenfield, 2010). Previous studies with topiramate in the addiction field have suggested that it may be effective in the treatment of alcohol dependence (Arbaizar et al., 2010) and methamphetamine dependence (Elkashef et al., 2012; Vocci, 2012). Concerning cocaine dependence, two trials with topiramate were conducted prior to the start of the current study, with mixed results. In a double-blind randomised trial in 40 (predominantly crack-) cocaine dependent patients, topiramate (200 mg/day), as an adjunct to cognitive behavioural therapy, was significantly more effective in promoting (sustained) abstinence than placebo (Kampman et al., 2004). However, in an uncontrolled study among 28 intranasal cocaine users who received topiramate (maximum 300 mg/day) and assertive strategic counselling, cocaine craving was significantly reduced, but only 25% of the urine samples were negative for cocaine metabolites (Reis et al., 2008).

In the present trial we evaluate the acceptance and efficacy of topiramate as an add-on to cognitive behavioural therapy (CBT) compared to CBT alone in crack-cocaine dependent patients with treatment retention as the primary outcome measure and with medication adherence, safety, cocaine and other substance use, cocaine craving, health, social functioning, and patient satisfaction as secondary outcome measures.

Methods

Design

The study was an open-label, randomised controlled feasibility trial. After screening and baseline assessment, participants were randomly assigned to the experimental group (outpatient CBT plus topiramate) or the control group (outpatient CBT only).

Given the high dropout rates in control groups in previous placebo-controlled trials in cocaine dependent participants (Kampman et al., 2005), and the feasibility character of this study, a pre-randomisation, double-consent design (Zelen, 1979) was used. Prior to randomisation, all participants were asked to provide informed consent about participating in a study evaluating the effectiveness of CBT. Following randomisation, a second informed consent, pertaining to the treatment with topiramate, was obtained only in those participants randomised to the experimental group. Hence, participants were only informed about the assigned treatment and not about the condition they were compared with (Nuijten et al., 2011). Randomisation was computer-generated and stratified by gender, cultural background (European/ non-European) and participation in methadone maintenance treatment (MMT).

The study has been registered in The Netherlands National Trial Register (NTR2576) and The European Union Drug Regulating Authorities Clinical Trials (EUdraCT 2009-010584-16).

Participants and treatment setting

Crack-cocaine dependent patients of Brijder Addiction Treatment in The Hague, the Netherlands, were asked to participate in the study. They were either new referrals to the addiction treatment service or existing patients in (methadone) treatment with continuing cocaine abuse. Enrolment occurred from August, 2010 to December, 2012. Eligible patients had to (a) be at least 18 years old, (b) be cocaine dependent according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), (c) regularly use cocaine (≥8 days in the previous month), (d) administer cocaine primarily by means of basing, (e) be able and willing to participate in the study treatment and associated assessments, and (f) provide written informed consent. Patients were excluded in case of (a) severe medical (e.g. renal insufficiency, cardiovascular problems) or psychiatric problems (e.g. acute psychosis, suicidality), (b) pregnancy or breastfeeding, (c) pharmacotherapy with a potentially effective medication for cocaine dependence (i.e. naltrexone, disulfiram, acamprosate, methylphenidate, modafinil, dexamfetamine or baclofen), (d) indication for residential treatment, (e) insufficient command of the Dutch language, and (f) current participation in another addiction treatment trial.

Treatments

Psychosocial treatment

All patients received outpatient CBT (Kadden, 2001; Monti et al., 1997; Project MATCH Research Group, 1993; Rohsenow et al., 2000), which is the standard psychosocial substance abuse treatment in the Netherlands (De Wildt et al., 2002). CBT was delivered in 12 weekly individual sessions of 45 min each by trained, experienced psychologists. Treatment goals included abstinence as well as reduction or stabilisation of cocaine use based on a process of shared decision making.

Pharmacological treatment

In the experimental group topiramate was prescribed for a period of 12 weeks as an add-on to CBT. Topiramate was initiated at 25 mg/day and was titrated within three weeks to a maximum oral dose of 200 mg/day, depending on the occurrence of adverse events. During the first treatment week, topiramate was prescribed daily at the treatment centre to monitor intake and adverse events. In the remaining trial period, topiramate was dispensed once weekly and self-reported topiramate intake was registered at each study visit.

Discontinuation of topiramate treatment had no consequences for the psychosocial treatment offer. Hence, CBT could be continued irrespective of topiramate adherence.

Assessments

Assessments were performed at baseline, week four and eight (experimental group only), and week 12. At baseline, DSM-IV cocaine, alcohol and opioid dependence diagnoses (American Psychiatric Association, 1994) were obtained using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) (Cottler, 1990; Cottler, 2000). The Addiction Severity Index (ASI) (Hendriks et al., 1989; Kokkevi and Hartgers, 1995; McLellan et al., 1992) was used to assess substance use and other clinical characteristics.

At all assessment points, the Time Line Follow-Back (TLFB) calendar method (Hjorthoj et al., 2012; Sobell and Sobell, 1992) was administered to collect information about the patients' self-reported crack-cocaine use in the 30 days preceding each assessment. Cocaine craving was measured with the short,

adapted version of the Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1996; De Wildt et al., 2005; Franken et al., 2002). The Maudsley Addiction Profile-Health Symptoms Scale (MAP-HSS) (Marsden et al., 1998) was used to assess physical health, and the Symptom Checklist-90 (SCL-90) (Arrindell and Ettema, 1986; Derogatis et al., 1973) to identify psychological problems. All post-baseline assessments included the ASI substance use items and questions about current illegal activities and social contacts with non-drug users. The week 12 assessment was supplemented with the Client Satisfaction Questionnaire (CSQ-8) (De Wilde and Hendriks, 2005; Larsen et al., 1979).

Co-medications and adverse events (AEs) were registered by trained research nurses at each study visit, and blood pressure and heart rate were measured at baseline and week 12. Urine samples were collected at baseline, and once weekly in the four weeks preceding the week 12 assessment, and were analysed on the presence of cocaine metabolites (benzoylecgonine [BE]). The 210 urine samples that were submitted in the final four weeks of the study (out of a planned total of 74 x 4=296 urine-samples; 70.9%), showed 91.5% agreement between self-reported cocaine use and BE-outcome (kappa=0.81). Pregnancy tests were conducted at baseline and every four weeks (experimental group only).

Participants received a remuneration of €120 (control subjects) or €150 (experimental subjects) for participating in the study assessments.

Outcome measures

The primary outcome measure was treatment retention defined as the number of CBT sessions attended (range 0-12). Secondary outcome measures were medication adherence, safety, cocaine use, cocaine craving, use of other substances, physical and mental health, social functioning, and patient satisfaction.

Power calculation

Given the feasibility character of the study, the sample size was limited and a lenient two-sided alpha of 0.10 was chosen to prevent type-II errors. With a minimum difference in 12-week retention between the treatment groups of 25%, a power of 0.80, and a two-sided alpha of 0.10, 36 patients were required in each treatment group (n_{total}=72).

Data analyses

An intent-to-treat (ITT) approach was used to examine between-group differences, incorporating all randomised patients who provided informed consent pertaining to their assigned treatment.

Baseline characteristics between groups were compared using Chi-square tests for dichotomous variables, and t-tests or Mann-Whitney U-tests for normal and non-normal distributed continuous variables, respectively.

The primary study question compared treatment retention in a Cox proportional hazards regression model, analysing group differences in retaining patients in treatment during the 12-week study period based on the log-rank (Kaplan-Meier) statistic, censoring the hazard at the tenth CBT session. Baseline to week 12 changes in cocaine use days was compared between the two groups using 2 (time) x 2 (group) repeated measures ANOVA. Similar analyses were conducted for craving, concurrent substance use, and other continuous and Likert-scale outcome measures.

Week 12 data was available for 89% of the ITT-population. Missing data of four participants in each group were estimated with multiple imputation, using five imputed datasets, with baseline variables as predictors.

The sum of BE positive weekly urine samples during the four weeks preceding the week 12 assessment was evaluated by means of Poisson regression analysis, considering missing urine samples as positive.

Topiramate treatment duration was assessed by the registered total days of self-reported intake. Mean topiramate dose was computed by summing the dose of all topiramate tablets that were ingested as registered in the medication file, divided by the total number of days that topiramate was taken.

Results

Participants flow

Of the 161 patients that were assessed for eligibility, 82 patients met all selection criteria and were randomised after giving the first informed consent (Figure 1). Thirty-six of the 44 participants (81.8%) in the experimental group accepted the additional treatment offer of topiramate and gave the second informed consent. The final ITT-population consisted of 36 patients in the experimental and 38 patients in the control group.

Figure 1. Flowchart of participants in the topiramate study.

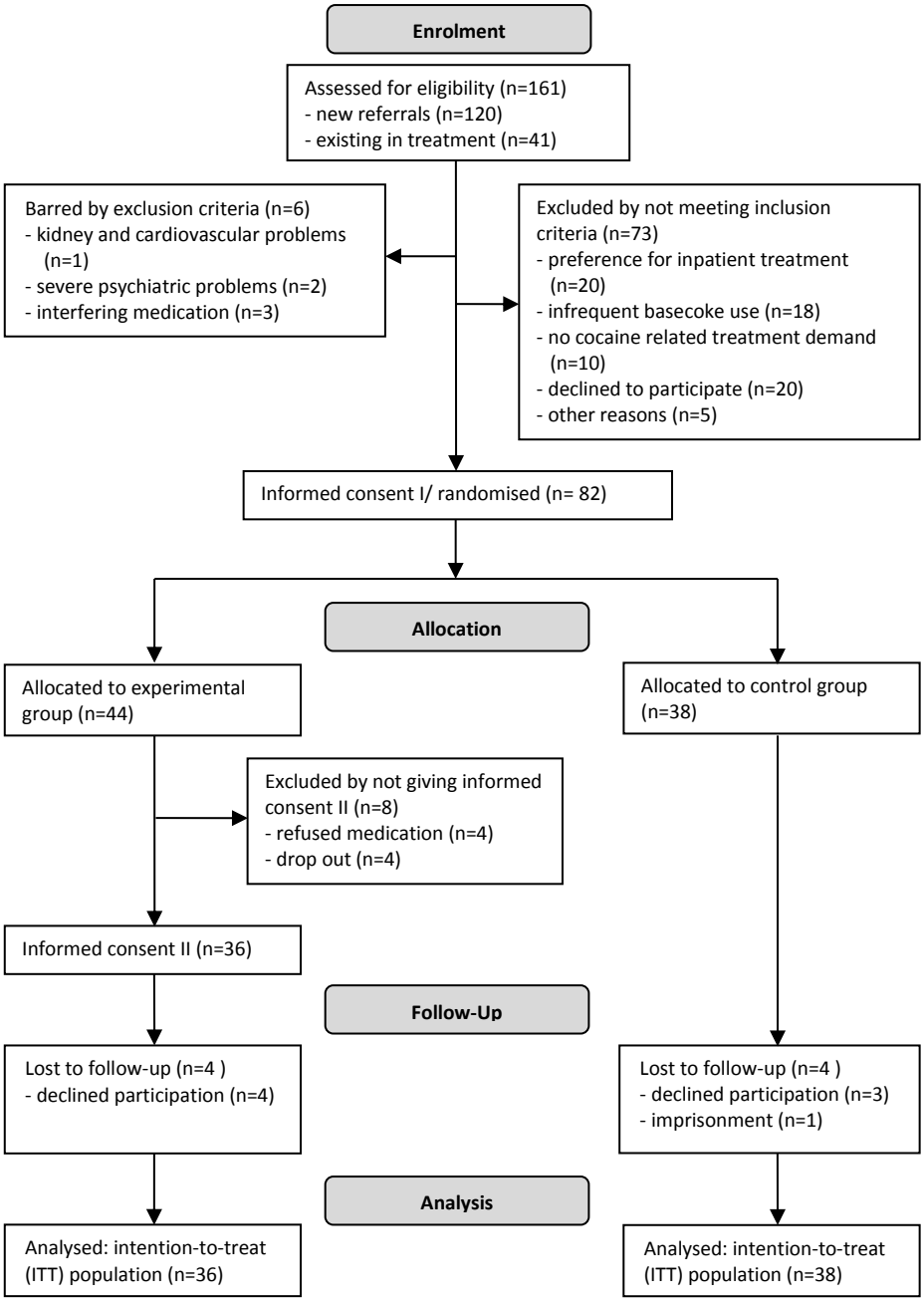

Table 1. Baseline characteristics of the study sample.

Variable	Experimental group (N=36) M (sd)/ %	Control group (N=38) M (sd)/ %	p-value[c]
Recruitment			
New referrals (%)	72.2	73.7	0.89
Existing in treatment (%)	27.8	26.3	
Demographic background			
Age (years)	43.3 (8.7)	41.3 (9.8)	0.36
Gender male (%)	81.6	81.6	0.60
European background (%)	66.7	60.5	0.58
Education (years)	11.3 (2.7)	11.1 (2.8)	0.66
Employed (%)[a,b]	33.3	39.5	0.58
Homeless (%)	5.6	7.9	0.69
Substance use			
Lifetime regular cocaine use (years)	11.9 (7.8)	13.8 (9.7)	0.54
BE-positive baseline urine (%)	77.8	84.2	0.48
Cocaine use (days)[a]	20.0 (7.6)	19.2 (7.0)	0.64
Alcohol use ≥5 units (%)[a,b]	38.9	28.9	0.37
Heroin use (%)[a,b]	27.8	31.6	0.72
Cannabis use (%)[a,b]	50.0	57.9	0.50
Treatment status& history			
Opioid dependence (%)	38.9	36.8	0.86
Alcohol dependence (%)	16.7	10.5	0.44
Prescribed medication for physical problems (%)	36.1	21.1	0.15
Prescribed medication for mental problems (%)	16.7	28.9	0.21
Methadone maintenance treatment (%)	36.1	36.8	0.95
Methadone dose (mg)	64.2 (36.4)	66.3 (32.3)	0.84
Multiple prior drug-related treatments (%)	58.3	57.9	0.97
Health & social functioning			
MAP total score (0-40)	14.1 (6.7)	12.0 (6.9)	0.19
SCL-90 total score (0-360)	91.4 (54.5)	86.1 (51.6)	0.96
OCDS total score (0-20)	8.7 (3.9)	9.1 (3.6)	0.60
Illegal activities to obtain money/ drugs (days)[a]	2.2 (5.1)	2.2 (6.1)	0.86
Social contacts with non-drug users (days)[a]	22.5 (11.8)	23.5 (11.5)	0.75

[a] In the preceding 30 days; [b] At least one day; [c] Using Chi-square tests for dichotomous variables; t-tests for continuous variables; nonparametric Mann-Whitney U tests for continuous variables with skewed distributions.

Baseline characteristics

Baseline characteristics of the participants are summarised in Table 1. Participants could be characterised as chronic cocaine dependent patients, with a history of multiple treatments and concurrent drug use. About one-third of the patients in both treatment conditions were also in methadone maintenance treatment. Baseline characteristics did not differ significantly between the treatment groups.

Medication adherence

Topiramate titration (3 weeks) was completed by 28 participants (77.6%). Of these, 27 participants were prescribed the maximum dose of 200 mg/day and one patient received 150 mg/day due to adverse events. Twenty-two patients (61.1%) received topiramate treatment for at least 6 weeks, nine patients (25.0%) for at least 9 weeks and five patients (13.9%) completed at least 11 weeks. The mean dose of topiramate in the 28 'titration completers' was 189 mg/day (sd=32.1).

Of the 31 patients who discontinued topiramate treatment before week 11, 10 received CBT for at least one more session after topiramate discontinuation (32.3%). Since the majority of patients who discontinued topiramate did not inform the clinical staff, reasons for medication non-adherence remained unclear for most patients.

Treatment retention

Participants in the experimental group attended a mean of 6.8 CBT sessions (sd=3.6) and those in the control group 5.2 (sd=4.1). Ten or more sessions were completed by 36.1% in the experimental group and 26.3% in the control group.

Cox regression survival analysis (Figure 2) indicated somewhat better treatment retention in the experimental group compared to the control group, but the difference was not significant (HR=0.67; 95% CI=0.4–1.2; p=0.15).

Crack-cocaine use

Baseline to week 12 reductions in self-reported crack-cocaine use days were significant in both groups combined (F=76.0; df=1; p<0.001; Cohen's d=1.11), but these reductions did not significantly differ between treatment groups (F=1.6; df=1; p=0.23) (Table 2).

In the experimental group 25.7% and in the control group 32.2% of the urine samples in the last four weeks were not submitted and hence considered BE-positive. The mean number of positive urine samples was rather high with 3.2 (sd=1.4) and 3.1 (sd=1.2) positive samples in the experimental and control group, respectively. Poisson regression analysis did not show significant group differences (Exp(B)=0.96; 95% CI=0.74–1.25; p=0.78).

Figure 2. Cox regression survival analysis.

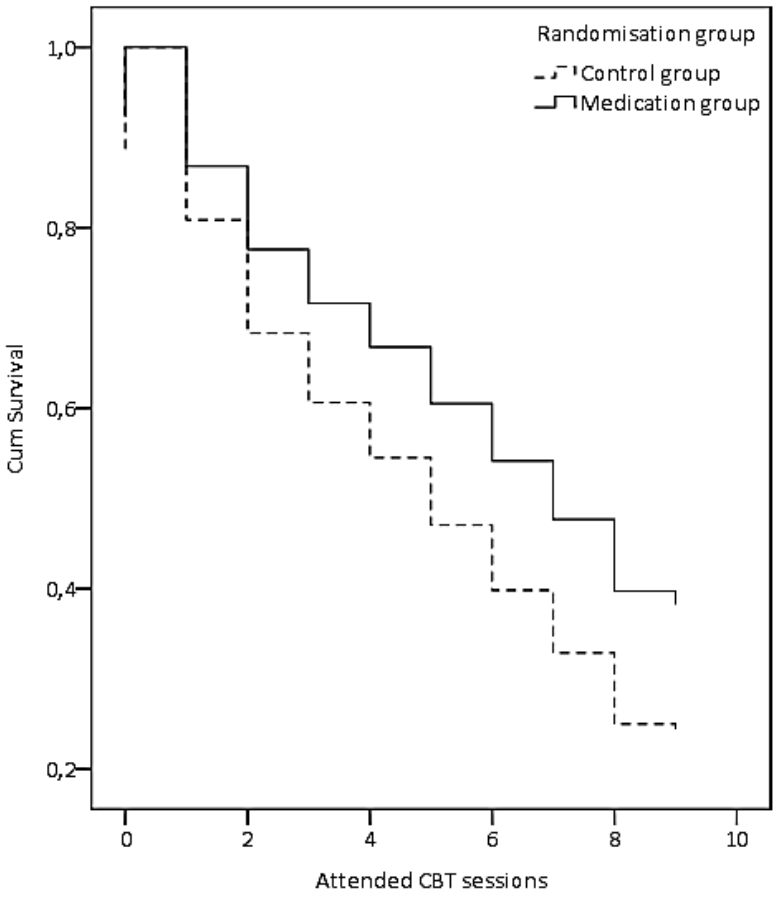

Table 2. Group differences in substance use, health and social functioning.

	Experimental group		Control group		Repeated measures ANOVA	
	Baseline	Week 12	Baseline	Week 12	Time	Treatment x time
Variable	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Baseline vs. week 12	Baseline vs. week 12
Cocaine and other substance use						
Days of cocaine use[a]	20.0 (7.6)	9.2 (9.1)	19.2 (7.0)	11.1 (10.0)	F=76.0; p=0.00 (d=1.11)	F=1.6; p=0.23 (d=0.29)
Cocaine positive urines		3.2 (1.4)		3.1 (1.2)		
Cocaine craving total score (0-20)	8.7 (3.9)	5.2 (3.8)	9.1 (3.6)	6.3 (4.4)	F=33.0; p=0.00 (d=0.81)	F=0.3; p=0.60 (d=0.13)
Days of alcohol use ≥ 5 units[a]	6.4 (11.0)	6.1 (10.5)	4.3 (8.3)	4.9 (7.9)	F=0.1; p=0.81 (d=0.03)	F=0.2; p=0.64 (d=0.11)
Days of heroin use[a]	5.9 (10.6)	3.0 (6.0)	4.1 (9.0)	4.0 (8.6)	F=2.4; p=0.14 (d=0.16)	F=2.2; p=0.15 (d=0.34)
Days of cannabis use[a]	8.3 (12.3)	9.4 (12.3)	11.7 (13.3)	11.2 (13.2)	F=0.1; p=0.79 (d=0.02)	F=0.8; p=0.40 (d=0.20)
Health and social functioning						
Physical health: MAP total score (0-40)	14.1 (6.7)	9.3 (7.8)	12.0 (6.9)	8.5 (6.7)	F=26.5; p=0.00 (d=0.59)	F=0.7; p=0.44 (d=0.29)
Mental health: SCL-90 total score (0-360)	91.4 (54.5)	51.7 (45.8)	86.1 (51.6)	60.0 (51.9)	F=34.8; p=0.00 (d=0.65)	F=1.5; p=0.23 (d=0.19)
Illegal activities to obtain money/ drugs[a]	2.2 (5.1)	1.4 (5.4)	2.2 (6.1)	2.8 (7.1)	F=0.2; p=0.75 (d=0.04)	F=0.9; p=0.37 (d=0.22)
Social contacts with non-drug users[a]	22.5 (11.8)	21.8 (12.4)	23.5 (11.5)	21.9 (11.8)	F=0.7; p=0.42 (d=0.10)	F=0.2; p=0.77 (d=0.07)

[a] In the preceding 30 days.

Other secondary outcome measures

For the other outcome variables (Table 2) there were significant baseline to week 12 time effects for craving (d=0.81), physical health (d=0.59) and mental health (d=0.65). However, repeated measures ANOVA did not show significant baseline to week 12 between-group differences for any of the outcome variables (Table 2).

Satisfaction with the treatment offer (CSQ-8) at the end of the study did not differ between groups ($M_{exp=}$26.0 [sd=3.5] vs. $M_{contr=}$26.6 [sd=3.2]; t=0.71; df=64; p=0.48).

Safety

No serious adverse events occurred. One or more adverse events were reported during the study by 72.2% in the experimental group and by 13.2% in the control group. The number of adverse events per patient in the experimental group varied between one (n=4) and 15 (n=1), with 38.5% (n=10) of the patients reporting two adverse events. Of the 95 reported adverse events in the experimental group, 27 (28.4%) were probably or definitely related to the study medication. The majority of the adverse events was transient and evaluated as mild (72.6%), with paraesthesia (29.5%), gastro-intestinal complaints (16.8%) and fatigue (12.6%) being most frequently reported.

Post hoc, exploratory analyses

Given the overall lack of treatment effect, we conducted two types of exploratory analyses to test whether differences in baseline characteristics may have confounded the effect of the topiramate treatment, in terms of treatment retention and reduction in crack-cocaine use. The following baseline characteristics that have been shown to affect treatment outcome in earlier studies, were selected: presence of baseline cocaine-positive urine (Ahmadi et al., 2009; Kampman et al., 2001; Poling et al., 2007; Sofuoglu et al., 2003), days of cocaine use in the month before baseline (Ahmadi et al., 2009; Means et al., 1989; Poling et al., 2007; Westhuis et al., 2001), cocaine craving (Sinha et al., 2006; Weiss et al., 1997), and concurrent alcohol use (Alterman et al., 2000; Poling et al., 2007). In addition, comorbid opioid dependence was included as a potential confounder. Continuous covariates were dichotomised based on the median due to non-linearity with the outcome variable. First, each baseline characteristic was

entered to the original model as a covariate. Baseline covariates that resulted in a change of at least 10% in the *B*-value of treatment condition, were entered into the final regression model. Second, we analysed whether the selected baseline characteristics differentially moderated treatment outcome, by adding their interaction with treatment group into the regression model.

Concerning treatment retention as outcome variable, adding number of cocaine use days in the month preceding baseline as a covariate to the original regression model resulted in a reduction in *B* from –0.41 to –0.49 (Table 3a). Similarly, opioid dependence resulted in more than 10% change in the *B*-value. Although alcohol use as a single variable resulted in ≥10% change in *B*, its contribution disappeared when this variable was added to the model together with the other covariates. In our final model – with baseline cocaine use and opioid dependence as covariates – CBT plus topiramate resulted in significantly better treatment retention than CBT only (B=–0.64; HR=0.53; 95% CI: 0.3–1.0; p=0.03).

Concerning baseline to week 12 changes in crack-cocaine use as an outcome variable, number of baseline cocaine use days was identified as a confounder (reduction in *B* from 2.67 to 2.13), but did not improve the model significantly (Table 3b).

Table 3a. Outcomes of explorative analyses: Treatment retention.

	Treatment retention: Original model: B=–0.41; HR=0.67; 95% CI: 0.4–1.2						
	Original model + covariate			Interaction group x covariate			
	B	HR	95% CI	B	HR	95% CI	p
Crack-cocaine use	–0.49	0.61	0.4–1.1	–0.16	0.85	0.3–2.6	0.78
Cocaine-positive urinalysis	–0.42	0.66	0.4–1.2	–0.02	0.98	0.3–3.8	0.97
Cocaine craving	–0.41	0.67	0.4–1.2	0.12	1.13	0.4–3.4	0.83
Alcohol use ≥5 units	–0.35	0.70	0.4–1.2	0.21	1.24	0.4–4.1	0.73
Opioid dependence	–0.49	0.61	0.4–1.1	–0.54	0.58	0.2–1.8	0.34

Table 3b. Outcomes of explorative analyses: Changes in crack-cocaine use.

	Baseline to week 12 crack-cocaine use days: Original model: B=2.67; T=1.21; 95% CI: –1.7–7.0				
	Original model + covariate		Interaction group x covariate		
	B	95% CI	B	95% CI	p
Crack-cocaine use	2.13	–2.0–6.2	1.72	–6.4–9.9	0.68
Cocaine-positive urinalysis	2.72	–1.7–7.1	1.08	–10.2–12.4	0.85
Cocaine craving	2.69	–1.7–7.1	–2.50	–11.2–6.2	0.57
Alcohol use ≥5 units	2.72	–1.7–7.1	1.43	–8.0–10.9	0.77
Opioid dependence	2.74	–1.6–7.0	9.14	0.4–17.9	0.04

No moderators of the effect of topiramate on treatment retention were found, but there was a significant interaction effect of treatment group x opioid dependence on the reduction of cocaine use (B=9.14; 95% CI: 0.4–17.9; p=0.04) (Table 3b). In the opioid dependent subgroup, topiramate plus CBT resulted in greater reductions of mean cocaine use days than CBT only (M=11.6 vs. M=3.1, resp.), whereas the reduction in cocaine use was very similar for the experimental and control condition in the subgroup without opioid dependence (M=10.3 vs. M=11.0).

Crack-cocaine use in treatment continuers

An additional, explorative repeated measures ANOVA of baseline to week 12 changes in crack-cocaine use was conducted among patients who attended at least six CBT sessions (both groups) and took topiramate for at least six weeks (experimental group only). Experimental 'treatment continuers' (n=19) reduced their mean crack-cocaine use from 18.4 days (sd=7.6) to 7.0 days (sd=7.1) and control 'treatment continuers' (n=16) from 17.0 days (sd=7.2) to 4.7 days (sd=5.6). There was a significant time effect (F=81.8; df=1; p<0.00), but the time x group interaction effect was not significant (F=0.1; df=1; p=0.74), indicating the absence of an add-on effect of topiramate treatment.

Discussion

In the present open-label, randomised controlled feasibility trial, acceptance, safety and efficacy of max. 200 mg/day topiramate as an add-on to cognitive behavioural therapy (CBT) in crack-cocaine dependent patients were tested. The study found that topiramate's acceptance was generally low. Although 82% of the patients in the experimental group agreed to start topiramate treatment (second informed consent), only 14% took topiramate for at least 11 of the 12 weeks. Similar patient satisfaction with the treatment received (i.e. CBT only versus CBT plus topiramate) in both groups suggested no perceived added value for topiramate. Topiramate was generally well-tolerated, with mostly mild and transient adverse events and no serious adverse events.

There were also no indications of efficacy of topiramate in CBT retention (low retention rates in both treatment conditions), crack-cocaine use and craving, concurrent substance use, health and social functioning. How do these findings relate to those of previous studies?

In the study of Kampman and colleagues (2004), topiramate-treated patients were more likely to be abstinent from cocaine than placebo-treated patients, but this effect occurred only during the last four weeks ('full-dose period') of the trial period. In a more recent study, Kampman et al. (2013) found no significant difference between topiramate and placebo in weekly cocaine abstinence during the total trial period. However, post hoc, exploratory analyses indicated that more topiramate-treated than placebo-treated patients had three consecutive weeks of cocaine abstinence at the end of the trial. Similarly, Johnson et al. (2013) found topiramate to be more efficacious than placebo at increasing the weekly proportion of cocaine abstinent days during the full-dose period (week 6-12) and topiramate increased the likelihood of cocaine abstinent weeks during both the full-dose and the total trial period. These results, however, were obtained in a model with age of onset of cocaine use, gender, ethnicity, and baseline cocaine use as covariates, and topiramate's unadjusted effects were not reported. Lastly, Mariani and colleagues (2012) found that combined treatment with extended-release mixed amphetamine salts (MAS-ER) plus topiramate was no better than placebo in achieving three consecutive weeks of cocaine abstinence during the trial period. Post hoc, exploratory analyses suggested that MAS-ER plus

topiramate was more effective in a subgroup of patients with high baseline cocaine use frequency.

In sum, the evidence for topiramate in the treatment of cocaine dependence is mixed, with two studies (Johnson et al., 2013; Kampman et al., 2004) showing a favourable effect of topiramate during the full-dose period according to the a priori planned analysis, and two studies (Kampman et al., 2013; Mariani et al., 2012) in which topiramate (with or without MAS-ER) was only better than placebo in post hoc, exploratory analyses or in subgroups. Our study most clearly represents a 'negative trial', with no effect of topiramate in any of the a priori planned analyses and with an indication of effect only in the subgroup with comorbid opioid dependence. Possible explanations for the negative findings in the current study are: (1) lower adherence to the study medication; (2) differences in patient characteristics; (3) differences in study design and treatment offer, and/ or (4) differences in treatment context.

First, low medication adherence is very likely to have contributed to the negative outcomes in the current study: topiramate adherence was much lower (only 14% treatment completers) than in previous RCTs (Johnson et al., 2013; Kampman et al., 2004; Kampman et al., 2013; Mariani et al., 2012). It should be emphasised that, in contrast to the present study, medication adherence in all these studies was encouraged by remuneration of study visits or returning medication packages, and by compensating for transportation costs per visit, i.e. incentive-based interventions that are effective in reducing non-adherence (DeFulio and Silverman, 2012; Weiss, 2004). Hence, the lack of reinforcement to comply with study procedures in our trial might be a possible explanation for the generally low medication adherence. Moreover, previous studies suggest that topiramate dose and duration of exposure play an important role (Johnson et al., 2003; Kampman et al., 2004). The limited and irregular intake of topiramate in the present study might have obscured the therapeutic potential of topiramate in our patients with crack-cocaine dependence.

Second, cocaine dependent patients in previous RCTs generally showed lower baseline levels of cocaine use, ranging from 6-8 days/month (Kampman et al., 2004) to 12-13 days/month (Johnson et al., 2013; Kampman et al., 2013; Mariani et al., 2012) and no serious polydrug use. In the current study, patients used crack-cocaine on 19-20 days/month at baseline. The lack of efficacy in our study

is, however, not likely to be caused by high cocaine addiction severity, because Mariani et al. (2012) and Kampman et al. (2013) found positive subgroup effects in frequent compared to less frequent cocaine users and in patients with more compared to patients with less severe cocaine withdrawal, respectively. Importantly, about one-third of the cocaine dependent patients in our study were also opioid dependent. Adjustments for both baseline cocaine use days and opioid dependence resulted in significant group differences in treatment retention, and efficacy of topiramate in crack-cocaine use reductions was observed in patients with comorbid opioid dependence. Thus, previous studies and our trial suggest that topiramate is more likely to be effective in patients with high cocaine addiction severity and/or comorbid opioid dependence.

Third, the present study also differs in study design compared to the previous trials. Although our 12-week study period was comparable, our trial differed in length of titration period: three weeks compared to six (Johnson et al., 2013; Mariani et al., 2012) or eight (Kampman et al., 2004; Kampman et al., 2013). Moreover, the 200 mg/day dose was lower than the 300 mg/day dose in the studies of Kampman et al. (2013), Mariani et al. (2012) and Johnson et al. (2013). Despite the fact that our patients could take advantage of the full topiramate dose for a longer period, the daily dosage of 200 mg may have been too low and could therefore have contributed to topiramate's observed inefficacy.

Finally, this is the first study of topiramate in cocaine dependent patients outside the USA, where the health care and social security systems are different. In the Netherlands, drug services are freely accessible for every citizen and social security is guaranteed for everyone. As a consequence, patients may feel less pressured to participate in a trial to receive (free) treatment. These contextual differences might have affected levels of motivation and, thus, adherence and treatment outcomes.

Several study limitations should be considered. First, the open-label character of the trial may have caused bias due to patients (and investigators) being aware of their treatment allocation, which may have influenced their post-randomisation treatment decisions and reported outcome. Given that no differences in treatment were found, we believe this bias did not occur, however. Second, urine samples were collected once-weekly and only during the last four weeks of study treatment. However, agreement between self-reported cocaine

use and urinalysis outcome was high (kappa=0.81), and both measures were consistent in showing no difference in treatment outcome between the two study groups.

In sum, topiramate with doses up to 200 mg/day was safe and well-tolerated in the treatment of crack-cocaine dependent patients, but its acceptance was low. Likely due to this low acceptance, there were no significant effects of topiramate on treatment retention, nor on cocaine and other substance use. Post hoc, exploratory analyses suggested that topiramate may be effective in reducing cocaine use in cocaine dependent patients with comorbid opioid dependence. To conclude, given the equivocal results of previous studies and the largely negative findings in our study, the potential of topiramate in the treatment of cocaine dependence seems limited.

Chapter 3

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

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Abstract

Background: Crack-cocaine dependence is a serious disorder with no approved pharmacological treatment. Modafinil is a promising medication with increased cocaine abstinence and reduced craving in some previous studies. In the present study, we examined the acceptance, safety and potential benefits of modafinil as an add-on treatment to cognitive behavioural therapy (CBT) in crack-cocaine dependent patients.

Methods: Sixty-five crack-cocaine dependent outpatients participated in an open-label, randomised feasibility trial. Patients were randomised to receive either 12-week individual CBT plus 400 mg/day modafinil or 12-week individual CBT only. The primary outcome measure was CBT treatment retention. Secondary outcomes included modafinil adherence, tolerability and safety, use of cocaine and other substances, cocaine craving, health, social functioning and patient satisfaction.

Results: Modafinil adherence was low, with only 10% treatment completers. Intent-to-treat analyses showed that modafinil did not improve CBT treatment retention or any of the secondary cocaine-related outcomes. Both groups showed similar, large reductions in cocaine use during the study treatment. Post hoc exploratory analyses within the CBT plus modafinil group showed significantly larger baseline to week 12 reductions in cocaine use days in high (≥8 weeks) modafinil adherent patients.

Conclusions: Acceptance and benefits of modafinil were not demonstrated in the present study. Since reduction in cocaine use was observed in high modafinil adherent patients, further research in the treatment of cocaine dependence, in which modafinil adherence is optimised, is warranted.

Introduction

Cocaine use disorder, particularly use of cocaine in its base form ('crack'), puts a heavy burden on both the user and society worldwide, including medical, socio-economic and judicial consequences (Degenhardt and Hall, 2012; United Nations Office on Drugs and Crime, 2012). In the Netherlands (16.8 million inhabitants), annual demand for cocaine-related addiction treatment increased from 8,500 cases in 1994 to almost 16,000 in 2008, and subsequently declined somewhat to almost 13,000 in 2012 (Trimbos-instituut, 2013). Smoking or 'basing' cocaine is the predominant route of administration (52%) and most cocaine dependent patients have a history of multiple treatment episodes (Wisselink et al., 2014).

With the exception of contingency management (Lussier et al., 2006; Prendergast et al., 2006), psychosocial interventions for cocaine dependence – including cognitive behavioural therapy (CBT) and relapse prevention – have shown modest results, and both study data and treatment practice indicate that poor compliance is a major factor complicating these treatments (Dutra et al., 2008; Knapp et al., 2007; Shearer, 2007). Nevertheless, since there is no approved medication for cocaine dependence and contingency management is not very well socially accepted, the current treatment offer for virtually all cocaine dependent patients still consists of CBT and relapse prevention (Lingford-Hughes et al., 2012).

However, increasing knowledge about the neurobiology of cocaine dependence has led to a growing number of studies searching for effective pharmacological agents with an effect on the neurochemistry of cocaine (Kampman et al., 2005; Karila et al., 2008; Preti, 2007). These agents include antipsychotics (Alvarez et al., 2013; Amato et al., 2007; Kishi et al., 2013), anticonvulsants (Alvarez et al., 2010; Minozzi et al., 2008), antidepressants (Pani et al., 2011), psychostimulants (Castells et al., 2010; Mariani and Levin, 2012; Shearer, 2008), other dopamine agonists (Amato et al., 2011; Herin et al., 2010; Perez-Mana et al., 2011), and anti-cocaine vaccines (Kosten et al., 2013). One of the most promising compounds directed at reduction of or abstinence from cocaine use is the alpha-adrenergic/glutamate agonist modafinil (Karila et al., 2008; Shearer, 2008; Van den Brink, 2012). Modafinil is a wakefulness-promoting agent that is registered for the treatment of narcolepsy. It possesses stimulant-like effects as a consequence of inhibiting dopamine reuptake (Volkow et al.,

2009) and it has been suggested that these neurobiological effects can normalise brain chemistry and reduce substance use (Herin et al., 2010).

Prior to the start of this study, promising effects of modafinil were found in terms of reduction of cocaine use and craving in two studies. In a randomised placebo-controlled trial of 62 cocaine dependent patients, 400 mg/day modafinil significantly increased weekly cocaine abstinence (primary outcome) and protracted abstinence (secondary outcome)(Dackis et al., 2005). In another placebo-controlled trial of 210 cocaine dependent treatment seeking patients, no differences in the percentage of cocaine abstinent days (primary outcome) were found between 200 and 400 mg/day modafinil and placebo, but 200 mg/day modafinil showed effect in two secondary outcomes: increased maximum number of consecutive cocaine abstinent days and reduced craving. Post hoc analyses showed increased weekly abstinence in patients without comorbid alcohol use (Anderson et al., 2009).

Given these promising findings, the present open-label randomised controlled feasibility trial evaluated the acceptance, safety and potential benefits of 400 mg/day modafinil as an add-on to CBT compared with CBT only, in crack-cocaine dependent patients, with retention in CBT treatment as the primary outcome measure and with medication adherence, tolerability and safety, use of cocaine and other substances, cocaine craving, health, social functioning and patient satisfaction as secondary outcome measures.

Materials and methods

Design

The study is the second trial of project CATCH (Cocaine Addiction Treatments to improve Control and reduce Harm) in which three pharmacological agents – topiramate, modafinil and slow-release dexamfetamine – are being investigated in three separate studies in crack-cocaine dependent patients in the Netherlands (Nuijten et al., 2011, 2014). Similar to the first trial of topiramate (Nuijten et al., 2014), this study was designed as an open-label, randomised controlled feasibility trial. After screening and baseline assessment, participants were randomly assigned to the experimental group (individual outpatient CBT plus modafinil) or the control group (individual outpatient CBT only). Earlier studies have shown selective treatment discontinuation of patients in (placebo) control groups

(Kampman et al., 2005; Karila et al., 2008; Preti, 2007). In order to minimise this non-compliance and loss to follow-up among control patients due to disappointment about being randomised to the less attractive non-experimental intervention, a pre-randomisation, double-consent design (Zelen, 1979) was used. In this design, a first informed consent, pertaining to the standard psychosocial treatment (i.e. CBT), was provided by all participants, and a second informed consent, pertaining to the pharmacological treatment (i.e. modafinil), was obtained from those participants randomised to the experimental group. Hence, participants were informed only about the assigned treatment and not about the condition with which they were being compared (see also Nuijten et al., 2011).

If indicated, patients received a short (maximum 7 days) inpatient detoxification and psychosocial stabilisation treatment. Randomisation was computer-generated and stratified by gender, cultural background (European/non-European), participation in methadone maintenance treatment (MMT; yes/no), and inpatient stabilisation (yes/no).

The CATCH study is registered in The Netherlands National Trial Register (NTR2576) and The European Union Drug Regulating Authorities Clinical Trials (EUdraCT 2009-010584-16).

Participants and treatment setting

Crack-cocaine dependent patients at three addiction treatment centres in the Netherlands (Mentrum, Jellinek and Brijder) were asked to participate in the study. Patients at Mentrum already received substance use-related treatment, including case management or MMT, but with inadequate or no results in terms of cocaine use. Patients from Jellinek and Brijder were new referrals. Enrolment occurred from April 2012 till March 2014.

Eligible patients had to: (a) be at least 18 years old; (b) be cocaine dependent according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (American Psychiatric Association, 1994); (c) have used cocaine on at least 8 days in the previous month; (d) administer cocaine primarily by means of basing; (e) be able and willing to participate in the study treatment and associated assessments; and (f) provide written informed consent. Patients were excluded in case of (a) severe medical (e.g. severe renal insufficiency or cardiovascular problems) or psychiatric (e.g. acute psychosis or suicidality)

problems; (b) pregnancy or breastfeeding; (c) pharmacotherapy with a potentially effective medication for cocaine dependence (i.e. naltrexone, disulfiram, acamprosate, methylphenidate, topiramate, dexamfetamine or baclofen); (d) need for residential treatment (>7 days); (e) insufficient command of the Dutch language; or (f) participation in another addiction treatment trial.

Treatments

Psychosocial treatment

Psychosocial treatment of all patients consisted of 12 weekly individual CBT sessions (Kadden, 2001; Monti et al., 1997; Project MATCH Research Group, 1993; Rohsenow et al., 2000), delivered by trained, experienced therapists. CBT is the standard psychosocial treatment for substance abuse in the Netherlands (De Wildt et al., 2002). Treatment goals were based on a shared decision making process, and included abstinence and reduction in use of crack-cocaine.

Pharmacological treatment

In the experimental group, modafinil was prescribed for a period of 12 weeks as an add-on to CBT. Modafinil was initiated at 200 mg/day and after 1 week increased to 400 mg/day, if tolerated. During the first treatment week, modafinil was prescribed daily at the treatment centre to monitor intake and adverse events. In the remaining trial period, modafinil was dispensed once weekly, and self-reported modafinil intake was registered at each study visit. In case of discontinuation of modafinil treatment, CBT could be continued.

Assessments

Study assessments were performed at baseline, weeks 4 and 8 (experimental group only) and week 12. At baseline only, DSM-IV cocaine, alcohol and opioid dependence diagnoses (American Psychiatric Association, 1994) were obtained using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) (Cottler, 1990; Cottler, 2000). The Addiction Severity Index (ASI) (Hendriks et al., 1989; Kokkevi and Hartgers, 1995; McLellan et al., 1992) was used to assess substance use, illegal activities, social contacts and other clinical characteristics.

At all assessments, the Timeline Follow-Back (TLFB) calendar method (Hjorthoj et al., 2012; Sobell and Sobell, 1992) was used to collect information about self-reported crack-cocaine use in the 30 days preceding each assessment. Cocaine craving was measured with a short, adapted version of the Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1996; De Wildt et al., 2005; Franken et al., 2002). The Maudsley Addiction Profile-Health Symptoms Scale (MAP-HSS) (Marsden et al., 1998) was used to evaluate physical health, and the Symptom Checklist-90 (SCL-90) (Arrindell and Ettema, 1986; Derogatis et al., 1973) was used to assess the presence of psychological problems. Week 4, 8 and 12 assessments also included ASI substance use items and questions about current illegal activities and social contacts with non-drug users. The week 12 assessment was supplemented with the Client Satisfaction Questionnaire (CSQ-8) (De Wilde and Hendriks, 2005; Larsen et al., 1979).

At each study visit, co-medications and adverse events were registered. Blood pressure and heart rate were measured at baseline and week 12. At baseline and every four weeks, pregnancy tests were conducted with female participants (experimental group only).

Urine samples were collected at baseline, and once weekly in the final four weeks of the study period, and were analysed for the presence of cocaine metabolites (benzoylecgonine). The 201 urine samples that were submitted in these weeks (out of a planned total of 65 x 4=260 urine-samples; 77.3%), showed 86.8% agreement between self-reported cocaine use and presence of benzoylecgonine (kappa=0.68), with no difference between the experimental and control groups (kappa=0.73 and 0.65, respectively).

Participants received a maximum of €120 (control subjects) or €150 (experimental subjects) as remuneration for participating in the study assessments.

Outcome measures

Treatment retention, defined as the number of CBT sessions attended (range 0–12), was the primary outcome measure. Secondary outcome measures included modafinil adherence, tolerability and safety, use of cocaine and other substances, cocaine craving, physical and mental health, social functioning and patient satisfaction.

Power calculation

Given the feasibility character of the study, a lenient two-sided alpha of 0.10 was chosen to prevent type II errors. With a minimum difference of 25% in 12-week CBT treatment retention between the groups, a power of 0.80, and a two-sided alpha of 0.10, 36 patients were required in each treatment group ($n_{total=}72$).

Data analyses

Between-group differences were tested in an intent-to-treat (ITT) approach, incorporating all patients who provided informed consent pertaining to their assigned treatment. Baseline characteristics between groups were compared using chi-square tests for dichotomous variables, and *t* tests or Mann-Whitney U-tests for normally and non-normally distributed continuous variables, respectively.

With regard to the primary outcome, CBT treatment retention was investigated using a Cox proportional hazards regression model, analysing group differences in retaining patients in CBT treatment during the 12-week study period based on the log-rank (Kaplan-Meier) statistic, censoring the hazard at the tenth session.

With regard to the secondary outcomes, time x group (2 x 2) repeated measures analyses of variance (ANOVAs) were conducted to compare baseline to week 12 changes between the two groups in cocaine use days, craving, concurrent substance use, and other continuous and Likert-scale outcome measures. As suggested by Carroll et al. (2014), maximum days of consecutive abstinence, protracted abstinence (i.e. ≥3 weeks) during the study period, and abstinence during the last two weeks of treatment were also analysed between groups, using the *t* test and chi-square test.

The sum of benzoylecgonine-positive urine samples during the four weeks preceding the week 12 assessment was evaluated using Poisson regression analysis; missing urine samples were considered as positive. Modafinil adherence was assessed by the self-reported total days of modafinil intake. Mean modafinil dose was computed by summing the dose of all modafinil tablets that were ingested, as registered in the medication file, divided by the total number of days of modafinil intake.

In addition, two types of exploratory analyses were performed with treatment retention and baseline to week 12 differences in number of crack-cocaine use days as dependent variables, treatment group as the independent variable and the following baseline variables as potential confounders: crack-cocaine use (Ahmadi et al., 2009; Poling et al., 2007; Westhuis et al., 2001), cocaine-positive urine (Ahmadi et al., 2009; Kampman et al., 2001; Poling et al., 2007; Sofuoglu et al., 2003), cocaine craving (Sinha et al., 2006; Weiss et al., 1997), concurrent alcohol use (Alterman et al., 2000; Anderson et al., 2009; Poling et al., 2007), and gender (Dackis et al., 2012). In addition, comorbid opioid dependence was included as a potential confounder, given its moderating effect on the efficacy of topiramate in the treatment of cocaine dependence in our earlier study (Nuijten et al., 2014). All continuous covariates were dichotomised based on the median, due to their non-linear relationship with both dependent variables. First, each baseline characteristic was entered into the original model to identify confounding. Baseline covariates that resulted in a change of at least 10% in the *B*-value of the treatment group were entered into the final regression model. Second, we analysed whether the baseline characteristics differentially moderated treatment outcome by adding their interaction with treatment group into the regression model.

Week 12 data were available for 91% of the ITT population. Missing data of four participants in the experimental group and two patients in the control group were estimated with multiple imputation, using five imputed datasets, with baseline variables as predictors.

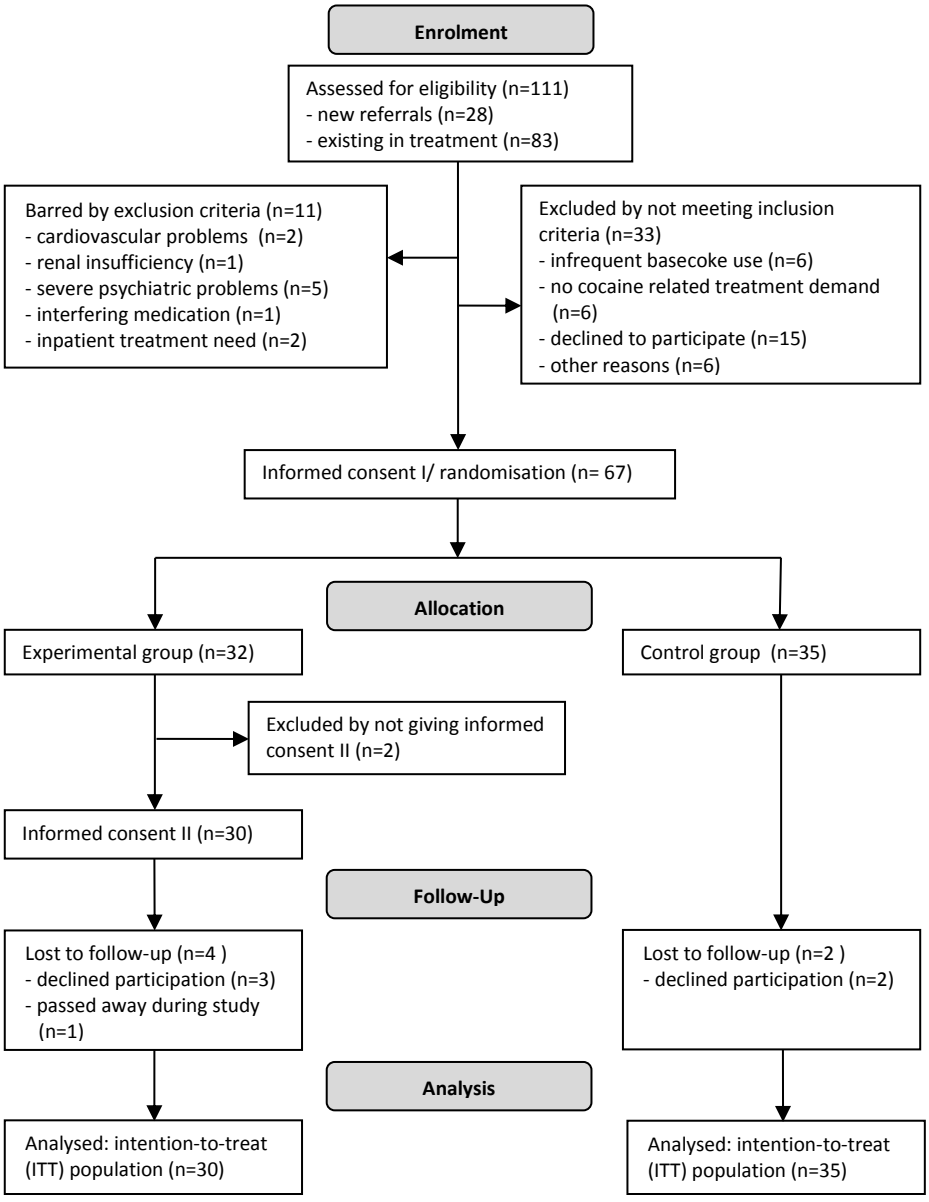
Results

Participant flow

Eligibility was assessed in 111 patients. Sixty-seven patients met all selection criteria and were randomised after giving first informed consent (Figure 1), 32 to the CBT + modafinil group and 35 to the CBT-only group. Thirty of the 32 patients randomised to the experimental group accepted the additional pharmacological treatment offer and gave second informed consent (94%), while two patients refused the offer of modafinil. The final ITT population consisted of 30 patients in the experimental group and 35 patients in the control group. Despite this

somewhat lower than intended sample size, the recruitment phase was terminated after 2 years due to time constraints.

Figure 1. Participant flow.



Baseline characteristics

Baseline characteristics of the participants are summarised in Table 1. Participants could be characterised as chronic cocaine dependent patients with a history of multiple treatments, who frequently used crack-cocaine (≥17 days/month on average) and other drugs and/or alcohol. The majority (77%) were already receiving substance use related treatment, including MMT (31%). There were no significant differences in patient characteristics between the two treatment groups, but the experimental group tended to use crack-cocaine on more days (p=0.06) and have more cocaine positive urine samples (p=0.07) at baseline.

Medication adherence

Modafinil intake was terminated within two weeks by 10 participants (33%). Among the patients who took modafinil at least two weeks (n=20), the mean dose was 361 mg/day (sd=32.7). Modafinil was taken for at least eight weeks by 11 patients (37%), for at least 10 weeks by six patients (20%) and for at least 11 weeks by three patients (10%).

Six patients in the experimental group (20%) stopped modafinil intake within 10 weeks due to adverse events that were probably or certainly related to modafinil (see also Tolerability and safety).

Primary outcome: CBT treatment retention

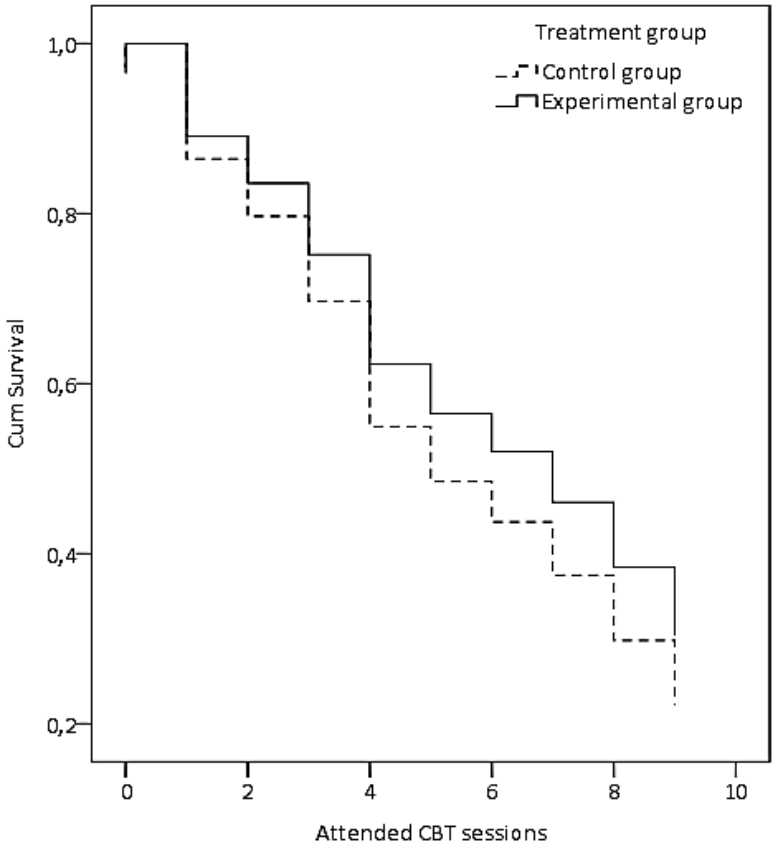
In the experimental group, participants attended a mean of 6.8 CBT sessions (sd=3.8), compared with 5.8 (sd=3.8) in the control group. At least 10 sessions were completed by 30.0% in the experimental group and 22.9% in the control group. Cox regression survival analysis (Figure 2) suggested slightly better CBT treatment retention in the experimental group compared with the control group, but the difference was not significant (Hazard Ratio=0.79; 95% confidence interval (CI)=0.5−1.4; p=0.42).

Table 1. Baseline characteristics of the study sample.

Variable	Experimental group (n=30) M (sd) / %	Control group (n=35) M (sd) / %	p-value [c]
Recruitment			
Already in treatment (%)	73.3	80.0	0.53
Demographic background			
Age (years)	47.1 (7.8)	45.3 (8.3)	0.31
Gender: male (%)	83.3	77.1	0.53
European background (%)	50.0	51.4	0.91
Employed (%)[a,b]	30.0	40.0	0.40
Homeless (%)	6.7	8.6	0.77
Substance use			
Lifetime regular crack-cocaine use (years)	11.0 (7.9)	11.9 (8.9)	0.68
Benzoylecgonine-positive baseline urine (%)	93.3	77.1	0.07
Cocaine use (days)[a]	20.9 (8.2)	17.2 (7.6)	0.06
Alcohol use (≥5 glasses/day) (%)[a,b]	36.7	34.3	0.84
Heroin use (%)[a,b]	10.0	22.9	0.17
Cannabis use (%)[a,b]	63.3	57.1	0.61
Treatment status and history			
Opioid dependence (%)	26.7	37.1	0.37
Alcohol dependence (%)	6.7	17.1	0.20
Medication prescribed for mental health (%)[a]	26.7	31.4	0.67
Methadone maintenance treatment (%)	23.3	37.1	0.23
Methadone dose (mg)	103.0 (82.0)	71.4 (38.9)	0.45
Multiple (≥2) prior drug-related treatments (%)	60.0	57.1	0.82
Inpatient stabilisation period (≤ 7 days) (%)	6.7	17.1	0.20
Health & social functioning			
MAP total score (0-40)	11.1 (7.8)	11.6 (6.1)	0.78
SCL-90 total score (0-360)	93.3 (77.2)	101.0 (77.6)	0.70
OCDS total score (0-20)	8.4 (3.7)	8.7 (4.9)	0.78
Illegal activities (days)[a]	1.3 (3.0)	3.0 (7.4)	0.71
Social contacts with non-drug users (days)[a]	21.4 (11.9)	19.0 (13.5)	0.35

MAP: Maudsley Addiction Profile; SCL-90: Symptom Checklist-90; OCDS: Obsessive Compulsive Drinking Scale; [a] In the preceding 30 days; [b] At least 1 day; [c] Using chi-square tests for dichotomous variables; t tests for continuous variables; nonparametric Mann-Whitney U tests for continuous variables with skewed distributions.

Figure 2. Cox regression survival analysis.



Main secondary outcome: crack-cocaine use

Reductions in self-reported crack-cocaine use days from baseline to week 12 were significant and substantial in both treatment groups ($F=63.0$; $df=1$; $p<0.01$; Cohen's $d=1.08$), but these self-reported reductions did not differ significantly between treatment groups ($F=2.1$; $df=1$; $p=0.17$) (Table 2). The mean longest duration of consecutive abstinence in the experimental group was 28.5 days compared with 22.4 days in the control group, with no significant between-group difference (t –0.91, 95% CI=–19.6–7.4, $p=0.37$). Protracted abstinence (≥3 weeks) was achieved by 12 patients in the experimental group (40.0%) and 11 in the control group (31.4%) and was not significantly different between groups ($X^2=0.52$, $df=1$, $p=0.47$); nor was abstinence during the last two weeks of

Table 2. Group differences in substance use, health and social functioning.

	Experimental group		Control group		Repeated measures ANOVA	
	Baseline	Week 12	Baseline	Week 12	Time	Treatment x time
Variable	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Baseline vs. week 12	Baseline vs. week 12
Cocaine and other substance use						
Days of cocaine use[a]	20.9 (8.2)	10.1 (8.5)	17.2 (7.6)	9.7 (9.0)	F=63.0; p<0.01 (d=1.08)	F=2.1; p=0.17 (d=0.36)
Cocaine positive urine samples (0-4)		3.1 (1.4)		3.2 (1.3)		
Cocaine craving total score (0-20)	8.4 (3.7)	5.4 (3.2)	8.7 (4.9)	7.3 (4.2)	F=23.7; p<0.01 (d=0.53)	F=2.9; p=0.10 (d=0.42)
Days of alcohol use (≥ 5 glasses/day)[a]	6.1 (11.1)	2.8 (6.2)	5.0 (9.9)	4.6 (8.9)	F=6.9; p=0.01 (d=0.19)	F=4.4; p=0.04 (d=0.51)
Days of heroin use[a]	2.4 (7.9)	1.9 (6.1)	1.7 (5.6)	0.7 (1.5)	F=1.7; p=0.20 (d=0.14)	F=0.2; p=0.72 (d=-0.09)
Days of cannabis use[a]	11.1 (13.2)	11.6 (12.9)	9.6 (12.2)	10.8 (12.9)	F=0.6; p=0.47 (d=-0.07)	F=0.1; p=0.75 (d=0.08)
Health and social functioning						
Physical health: MAP total score (0-40)	11.1 (7.8)	9.3 (7.2)	11.6 (6.1)	11.6 (8.0)	F=1.8; p=0.20 (d=0.12)	F=1.7; p=0.22 (d=0.32)
Mental health: SCL-90 total score (0-360)	93.3 (77.2)	65.8 (74.5)	101.0 (77.6)	86.6 (66.7)	F=12.4; p<0.01 (d=0.28)	F=1.2; p=0.28 (d=0.27)
Illegal activities to obtain money/ drugs[a]	1.3 (2.6)	1.3 (3.0)	3.0 (7.4)	2.5 (5.5)	F=0.3; p=0.64 (d=0.05)	F=0.3; p=0.64 (d=-0.12)
Social contacts with non-drug users[a]	21.4 (11.9)	24.1 (9.3)	19.0 (13.5)	21.9 (12.0)	F=3.3; p=0.08 (d=-0.24)	F=0.0; p=0.93 (d=0.02)

ANOVA: analysis of variance; MAP: Maudsley Addiction Profile; SCL-90: Symptom Checklist-90. [a] In the preceding 30 days.

treatment, which was accomplished by five (16.7%) and seven (20.0%) patients, respectively (X^2=0.12, df=1, p=0.73).

Of the urine samples expected in the last four weeks, 24.2% in the experimental group and 21.4% in the control group were not submitted and hence considered benzoylecgonine-positive. The mean number of cocaine-positive urine samples was 3.1 (sd=1.4) in the experimental group and 3.2 (sd=1.3) in the control group. Poisson regression analysis did not show a significant group difference (Exp(B)=1.02; 95% CI=0.8–1.3; p=0.88). Restricting the analysis to submitted urine samples resulted in 27.8% cocaine-negative samples in the experimental group versus 25.9% in the control group.

Other secondary outcome measures

For the other secondary outcome variables (Table 2) there were significant baseline to week 12 improvements in cocaine craving, alcohol use days (≥5 glasses/day), and mental health. Repeated measures ANOVA showed significant time x group effects for alcohol use in the preceding 30 days, with a mean reduction of 3.3 days in the experimental group compared with 0.4 days in the control group (F=4.4; df=1; p=0.04). None of the other secondary outcome variables showed significant time x group interactions. Additionally, satisfaction with the treatment offer (CSQ-8; range 8-32) at the end of the study did not differ between groups ($M_{exp=}$26.5 (sd=4.7) vs. $M_{contr=}$25.2 (sd=3.9); *t* –1.14; df=57; p=0.26).

Tolerability and safety

A total of 106 adverse events were reported during the study, by 24 patients (80%) in the experimental group and two patients (6%) in the control group. The majority of the reported adverse events in the experimental group (n=55; 53.9%) were probably or certainly related to modafinil intake: tachycardia (18%), agitation, including restlessness and irritability (16%), and headache (13%) were most frequently (≥10%) reported. Of these adverse events, 22 were evaluated as severe (tachycardia 27%; agitation 18%; headache 14%). In two cases the modafinil dose was reduced due to adverse events, but nevertheless these patients prematurely withdrew from modafinil treatment.

There were two serious adverse events, neither of which was related to modafinil. In the experimental group, one patient died during the study period. In the control group, one patient was hospitalised for several days due to constipation.

Exploratory analyses

The relation of treatment group with both treatment retention and baseline to week 12 differences in crack-cocaine use days changed (*B*-change >10%) by adding baseline crack-cocaine use days and cocaine-positive urine as covariates in the original model (see Table 3a,3b). However, the adjusted models containing both covariates did not reach statistical significance. For both outcome variables, there were no significant interactions between treatment group and any of the covariates (Table 3a,3b), indicating that the effects of modafinil were not moderated by these patient characteristics.

A final post hoc comparison between low (<2 weeks), medium (2–7 weeks) and high (≥8 weeks) modafinil adherent patients showed baseline to week 12 reductions in crack-cocaine use days in all subgroups (Figure 3). Repeated measures ANOVAs showed significant time differences ($F=45.6$, $df=1$, $p<0.01$) and significant time x group differences in crack-cocaine use days ($F=6.39$, $df=2$, $p=0.01$) in favour of the high adherent subgroup.

Figure 3. Modafinil adherence and days of crack-cocaine use.

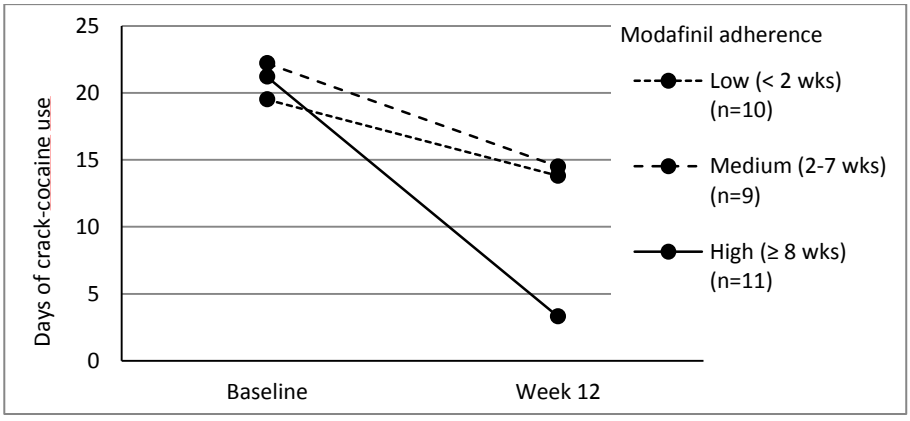


Table 3a. Exploratory analyses: Confounders and moderators of treatment retention.

	Treatment retention: Original model: B=−0.24; HR=0.79; 95% CI: 0.5−1.4						
	Original model + covariate			Interaction group x covariate			
	B	HR	95% CI	B	HR	95% CI	p
Crack-cocaine use	−0.34	0.71	0.4–1.3	−0.59	0.55	0.2–1.8	0.32
Cocaine-positive urinalysis	−0.46	0.63	0.4–1.1	−0.85	0.43	0.0–4.4	0.48
Cocaine craving	−0.24	0.79	0.5–1.4	0.12	1.12	0.4–3.6	0.85
Alcohol use (≥5 glasses/day)	−0.23	0.79	0.5–1.4	−0.07	0.93	0.3–3.1	0.91
Opioid dependence	−0.23	0.79	0.5–1.4	−0.38	0.69	0.2–2.5	0.56
Gender	−0.23	0.80	0.5–1.4	0.25	1.28	0.3–5.3	0.73

HR: Hazard Ratio; CI: confidence interval.

Table 3b. Exploratory analyses: Confounders and moderators of changes in days of crack-cocaine use.

	Baseline to week 12 crack-cocaine use days: Original model: B=3.29; t=1.40; 95% CI: −1.3−7.9				
	Original model + covariate		Interaction group x covariate		
	B	95% CI	B	95% CI	p
Crack-cocaine use	1.52	−2.7–5.8	3.98	−4.4–12.4	0.35
Cocaine-positive urinalysis	3.67	−1.1–8.4	6.12	−10.1–22.3	0.46
Cocaine craving	3.30	−1.4–8.0	−2.79	−12.4–6.8	0.57
Alcohol use (≥5 glasses/day)	3.45	−1.1–7.8	4.28	−5.1–13.6	0.37
Opioid dependence	3.61	−1.0–8.2	2.10	−7.9–12.1	0.68
Gender	3.29	−1.4–8.0	0.42	−11.5–12.3	0.95

CI: confidence interval.

Discussion

The acceptance, safety and potential benefits of 400 mg/day modafinil as an add-on treatment to CBT in crack-cocaine dependent patients were tested in an open-label, randomised controlled feasibility trial. The study found that modafinil acceptance was limited, given the low modafinil adherence. Modafinil was evaluated as an agent with considerable medication-related adverse events, which caused termination of modafinil intake in 20% of the patients within 10 weeks of treatment. Modafinil did not improve CBT treatment retention or any of the secondary cocaine-related outcomes. However, a post hoc analysis suggested that modafinil was associated with large reductions in cocaine use among patients who took the medication for at least eight weeks.

The observed overall lack of modafinil benefits can be explained at least partly by its low acceptance, as indicated by the 10% treatment completion rate in our study, which was much lower than the completion rates of around 50–60% in all other studies of modafinil in cocaine dependent patients (Anderson et al., 2012; Dackis et al., 2005; Dackis et al., 2012; Schmitz et al., 2014; Schmitz et al., 2012). Moreover, the most important reason for non-adherence in our study was the occurrence of medication-related adverse events. Compared with previous studies, dropout due to adverse events was considerable in our study, at 20%. In the randomised controlled trial of Dackis et al. (2005), in six cases (20%) the modafinil dose was reduced from 400 to 300 or 200 mg/day due to adverse events, but all patients continued treatment. Anderson et al. (2009) found that modafinil discontinuation due to adverse events occurred more often in the 400 mg/day group (10 out of 68; 14.7%) compared with the 200 mg/day group (1 out of 68; 1.5%). Hence, the observed high rate of treatment discontinuation due to adverse events in our study may have been dose related.

Several laboratory studies have found that modafinil diminished cocaine-related euphoria and craving in cocaine-using non-treatment-seeking participants (Dackis et al., 2003; Hart et al., 2008; Malcolm et al., 2006; Verrico et al., 2014). In the context of treatment, however, we did not observe reductions in craving for cocaine in our study, and neither did Dackis et al. (2005; 2012). Therefore, disappointment about the perceived lack of effect of modafinil on craving and

cocaine use may have led the (chronic) crack-cocaine dependent patients in our study to discontinue medication intake.

Finally, differences in treatment and/or study procedures may possibly explain the low medication adherence in our study. In all studies except ours, patients had to attend the clinic three times a week (Anderson et al., 2009; Dackis et al., 2005; Dackis et al., 2012; Schmitz et al., 2014; Schmitz et al., 2012), which created the opportunity to motivate and inform patients, stress the importance of medication adherence and discuss problems with medication intake. In addition, in both studies of Dackis et al. (2005; 2012), patients were remunerated for returning blister packages, and Schmitz et al. (2014) used a contingency management intervention to target medication compliance. The absence of incentives, combined with the less frequent opportunity to motivate patients in our study, may have contributed to low modafinil adherence (DeFulio and Silverman, 2012; Volpicelli et al., 2001; Weiss, 2004).

Low adherence is very common and a major problem in medication trials (Servick, 2014). Strategies to improve adherence are essential if the efficacy of the study medication is to be validly determined, including strategies to improve the therapeutic alliance, provide external reinforcement, and formulation and dosing strategies (Weiss, 2004). Medication management interventions, such as BRENDA (an acronym for its six components: a biopsychosocial evaluation; a report of findings from the evaluation given to the patient; empathy; addressing patient needs; providing direct advice; and assessing patient reaction to advice and adjusting the treatment plan as needed (Starosta et al., 2006)), in which treatment motivation and individual patient needs are discussed on an ongoing basis during treatment (Volpicelli et al., 2001), and reinforcement of medication intake with (financial) incentives, have already demonstrated improved medication adherence (Petry et al., 2012; Starosta et al., 2006; Stitzer and Vandrey, 2008). In addition, we need more knowledge about the relationship of patient characterics with medication adherence and treatment response. With regard to the latter issue, it has been shown that modafinil was only effective in alcohol dependent patients with poor response inhibition at baseline (Joos et al., 2013a) and in pathological gamblers with high self-reported impulsivity (Zack and Poulos, 2009).

Overall, our negative study findings are in line with most recent randomised controlled trials in which modafinil did not show any effects on cocaine use (Schmitz et al., 2014; Schmitz et al., 2012). In fact, the positive results of modafinil in the treatment of cocaine dependence found by Dackis et al. (2005) have never been replicated. In subsequent studies, positive results in favour of modafinil were found only in secondary outcomes or in post hoc defined subgroups (Anderson et al., 2009; Dackis et al., 2012).

The present study differed from most previous studies in that patients with comorbid opioid or alcohol dependence were not excluded. Moreover, in our study the majority of patients had already had two or more prior treatment episodes. Together, these factors may reflect a more severe population with a worse prognosis (Ahmadi et al., 2009; Kampman et al., 2001; Poling et al., 2007).

Limitations

Our trial was limited by the once-weekly collection of urine samples in the last four weeks of study treatment. However, agreement between self-reported cocaine use and urinalysis outcome was good in both the experimental and the control group, and both measures were consistent in showing no difference in treatment outcome between the two study groups. Furthermore, fewer patients than planned according to our power calculation participated in our study. However, the observed results did not approach statistical significance and, hence, lack of power is unlikely to explain our negative results. Finally, given the feasibility character of our study, and in order to avoid selective non-compliance and dropout among control patients, we chose an open-label, non-placebo-controlled design. As a consequence, this may have caused bias among patients, treatment staff and investigators. Since we did not find differences between the treatment groups in terms of retention in CBT and secondary, cocaine-related outcome variables, we believe this strategy was justified and did not bias our results.

Conclusion

In sum, the acceptance, safety and benefits of 400 mg/day modafinil for the treatment of crack-cocaine dependence were not demonstrated in the present study. Medication adherence was low, partly attributable to adverse events, and

modafinil was not related to improvement in CBT treatment retention, cocaine use and other secondary outcomes. However, given that in a subgroup of high modafinil adherent patients crack-cocaine use was strongly reduced, the results of this study are inconclusive, and further research of the potential of modafinil in the treatment of cocaine dependence, in which modafinil adherence is optimised, is warranted.

Chapter 4

Impulsivity and attentional bias as predictors of modafinil treatment outcome for retention and drug use in crack-cocaine dependent patients: Results of a randomised controlled trial

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Abstract

Background: High impulsivity and attentional bias are common in cocaine dependent patients and predict poor treatment outcomes. The pharmacological agent modafinil is studied for its cognitive-enhancing capacities and may therefore improve clinical outcomes in crack-cocaine dependent patients. In this study, we investigated first whether pre-treatment impulsivity and attentional bias predict treatment outcome; next whether the drug modafinil given as an add-on treatment to cognitive behavioural therapy (CBT) improves impulsivity and attentional bias; and last, whether changes in impulsivity and attentional bias are related to improvements in treatment outcome.

Methods: Crack-cocaine dependent outpatients (n=65) were randomised to 12 weeks CBT plus modafinil (400 mg/day) or only CBT. Self-reported impulsivity was assessed at baseline using the Barratt Impulsiveness Scale. At baseline and week 12, we assessed inhibitory control as behavioural measure of impulsivity, in terms of cognitive interference (Stroop task) and response inhibition ('stop-signal task'), and attentional bias with the addiction Stroop task. Clinical outcomes were CBT retention and crack-cocaine use.

Results: At baseline, low self-reported impulsivity predicted better CBT retention; low self-reported and behavioural impulsivity and attentional bias predicted less crack-cocaine use. Changes in cognitive performance were not modafinil-related, but most likely due to low adherence. Improvements in impulsivity or attentional bias were not associated with CBT retention nor changes in crack-cocaine use.

Conclusions: Baseline impulsivity and attentional bias predicted clinical outcomes in crack-cocaine dependent patients. There were no firm indications that modafinil reduced impulsivity nor attentional bias in this population. Future studies involving cognitive-enhancing medications should include strategies to optimise adherence, to be better able to evaluate their potential.

Introduction

To date, there is no proven effective pharmacological treatment for cocaine dependence, despite the considerable research efforts undertaken in this area, pertaining to a wide range of pharmacological agents (Alvarez et al., 2010; Kishi et al., 2013; Minozzi et al., 2015a; Minozzi et al., 2015b; Pani et al., 2011; Rush and Stoops, 2012; Van den Brink, 2012). Of these agents, the psychostimulant modafinil has shown promising effects, in terms of increased and protracted cocaine abstinence, in several studies (Anderson et al., 2009; Dackis et al., 2005; Kampman et al., 2015); however, in a recent randomised controlled study in crack-cocaine dependent patients, we found that modafinil as an add-on to cognitive behavioural therapy (CBT) did not improve treatment retention or cocaine-related outcomes, compared with CBT alone, possibly due to low modafinil adherence (Nuijten et al., 2015). The current study aims to explore the role of impulsivity and attentional bias in the overall negative findings of this trial.

High impulsivity and attentional bias are common in patient groups with substance use disorders, including cocaine use disorder (Fernandez-Serrano et al., 2012; Liu et al., 2011; Madoz-Gurpide et al., 2011; Potvin et al., 2014; Spronk et al., 2013). Impulsivity is a multifaceted construct and is generally regarded to be a part of impaired executive functioning (Bari and Robbins, 2013). Inhibitory control represents different cognitive processes, including impulsive action, which can be divided into response inhibition (or motor inhibition) and cognitive interference (or interference control) (Nigg, 2000; Stevens et al., 2014). Response inhibition is the ability to inhibit a pre-potent action in a situation in which this is inappropriate (Stevens et al., 2014; Verbruggen and Logan, 2008a), whereas cognitive interference refers to the ability to focus attention during the presentation of interfering cognitive stimuli (Nigg, 2000). Attentional bias means that attention is distracted by emotionally (drug-related) salient stimuli in the environment (Cox et al., 2006; Field and Cox, 2008). Several studies suggest that the strength of attentional bias is reciprocally related to the degree of impairment of inhibitory control (Coskunpinar and Cyders, 2013; Field and Cox, 2008; Stevens et al., 2014), and that high impulsivity and attentional bias are predictive of poor outcomes of substance abuse treatment (Aharonovich et al., 2006; Sofuoglu, 2010; Sofuoglu et al., 2013; Stevens et al., 2014; Verdejo-Garcia et al., 2012). Hence, cognitive enhancement may be an important target in the treatment of

substance dependence (Mereu et al., 2013; Sofuoglu et al., 2013), and given its cognitive-enhancing properties (Ballon and Feifel, 2006; Kumar, 2008; Minzenberg and Carter, 2008), treatment with modafinil may be a strategy to improve both cognitive functioning and clinical outcomes in patients with a substance use disorder, including cocaine dependence.

In two randomised, placebo-controlled studies in patients with cocaine dependence, short 4–5-day modafinil treatment significantly improved performance on two measures of working memory span and normalised risk taking (Canavan et al., 2014; Kalechstein et al., 2013). In addition, in a randomised placebo-controlled cross-over study, a single dose of modafinil attenuated neural reactivity to cocaine-related cues and self-reported craving in treatment seeking cocaine dependent patients (Goudriaan et al., 2013).

Modafinil was also studied in other addictive behaviours, for its cognitive-enhancing effects. In a randomised, placebo-controlled crossover study in alcohol dependent patients, a single dose of modafinil resulted in improvements in cognitive control (Schmaal et al., 2013a) and impulsive decision making (Schmaal et al., 2014), and in improved response inhibition in patients with poor baseline response inhibition (Schmaal et al., 2013b). In another randomised, placebo-controlled parallel trial in alcohol dependent inpatients, a 10-week modafinil treatment did not improve response inhibition and was not associated with reduced alcohol consumption; however, subgroup analyses showed that modafinil did prolong the time to alcohol relapse in patients with poor response inhibition at baseline (Joos et al., 2013a). Additional subgroup analyses showed that modafinil treatment was also associated with improvements in working memory and verbal short-term memory in alcohol dependent patients with the lowest baseline working memory skills, compared with patients with the highest baseline working memory skills (Joos et al., 2013b).

Similarly, in methamphetamine dependent patients, four double-blind, randomised, placebo-controlled trials were conducted, with promising results for modafinil. Modafinil improved verbal memory recall after 5 days of administration (Hester et al., 2010); and modafinil-related improvements in working memory were found in a subgroup of methamphetamine dependent volunteers with poor baseline performance, as compared with high performers, after 3 days of administration (Kalechstein et al., 2010). In two other studies, a single dose of

modafinil was associated with overall improvements in learning performance (Ghahremani et al., 2011), and in inhibitory control and processing speed in a subgroup of methamphetamine dependent patients with high baseline frequency methamphetamine use, versus a subgroup with low baseline frequency methamphetamine use (Dean et al., 2011).

Finally, a small, placebo-controlled, double-blind study in pathological gamblers showed that a single dose of modafinil decreased the desire to gamble, salience of gambling words, disinhibition and risky decision-making in high-impulsive pathological gamblers, whereas the opposite was found in low-impulsive pathological gamblers (Zack and Poulos, 2009), and increased the salience of environmental rewards in both the low and high impulsive gamblers (Smart et al., 2013).

In summary, modafinil seemed to improve different aspects of cognitive functioning, especially in patients with suboptimal cognitive functions at baseline; however, with the exception of the study by Joos et al. (2013a) in alcohol dependent patients, there are no studies in substance use disordered patients that investigate modafinil-associated changes in cognitive functioning in relation to clinical treatment outcomes.

The present study investigates the role of impulsivity and attentional bias as predictors of modafinil treatment on treatment outcome, in the sample of crack-cocaine dependent patients that participated in a previous randomised controlled trial (RCT) that we performed (Nuijten et al., 2015). The following research questions were examined:

1. What are the effects of pre-treatment self-reported impulsivity, inhibitory control and attentional bias on CBT retention and crack-cocaine use?
2. Is modafinil, as an add-on to CBT, effective in improving inhibitory control and reducing attentional bias, compared with CBT alone?
3. Are changes in inhibitory control and attentional bias during (modafinil) treatment related to CBT retention and changes in crack-cocaine use?

Methods and materials

Design

This study was designed as an open-label, parallel-group, randomised controlled feasibility trial. After screening and baseline assessment, participants were randomly assigned to the experimental group (12 weeks individual, outpatient CBT plus modafinil) or the control group (12 weeks individual, outpatient CBT only), using a pre-randomisation, double-consent design (Zelen, 1979). For more details, see Nuijten et al. (2015).

The study was approved by the medical ethics committee of the Academic Medical Centre in Amsterdam and all participants provided written informed consent.

The study is registered in The Netherlands National Trial Register (NTR2576) and The EU Drug Regulating Authorities Clinical Trials (EUdraCT 2009-010584-16).

Participants

Eligible patients were at least 18 years old, were cocaine dependent according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), and had used cocaine by means of basing (crack-cocaine) for at least 8 days in the previous month.

Exclusion criteria were severe medical or psychiatric problems, being pregnant or breastfeeding, or receiving pharmacotherapy with a drug that could potentially be effective for treating cocaine dependence (e.g. naltrexone, disulfiram, acamprosate, methylphenidate, topiramate, dexamfetamine or baclofen).

The intent-to-treat (ITT) population of the study consisted of 30 patients who were randomised to the experimental treatment group (CBT plus modafinil) and of 35 patients who were randomised to the control treatment group (CBT only group) as was shown in the participant flow in Nuijten et al. (2015).

Treatments

Psychosocial treatment

All patients were offered 12 weekly individual CBT sessions (Kadden, 2001; Monti et al., 1997; Project MATCH Research Group, 1993; Rohsenow et al., 2000), provided by trained, experienced therapists. The treatment goals were based on a

shared decision-making process that included abstinence or reduction of crack-cocaine use.

Pharmacological treatment

Patients in the experimental group were offered modafinil for a period of 12 weeks as an add-on treatment to CBT. Modafinil was initiated at 200 mg/day in the first week (week 1) and was then administered in 400 mg/day doses (week 2–12), if tolerated. During week 1, modafinil was prescribed on a daily basis at the treatment centre; in the remaining trial period, modafinil was dispensed to the patient once a week, and the self-reported intake was registered at each study visit.

Assessments

Baseline and clinical characteristics

At baseline, we obtained the DSM-IV cocaine dependence diagnosis (American Psychiatric Association, 1994) using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) (Cottler, 1990; Cottler, 2000). We used sections of the Addiction Severity Index (ASI) (Hendriks et al., 1989; Kokkevi and Hartgers, 1995; McLellan et al., 1992) to collect sociodemographic and clinical baseline characteristics. In addition, at baseline and week 12, we used the Time Line Follow-Back (TLFB) calendar method (Hjorthoj et al., 2012; Sobell and Sobell, 1992) to collect detailed information about self-reported crack-cocaine use in the 30 days preceding the assessments; and the short, adapted version of the Obsessive Compulsive Drinking Scale (OCDS) to measure the level of the patients' cocaine craving (Anton et al., 1996; De Wildt et al., 2005; Franken et al., 2002).

Impulsivity

*S*elf-reported impulsivity was assessed with the Barratt Impulsiveness Scale, version 11 (BIS-11) (Patton et al., 1995). Given that the BIS-11 measures impulsive personality traits over an extended period of time, this measure was only administered at baseline; and, hence, it could only be used as a predictor variable and not as an intermediate or outcome measure.

Inhibitory control as a behavioural measure of impulsivity, assessed in terms of response inhibition and cognitive interference, was measured with the stop-signal

task (SST) (Logan et al., 1984; Verbruggen and Logan, 2008b) and the Stroop colour-word task (Stroop, 1935), respectively. Both tasks were performed at baseline and week 12.

To assess response inhibition, we used the computerised SST, programmed in E-Prime. Participants had to respond to an airplane facing left or right on the computer screen as fast and accurately as possible (i.e. the go-trial) via the keyboard (Schmaal et al., 2013b). Occasionally, on 20% of the trials, a stop-signal was presented, consisting of a crossed out airplane (i.e. the stop-trial) where the participants had been instructed to try to withhold the response (Bari and Robbins, 2013). The timing of that stop-signal (stop-signal delay (SSD)) was dynamically adjusted and the difficulty of stopping was varied using a staircase procedure (De Jong et al., 1990), targeted at 50% correct self-inhibitions. Upon successful stopping by the study participant, the SSD on the next stop-trial was increased by 50 milliseconds (ms), making it more challenging for the study subject to inhibit this stop-trial. The study subject's failures to inhibit were followed by a 50 ms decrease in SSD, making it easier for that subject to withhold their response at the next stop-trial. The time required for the stop-signal to be successfully processed, the subject's stop-signal reaction time (SSRT), was computed by subtracting the mean SSD from the mean go reaction time. A longer SSRT (in ms) indicated a poorer response inhibition.

To assess cognitive interference, we used a computerised classic Stroop colour-word paradigm (Schmaal et al., 2013a), programmed in E-Prime. In this task, congruent colour words and incongruent colour words (e.g. the word 'red' written in green ink) were presented; participants were instructed to respond via the keyboard, as quickly and accurately as possible to the colour in which each word was presented, while attempting to ignore the meaning of the word given. The difference in mean reaction time (RT) between the incongruent and congruent Stroop words was interpreted as a measure of cognitive interference. Longer RTs (given in ms) indicate higher cognitive interference.

Attentional bias

In order to assess the subjects' attentional bias to cocaine-related stimuli, the addiction Stroop task (Cox et al., 2006) was combined with the classic Stroop colour-word task in a block design, in which the congruent, incongruent, cocaine-

related and neutral blocks were counterbalanced. The stimuli of the addiction Stroop task consisted of cocaine-related words (e.g. crack, high, 'basecoke', dealer) and neutral words that were traffic-related (e.g. gasoline, bike, ferry, road), presented in four different colours. Instructions were similar to the classic Stroop colour-word task, including the task administration at baseline and at week 12. The difference in the study subjects' mean RT between the cocaine-related and the neutral stimuli was interpreted as a measure of attentional bias. Longer RTs (in ms) indicate that there is higher attentional bias.

Outcome variables

The clinical outcome measures were: Treatment retention, defined as the number of CBT sessions attended (range, 0–12); self-reported crack-cocaine use days within the 30 days preceding the assessment at week 12; and the change in self-reported crack-cocaine use days, from baseline to week 12.

The cognitive outcome measures were: The changes in response inhibition, cognitive interference and attentional bias. They were calculated by subtracting the week 12 performance from the baseline performance.

Data-analyses

In our data analyses, we defined the outliers as the extreme values indicated by the statistics program, combined with considerations from the field (Band et al., 2003; Congdon et al., 2012; Franken et al., 2004; Ratcliff, 1993).

For the stop-signal task, we had missing baseline data for one patient, due to technical problems, and nine of the patients were outliers (>25% extreme reaction times: <200 ms or >3 SDs above the mean reaction time in their go-trials; >25% omissions; a negative trial delay (i.e. the stop-trial occurred before the go-trial) in >50% of the stop-trials; or the correct inhibition percentage was <30% or >70%). Thus, the analyses of response inhibition at baseline included 28 patients in the experimental group and 27 patients in the control group. The week 12 data were missing for seven more patients. Analyses of the changes between baseline and week 12 SSRTs were therefore analysed in 48 patients (24 in the experimental group and 24 in the control group), as seen in the flowchart in Figure 1. Furthermore, due to study dropout, the week 12 data about crack-cocaine use were missing in six patients.

For the Stroop task, we had the baseline data of one patient missing due to technical problems and one patient was considered an outlier (i.e. >25% extremely fast reaction times (<200 ms) in the cocaine-related or neutral trials). Thus, baseline attentional bias was analysed in 30 patients in the experimental group and 33 patients in the control group. Of these 63 patients, the week 12 Stroop data of seven patients were missing. Analyses of the changes between baseline and week 12 in attentional bias therefore included 56 patients (Figure 1).

Cases that met the criteria of an outlier, and missing cases resulting from technical problems or study dropout, were excluded from the data analyses. There were no significant differences in the baseline level of self-reported impulsivity between the outliers and those retained.

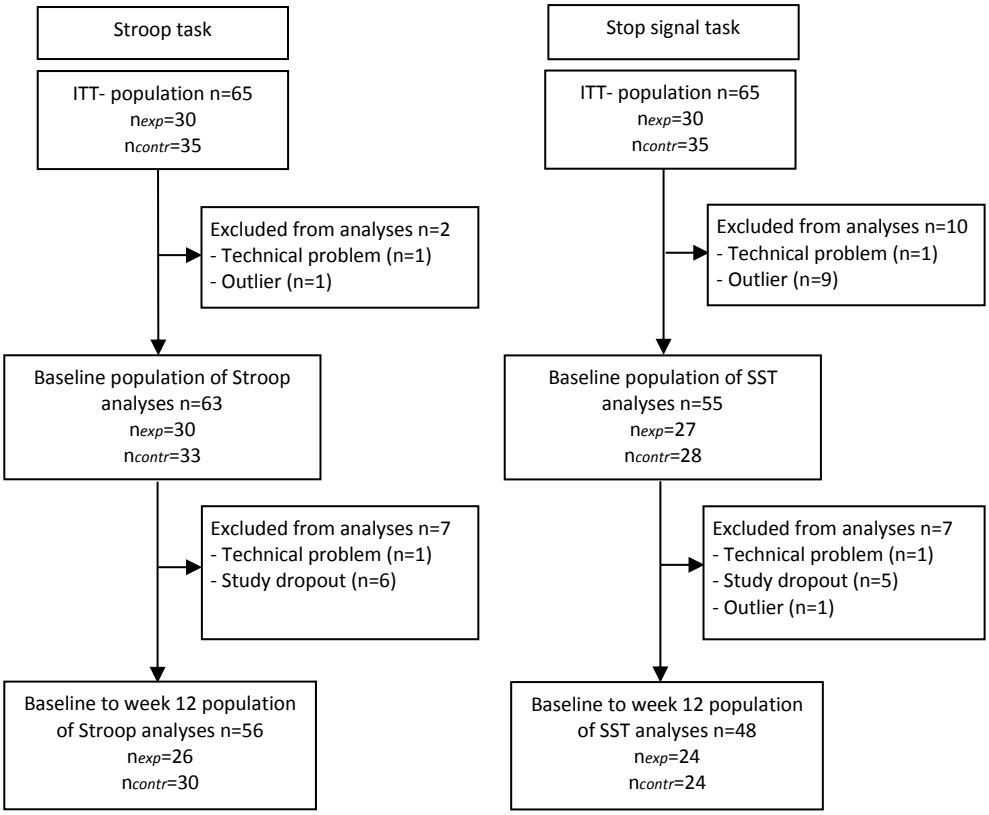
Between-group (experimental versus control) differences in baseline and clinical characteristics, baseline self-reported impulsivity, baseline inhibitory control and baseline attentional bias were analysed using the Chi-square test for dichotomous variables and the t-test for continuous variables.

We investigated research question one addressing the effects of pre-treatment measures of self-reported impulsivity, inhibitory control and attentional bias on CBT retention and crack-cocaine use in the last 30 treatment days, using Poisson regression analyses. Because the independent variables of baseline self-reported impulsivity, inhibitory control and attentional bias were not linearly related to the dependent count variables (i.e. CBT retention and cocaine use), these independent variables were dichotomised based on the median score (Table 1).

Table 1. Baseline cognitive measure ranges after dichotomisation.

Variable	n	Low/good range	n	High/ poor range
Self-reported impulsivity	32	49.0–68.0	33	69.0–97.0
Response inhibition	27	188.7–259.7	28	262.3–426.3
Cognitive interference	31	–101.2–114.6	32	115.2–676.3
Attentional bias	31	–260.9–36.2	32	38.9–556.0

Figure 1. Flowchart of participants in the data-analyses.



ITT: intent-to-treat; exp: experimental group; contr: control group; SST: stop-signal task.

With regard to the second research question, the effect of modafinil on inhibitory control and attentional bias, we conducted 2 x 2 (treatment group x time: baseline versus week 12) repeated measures analyses of variance (ANOVA) to compare the baseline to week 12 changes in response inhibition, cognitive interference and attentional bias between the experimental and control treatment groups. In advance, we knew that modafinil adherence in the trial was found to be generally low (Nuijten et al., 2015); and hence, the contrast in actually received treatment between the experimental and control groups was limited. Therefore, we also explored the changes in inhibitory control and attentional bias within the experimental treatment group, comparing the low (<8 weeks) versus

the high (≥8 weeks) modafinil-adherent patients, using a 2 x 2 (low versus high adherence x time: baseline versus week 12) repeated measures ANOVA.

For the analyses of our research question three, we correlated the baseline to week 12 changes in cognitive performance with the treatment retention and changes in crack-cocaine use days, and we assessed whether these correlations differed between the low and high modafinil-adherent patients within the experimental treatment group. The correlations were standardised using Fisher's r-to-z transformations, and together with a pooled standard error, Wald-tests for significance were conducted.

In the case of significant results (p-values <0.05), we calculated the standardised effect sizes (Cohen's d).

Results

Baseline characteristics

Table 2 shows the baseline characteristics of the participants. Patients in the experimental group tended to use crack-cocaine on more days (p=0.06) and have more cocaine-positive urine tests (p=0.07) than those in the control group. Self-reported impulsivity and neurocognitive task performance were similar for both treatment groups. The correlations between baseline self-reported impulsivity, response inhibition, cognitive interference and attentional bias were low (r=–0.01–0.18) and non-significant, except for the correlation between response inhibition and cognitive interference (r(52)=0.27, p=0.05; data not shown).

Modafinil adherence

Five patients (17%) suffered from adverse events at a modafinil dose of 200 mg/day and their dose was not increased to the intended 400 mg/day after the first titration week: three of these patients discontinued modafinil treatment and two continued at a lower dose of 300 mg/day. During the study period, the modafinil dose was reduced due to adverse events in two patients, but they nevertheless withdrew prematurely from modafinil treatment.

Modafinil intake was terminated within 2 weeks by 10 participants (33%). Modafinil was taken for at least 8 weeks by 11 patients (37%), for at least 10

weeks by six patients (20%) and for at least 11 weeks by three patients (10%) (Nuijten et al., 2015).

Table 2. Baseline characteristics of the study sample.

Variable	Experimental group (n=30) M / % (sd)	Control group (n=35) M / % (sd)	*p*-value[b]
Demographic background			
Age (years)	47.1 (7.8)	45.3 (8.3)	0.31
Gender male (%)	83.3	77.1	0.53
Substance use			
Lifetime regular crack-cocaine use (years)	11.0 (7.9)	11.9 (8.9)	0.68
Cocaine-positive baseline urine (%)	93.3	77.1	0.07
Cocaine use (days in preceding 30 days)	20.9 (8.2)	17.2 (7.6)	0.06
Treatment goal: abstinence (%)	86.7	80.0	0.48
Neurocognitive functioning			
Self-reported impulsivity (BIS-11; range 30-120)	67.8 (12.9)	72.0 (10.1)	0.15
Stop signal task[a,c]			
Go-trials reaction time	652.4 (93.7)	646.7 (108.5)	0.84
SSRT	278.0 (54.5)	268.8 (41.5)	0.48
Stroop task[a,d]			
Cognitive interference	169.7 (210.2)	156.5 (123.6)	0.77
Reaction time for congruent trials	818.7 (187.3)	839.7 (161.5)	0.63
Reaction time for incongruent trials	988.3 (241.8)	996.2 (220.7)	0.89
Attentional bias	32.4 (127.5)	61.6 (115.6)	0.34
Reaction time for neutral trials	841.2 (169.3)	878.0 (159.3)	0.38
Reaction time for cocaine trials	873.5 (163.7)	939.6 (207.5)	0.17

[a] Responses measured in milliseconds. [b] Using Chi-square tests for dichotomous variables and *t*-tests for continuous variables. [c] Stop signal task n=55 (n_{exp}=27; n_{contr}=28). [d] Stroop task n=63 (n_{exp}=30; n_{contr}=33). BIS-11: Barratt impulsiveness scale - 11; SSRT: stop signal reaction time.

Table 3a. Baseline cognitive functioning related to number of CBT sessions.

Baseline cognitive functioning		CBT sessions			
		Mean (sd)	Exp(B)	95%-CI	p
Self-reported impulsivity	- low	7.3 (3.7)			
	- high	5.3 (3.7)	0.73	0.6-0.9	<0.01
Response inhibition	- good	6.3 (3.7)			
	- poor	6.9 (3.8)	1.09	0.9-1.3	0.42
Cognitive interference	- low	6.7 (3.3)			
	- high	5.6 (4.1)	0.84	0.7-1.0	0.08
Attentional bias	- low	5.8 (3.7)			
	- high	6.5 (3.8)	1.12	0.9-1.4	0.27

CBT: Cognitive Behavioural Therapy.

Table 3b. Baseline cognitive functioning related to cocaine use.

Baseline cognitive functioning		Crack-cocaine use days in last 30 treatment days				
		Mean (sd)		Exp(B)[a]	95%-CI	p[a]
		Baseline	Week 12			
Self-reported impulsivity	- low	19.0 (8.3)	6.8 (5.9)			
	- high	18.1 (8.0)	11.8 (9.8)	1.82	1.53-2.17	<0.01
Response inhibition	- good	19.2 (8.0)	8.3 (6.0)			
	- poor	18.4 (8.2)	10.6 (9.3)	1.30	1.08-1.56	0.01
Cognitive interference	- low	19.1 (8.0)	8.2 (6.1)			
	- high	18.2 (8.4)	10.3 (9.9)	1.30	1.09-1.54	<0.01
Attentional bias	- low	17.9 (8.5)	7.9 (7.1)			
	- high	19.4 (7.9)	10.7 (9.2)	1.29	1.09-1.54	<0.01

[a] Poisson regression analyses were performed with baseline crack-cocaine use days as covariate.

Prediction of treatment outcomes by baseline impulsivity and attentional bias

Table 3a shows that patients with low self-reported baseline impulsivity attended significantly more CBT sessions than the high impulsivity patients (7.3 vs. 5.3 sessions, respectively; $p<0.01$, $d=0.54$). The patients with good versus poor baseline response inhibition, patients with low versus high cognitive interference, and those with low versus high baseline attentional bias did not differ in the number of CBT sessions that they attended.

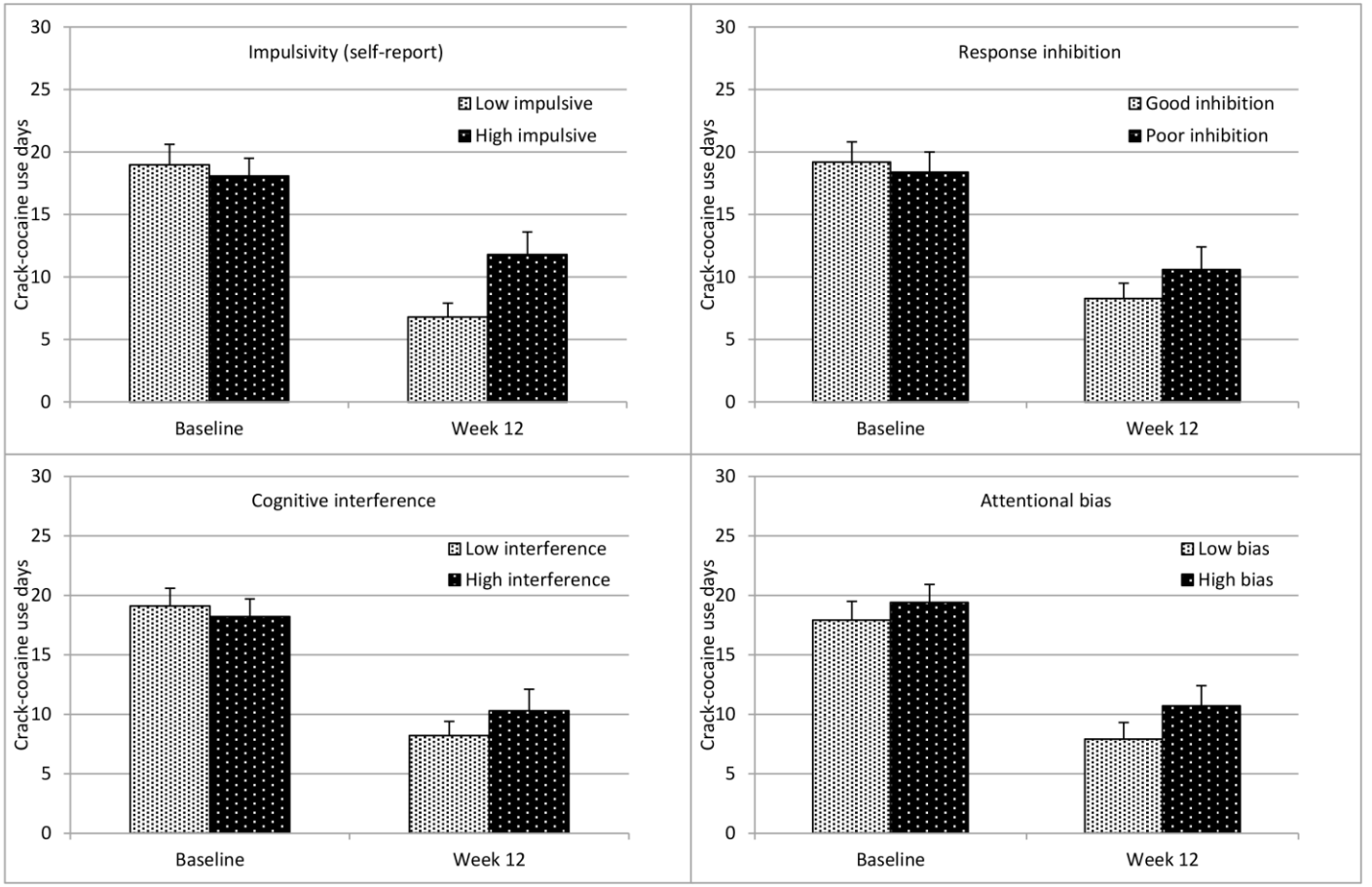
Concerning crack-cocaine use, Table 3b and Figure 2 show that the number of crack-cocaine use days within the last 30 treatment days was significantly lower in the patients with low self-reported baseline impulsivity than in those with high baseline impulsivity (6.8 versus 11.8 days, respectively; $p<0.01$, $d=0.72$), as well as in the patients with good compared with poor baseline response inhibition (8.3 vs. 10.6 days, respectively; $p=0.01$, $d=0.38$) and in patients with low compared with high baseline cognitive interference (8.2 vs. 10.3 days, respectively; $p<0.01$, $d=0.36$). Similarly, patients with low baseline attentional bias used cocaine on fewer days than those with high baseline attentional bias (7.9 vs. 10.7 days, respectively; $p<0.01$, $d=0.15$)

Effects of modafinil on inhibitory control and attentional bias

Table 4 shows that the baseline to week 12 changes in response inhibition and attentional bias in both treatment groups combined did not reach statistical significance, but cognitive interference did significantly decrease over time ($F(1,54)=7.53$; $p=0.01$; $d=0.27$). The changes in cognitive measures over time were not significantly different between the experimental and the control treatment groups, as indicated by the non-significant treatment-by-time interaction terms.

Regarding our additional exploration within the experimental treatment group only, we found that cognitive interference significantly improved over time ($F1,24)=7.28$; $p=0.01$; $d=0.44$), but the baseline to week 12 changes in cognitive performance did not differ between the patients with low and high modafinil adherence (Table 5).

Figure 2. Mean crack-cocaine use days (past 30 days), per level of cognitive performance at baseline and at week 12.



Error bars represent the SEM. SEM: standard error of the mean.

Table 4. Relationship between treatment group and changes in cognitive measures (in ms).

	Experimental group		Control group		Time	Treatment x time
	Baseline	Week 12	Baseline	Week 12		
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)		
Response inhibition	280.6 (57.4)	277.5 (61.0)	265.6 (42.3)	282.1 (65.0)	F=0.48; p=0.49	F=1.02; p=0.32
Cognitive interference	191.3 (216.6)	132.2 (218.7)	149.1 (115.8)	102.0 (145.8)	F=7.53; p=0.01	F=0.10; p=0.76
Attentional bias	48.5 (120.1)	19.6 (74.8)	56.6 (120.1)	11.9 (79.3)	F=3.54; p =0.07	F=0.16; p=0.69

F: F-statistic; ms: milliseconds.

Table 5. Relationship between modafinil adherence and changes in cognitive measures (in ms).

	Low modafinil adherence		n	High modafinil adherence		n	Time	Adherence x time
	Baseline	Week 12		Baseline	Week 12			
	Mean (sd)	Mean (sd)		Mean (sd)	Mean (sd)			
Response inhibition	283.4 (47.6)	277.7 (67.5)	15	275.9 (74.0)	277.2 (52.1)	9	F=0.02; p=0.88	F=0.06; p=0.81
Cognitive interference	182.1 (187.7)	161.9 (197.1)	16	206.0 (266.9)	84.6 (253.1)	10	F=7.28; p=0.01	F=3.71; p=0.07
Attentional bias	52.1 (60.6)	30.8 (53.4)	16	42.7 (184.1)	1.5 (101.1)	10	F=0.97; p=0.34	F=0.10; p=0.76

ms: milliseconds

Relationship between changes in neurocognitive task performance and clinical outcomes

Tables 6a and 6b show the correlations between baseline to week 12 changes in cognitive performance and treatment outcomes. In the total study sample, the correlations between the changes in the various measures of cognitive performance and CBT retention, as well as between changes in cognitive performance and changes in cocaine use, were low and non-significant (r=–0.05–0.16).

Within the experimental treatment group only, the Wald-tests showed that the relationships between the various cognitive measures and treatment outcomes were not significantly different between the low and high modafinil-adherent patients.

Table 6a. Correlations between baseline to week 12 changes in cognitive performance and CBT retention.

Cognitive measure	Total study sample	Within experimental treatment group			
	CBT retention	CBT retention			
	Pearson's r	Low adherence	High adherence	Wald[a] X^2	p-value
		Pearson's r	Pearson's r		
Δ Response inhibition	0.00	–0.00	–0.03	0.06	0.52
Δ Cognitive interference	–0.01	0.12	0.30	0.40	0.66
Δ Attentional bias	0.16	0.27	–0.07	0.75	0.77

[a] Wald X^2 tests were performed between low and high modafinil adherent patients; CBT: cognitive behavioural therapy; delta: change in.

Table 6b. Correlations between baseline to week 12 changes in cognitive performance and changes in cocaine use.

Cognitive measure	Total study sample	Within experimental treatment group			
	Δ Cocaine use	Δ Cocaine use			
	Pearson's r	Low adherence	High adherence	Wald[a] X^2	p-value
		Pearson's r	Pearson's r		
Δ Response inhibition	–0.05	–0.49	–0.51	0.04	0.52
Δ Cognitive interference	0.11	0.04	–0.27	0.68	0.75
Δ Attentional bias	0.08	–0.02	0.21	0.49	0.69

[a] Wald X^2 tests were performed between low and high modafinil adherent patients; delta: change in.

Discussion

In a previous report on this open-label, randomised controlled study among 65 crack-cocaine dependent patients, we showed that 12 weeks of treatment with modafinil in addition to CBT did not improve treatment retention nor cocaine-related outcomes, compared with CBT alone (Nuijten et al., 2015). In the present study, we found that CBT retention was better among the patients with low baseline self-reported impulsivity, and crack-cocaine use in the last 30 treatment days was lower among the patients with low self-reported impulsivity, good response inhibition, low cognitive interference and low attentional bias at baseline. Moreover, cognitive interference decreased during treatment, but this cognitive improvement during treatment was not related to better CBT retention nor to crack-cocaine use reductions. Changes in impulsivity or attentional bias did not differ between the CBT plus modafinil and CBT-only treatment groups, which could be expected given the low modafinil adherence in the trial; and hence, the limited contrast in actually received treatment between the two conditions. Additional analyses within the CBT plus modafinil treatment group to explore the changes in cognitive performance between the low and high modafinil-adherent subgroups did not show an advantage for modafinil intake either.

Our findings that high baseline self-reported and behavioural impulsivity did predict poorer treatment outcomes can be added to the conclusions of two recent reviews indicating that impulsivity is likely to be a robust predictor of treatment outcomes (Loree et al., 2014; Stevens et al., 2014); therefore, our prognostic findings are of clinical relevance.

Regarding our findings on attentional bias, there is less consistency in the literature. Although the predictive value of attentional bias on cocaine use in our study is in line with some previous findings in various substance use disorders (Field and Cox, 2008), to our knowledge only one study in cocaine dependent patients shows that having a better baseline Stroop performance is related to better treatment outcomes (Carpenter et al., 2006). Moreover, in more recent studies, the relationship between attentional bias and relapse is described as equivocal (Carpenter et al., 2006; Christiansen et al., 2015; Field et al., 2014); and thus, given the small effect size pertaining to the predictive value of attentional bias on cocaine use, careful interpretation of our findings is warranted.

Several more fundamental factors also have called into question the prognostic value of attentional bias on treatment outcomes. First, attentional bias is not a stable characteristic, but is susceptible to motivational and affective states, as well as contextual factors (Christiansen et al., 2015; Leeman et al., 2014). To control for possible situational influences on attentional bias, our baseline and week 12 assessments took place approximately at the same time of the day, in the same place and order, and mostly with the same researcher. Recent use of alcohol, drugs, coffee and nicotine prior (i.e. ≤24 hours) to the Stroop task was not related to patients' performance, and neither was cocaine craving (data not shown). Nevertheless, other individual differences, including motivation, were not assessed and might have affected attentional bias.

Secondly, the cognitive process of attentional bias may not have been completely captured by the Stroop task, because it has been questioned whether the Stroop task measures attentional bias specifically, or a broader process of inhibitory control regarding distracting word content (Christiansen et al., 2015). Also, it was recently suggested that attentional bias can be assessed more adequately with visual, rather than manual, responses to drug-related stimuli (Dias et al., 2015; Marks et al., 2014b), given that eye fixation time is a sensitive and reliable method for measuring attention allocation to cocaine-related cues with a high test-retest reliability, in contrast to motor response time (Marks et al., 2014a). In summary, it is widely accepted that attentional bias to cocaine-related cues is present in cocaine dependent patients (Leeman et al., 2014), but its prognostic value as measured with the addiction Stroop task remains to be more firmly established.

Various pharmacological and behavioural treatments have focused on improving the cognitive deficits in patients with substance use disorder (Keshavan et al., 2014; Sofuoglu, 2010; Sofuoglu et al., 2013; Vocci, 2008), based on the assumption that an improvement in cognitive functioning is likely to improve treatment outcomes; however, there are hardly any studies addressing this relationship. In our study, we did not find support for this assumption: From all investigated cognitive measures, only cognitive interference showed a decrease over time (d=0.27), and although crack-cocaine use decreased as well (d=1.08; (Nuijten et al., 2015)), both improvements were not interrelated. Hence, our study suggested that patients had reduced their cocaine use, regardless of the

occurrence of cognitive improvements. Nevertheless, we did find some trend-level indications that suggested that within the experimental group, better modafinil adherence might be associated with more improvements in cognitive interference (Table 5); and if so, this would argue for more intensive measures to improve medication adherence, including compliance enhancement therapy (Weiss, 2004) or contingency management directed at medication adherence (Petry et al., 2012), as well as cocaine abstinence (Prendergast et al., 2006).

Some of the limitations of our study (e.g. low modafinil adherence and a relatively short treatment period) have already been discussed above or in our previous paper about the study (Nuijten et al., 2015). Regarding the study design, we chose an open-label, non-placebo-controlled design in order to avoid selective non-compliance and dropout among control patients, as explained in Nuijten et al. (2015); however, as a consequence, due to the absence of a blinded placebo-controlled condition, the role of placebo or expectancy effects in the responses to clinical outcomes could not be established. A further limitation was that valid cognitive assessments could not be obtained for all patients, resulting in a smaller sample and reduced power.

To our knowledge, this is the first study simultaneously assessing (changes in) cognitive function and clinical outcomes in a pharmacological trial with a cognitive enhancer, modafinil, as an add-on treatment to CBT for crack-cocaine dependence. We have concluded that self-reported impulsivity, response inhibition, cognitive interference and attentional bias may all be valuable predictors of CBT retention and subsequent crack-cocaine use; however, we found no firm indications that modafinil reduces impulsivity nor attentional bias in this population. Future studies involving cognitive-enhancing medications should include multiple strategies to optimise adherence, to be better able to evaluate the potential of such medications.

Chapter 5

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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Abstract

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.

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.

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 (Ferri et al., 2011) and two cohort studies (Blanken et al., 2010b; Rehm et al., 2001). However, many heroin dependent patients are also cocaine dependent, which worsens the prognosis of treatment (Marsden et al., 2009), as is also shown among patients in heroin-assisted treatment, who often show no or only slight reductions in cocaine use (Blanken et al., 2010b). 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 (Dürsteler-MacFarland et al., 2013).

Reviews of substitution treatments for cocaine dependence, including psychostimulants and (other) dopamine agonists (Castells et al., 2010; Herin et al., 2010), 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 (Grabowski et al., 2001; Grabowski et al., 2004a; Shearer et al., 2003).

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.

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 (Nuijten et al., 2011).

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 et al., 2003); (2) met cocaine dependence criteria according to the Diagnostic and Statistical Manual of Mental Disorders IV edition (American Psychiatric Association, 1994) 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.

Patients were excluded in case of (1) severe medical problems (e.g. electrocardiography or blood abnormalities) or severe psychiatric problems (e.g. acute psychosis or suicidality); (2) pregnancy or breastfeeding; (3) pharmacotherapy with a potentially effective drug for cocaine dependence (i.e. 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 (https://www.brijder.nl/study_protocol_sr_dexamfetamine).

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) (Cottler, 2000) and the Mini-International Neuropsychiatric Interview on suicide risk (Sheehan et al., 1998) were undertaken. At all assessments we administered the substance use section of the Addiction Severity Index, supplemented with questions about illegal activities (Hendriks et al., 1989; Van den Brink et al., 2003); the Time Line Follow-Back on self-reported cocaine use (Sobell and Sobell, 1992); the Obsessive Compulsive Drug Use Scale on past week cocaine craving (De Wildt et al., 2005); the Maudsley Addiction Profile Health Symptoms Scale (MAP-HSS) on physical health (Marsden et al., 1998); and the Brief Symptom Inventory (BSI) on mental health (Derogatis and Melisaratos, 1983). 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) (De Wilde and Hendriks, 2005). 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 (i.e. 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 (i.e. [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; i.e. 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) (Nuijten et al., 2011). 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 – i.e. 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 (i.e. 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 – i.e. 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) (Blanken et al., 2010b).

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

Figure 1. Trial profile.

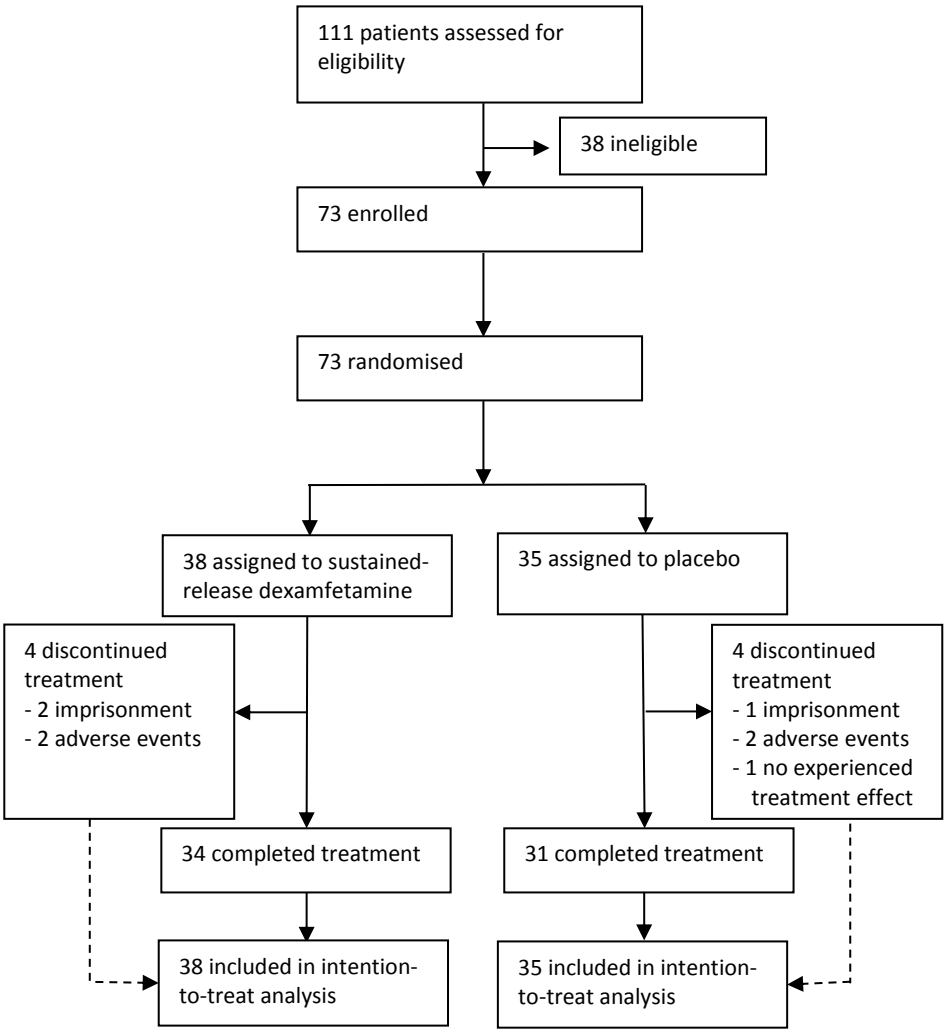

Table 1. Baseline characteristics.

	Sustained-release dexamfetamine group (n=38)	Placebo group (n=35)
Demographic background		
Age (years)	48.4 (6.6)	49.0 (5.3)
Men	35 (92.1%)	31 (88.6%)
European descent	26 (68.4%)	23 (65.7%)
Substance use		
Lifetime regular crack-cocaine use (years)	19.1 (7.7)	19.9 (7.1)
Cocaine-positive baseline urine	38 (100.0%)	34 (97.1%)
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/day) alcohol use (≥1 day, past month)	13 (34.2%)	12 (34.3%)
Cannabis use (≥1 day, past month)	21 (55.3%)	13 (37.1%)
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 (%).

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 1). 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).

Table 2. Primary and secondary cocaine use-related outcomes.

	SR DEX (n=38)	PLAC (n=35)	Exp(B) (95%-CI)	Wald X^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 (28.9%)	2 (5.7%)	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

SR DEX=sustained-release dexamfetamine group; PLAC=placebo group. 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.

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 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 1).

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

		Estimated marginal means*				GEE parameters (baseline – week 12)*		
	Group	Base-line	Week 4	Week 8	Week 12	Time	Group	Group x Time
Cocaine craving (range 0-20)	SR-DEX	8.74	6.00	5.80	5.11	Wald=52.36	Wald=6.52	Wald=4.58
	PLAC	9.80	8.13	7.06	7.29	p<0.001	p=0.011	p=0.205
Illicit (non-prescribed) heroin use (≥1 day past month)	SR-DEX	0.21	0.24	0.19	0.24	Wald=2.76	Wald=1.44	Wald=0.22
	PLAC	0.34	0.34	0.26	0.31	p=0.431	p=0.230	p=0.975
Heavy (≥5 units per day) alcohol use (≥1 day past month)	SR-DEX	0.34	0.24	0.24	0.34	Wald=8.58	Wald=0.68	Wald=5.92
	PLAC	0.34	0.34	0.40	0.40	p=0.035	p=0.411	p=0.115
Cannabis use (≥1 day past month)	SR-DEX	0.55	0.50	0.47	0.49	Wald=2.70	Wald=0.10	Wald=6.30
	PLAC	0.37	0.46	0.49	0.57	p=0.440	p=0.758	p=0.098
Physical health problems†	SR-DEX	0.76	0.62	0.60	0.52	Wald=15.90	Wald=0.91	Wald=3.88
	PLAC	0.57	0.54	0.57	0.46	p=0.001	p=0.340	p=0.275
Mental health problems‡	SR-DEX	0.37	0.33	0.30	0.28	Wald=5.14	Wald=0.09	Wald=0.57
	PLAC	0.43	0.31	0.34	0.31	p=0.162	p=0.764	p=0.904
Illegal activities (≥1 day past month)	SR-DEX	0.13	0.19	0.22	0.13	Wald=4.48	Wald=2.01	Wald=0.69
	PLAC	0.20	0.29	0.33	0.29	p=0.214	p=0.157	p=0.875

SR-DEX=sustained-release dexamfetamine group (n=38); PLAC=placebo group (n=35). 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 x 73] assessments; 2%) were missing completely at random. † Maudsley Addiction Profile ≥8. ‡ Brief Symptom Inventory (≥0.71 [women] or ≥0.56 [men]).

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%) 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.

Table 4. Adverse events reported by at least two patients.

	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).

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.

Table 5. Baseline to week 12 changes in heart rate, blood pressure, and body weight.

	Sustained-release dexamfetamine group (n=36)		Placebo group (n=35)		Group x 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
Body weight (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.

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 (Grabowski et al., 2001; Grabowski et al., 2004a), 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 (Shearer et al., 2003). 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 (Schmitz et al., 2012). 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 (Mooney et al., 2015). 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 (Weiss, 2004). Additionally, increased doses of sustained-release dexamfetamine, such as 60 mg/day, are likely to result in more

robust findings (Grabowski et al., 2004a; Mooney et al., 2015). 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 (Maisel et al., 2013) and many other psychiatric and general medical conditions (Leucht et al., 2012).

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 (Blanken et al., 2010b). 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 overestimated 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 (Weiss, 2004) or contingency management directed at treatment attendance and cocaine-free urines (Petry et al., 2012; Prendergast et al., 2006). 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 (Grabowski et al., 2001; Grabowski et al., 2004a; Schmitz et al., 2012), 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 (Weiss, 2004), combined with providing relevant incentives for both treatment attendance and cocaine abstinence (Schierenberg et al., 2012) 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 (Galloway et al., 2011). 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.

Chapter 6

Summary and general discussion

Summary

Introduction

Compulsive cocaine use, particularly crack-cocaine (i.e. smoking or 'basing' cocaine), is associated with a great burden for both the user and society, including physical and mental health problems and social marginalisation. In Dutch addiction care, about half of the cocaine-related treatment demand concerns crack-cocaine use, and the majority of these patients have relatively long and recurrent treatment episodes, as well as concurrent use of other substances, including heroin and alcohol. The efficacy of cognitive behavioural therapy for (crack-)cocaine dependence, which is the most common psychosocial treatment in addiction care, is modest at best and there are no proven effective pharmacological treatments to date, despite numerous research attempts. Hence, crack-cocaine dependence is a serious and complex problem with as yet no adequate treatment.

The CATCH project (Cocaine Addiction Treatments to improve Control and reduce Harm) was initiated to explore new pharmacological treatment options for crack-cocaine dependence in the Netherlands. In three separate parallel-group, randomised controlled, feasibility trials, three promising medications were investigated for their acceptance, efficacy, and safety in the treatment of crack-cocaine dependence: (1) topiramate 200 mg/day, (2) modafinil 400 mg/day, and (3) sustained-release (SR) dexamfetamine 60 mg/day. The aim was to identify one or more candidate medications for future investigation in a large-scale confirmatory trial. The selection of these medications and the design of the studies are presented in **Chapter 1**.

Topiramate pharmacotherapy

Topiramate is an anticonvulsant with gamma-aminobutyric acid (GABA) enhancing and glutamatergic antagonizing properties, which modulates the reward system. In cocaine dependence, topiramate had been shown to promote (sustained) cocaine abstinence and to reduce cocaine craving in two studies that were conducted before the start of the CATCH project, and was thus considered to be a promising pharmacotherapy.

Therefore, in the first trial of the CATCH project, topiramate was studied as an add-on to cognitive behavioural therapy (CBT) in crack-cocaine dependent

patients (**Chapter 2**). Seventy-four crack-cocaine dependent outpatients participated in an open-label, randomised, feasibility trial. They were randomised to receive either 12-week CBT plus 200 mg/day topiramate (n=36) or 12-week CBT only (n=38). The primary outcome measure was CBT treatment retention. Secondary outcomes included medication adherence, safety, cocaine and other substance use, cocaine craving, health, social functioning, and patient satisfaction.

Adherence to topiramate treatment was low with only 14% of the patients who completed the 12-week topiramate treatment, and reasons for non-adherence remained largely unknown. In the intent-to-treat analyses, topiramate neither improved treatment retention nor reduced cocaine and other substance use. Post hoc, exploratory analyses suggested a moderation effect of comorbid opioid dependence, with a significant favourable effect of topiramate on cocaine use only in crack-cocaine dependent patients with comorbid opioid dependence. An explorative comparison between patients with low (<6 weeks) and high (≥6 weeks) topiramate adherence did not show differences in the reduction of crack-cocaine use. Finally, topiramate was related to adverse events, mostly paraesthesia, gastro-intestinal complaints and fatigue, which were generally mild and transient. There were no serious adverse events.

It was concluded that topiramate was safe and well-tolerated in this sample of crack-cocaine dependent patients, but efficacy was not supported, probably due to low acceptance of the treatment.

Modafinil pharmacotherapy

Clinical outcomes

Modafinil is a wakefulness-promoting agent that possesses stimulant effects, mainly as a consequence of dopamine reuptake inhibition, which is suggested to normalise brain chemistry in dependent people and to reduce substance use. Before the start of the CATCH project, promising effects of modafinil were reported in terms of reductions of cocaine use and craving. In **Chapter 3**, the acceptance, efficacy and safety of 400 mg/day modafinil as an add-on treatment to cognitive behavioural therapy (CBT) in crack-cocaine dependent patients were examined.

Sixty-five crack-cocaine dependent outpatients participated in an open-label, randomised, feasibility trial. Patients were randomised to receive either 12-week

individual CBT plus 400 mg/day modafinil (n=30) or 12-week individual CBT only (n=35). The primary outcome measure was CBT treatment retention. Secondary outcomes included modafinil adherence, tolerability and safety, use of cocaine and other substances, cocaine craving, health, social functioning and patient satisfaction.

Modafinil adherence was low, with only 10% treatment completers. In 20% of the modafinil-treated patients, discontinuation of modafinil treatment was related to adverse events. Intent-to-treat analyses showed that modafinil did not improve CBT treatment retention or any of the secondary cocaine-related outcomes. Both groups showed similar, large reductions in cocaine use during the study treatment. Post hoc exploratory analyses within the CBT plus modafinil group showed significantly larger baseline to week 12 reductions in cocaine use days in patients with at least 8 weeks of modafinil adherence, compared with patients using modafinil for less than 8 weeks. Satisfaction with the treatment offer did not differ between the CBT plus modafinil and CBT only groups. Most adverse events occurred in the CBT plus modafinil group and tachycardia, agitation and headache were the most frequently reported adverse events. There were two serious adverse events, but they were not related to modafinil.

To conclude, acceptance and benefits of modafinil were not demonstrated in the present study, most likely due to low adherence. However, in a post hoc analysis, substantial cocaine use reductions were found in the high modafinil-adherent subgroup.

Cognitive functioning

High impulsivity and attentional bias are common in cocaine dependent patients and have been shown to predict poor treatment outcomes in earlier studies. Modafinil has been shown to improve cognitive functions and this may mediate improvements in clinical outcomes in crack-cocaine dependent patients. In **Chapter 4**, we investigated: (1) whether pre-treatment impulsivity and attentional bias predicted treatment outcome; (2) whether modafinil as an add-on treatment to cognitive behavioural therapy (CBT) improved impulsivity and attentional bias; and (3) whether changes in impulsivity and attentional bias were related to improvements in treatment outcome.

This study was an extension of the main modafinil trial and the study population thus consisted of the same 65 crack-cocaine dependent outpatients, who were randomised to either 12-week CBT plus modafinil or 12-week CBT only. Self-reported impulsivity was assessed at baseline using the Barratt Impulsiveness Scale (BIS-11). At baseline and week 12, we assessed inhibitory control as a behavioural measure of impulsivity, in terms of cognitive interference (Stroop task) and response inhibition ('stop-signal task'), and attentional bias with the addiction Stroop task. Clinical outcomes were CBT retention and crack-cocaine use.

At baseline, low self-reported impulsivity predicted better CBT retention, whereas low self-reported and behavioural impulsivity and attentional bias predicted less crack-cocaine use at week 12. Cognitive performance improved during treatment, but the improvements were not modafinil-related and this was most likely due to low modafinil adherence. Post hoc comparisons within the modafinil treatment group suggested the presence of improved cognitive interference in high modafinil adherent (≥8 weeks) compared to low modafinil adherent (<8 weeks) patients. However, improvements in impulsivity or attentional bias were not associated with CBT retention or with changes in crack-cocaine use.

It was concluded that baseline impulsivity and attentional bias predict CBT retention and clinical outcomes in crack-cocaine dependent patients, but modafinil did not seem to reduce impulsivity or attentional bias in this population. Future studies involving cognitive-enhancing medications should include strategies to optimise adherence, to be better able to evaluate their potential for improving cognitive functioning and reducing cocaine use.

Dexamfetamine pharmacotherapy

Heroin-assisted treatment is effective for methadone treatment-refractory heroin dependent patients, but their continued comorbid cocaine dependence remains problematic. Sustained-release (SR) dexamfetamine is a promising agonist pharmacotherapy for the treatment of (comorbid) cocaine dependence. In **Chapter 5**, the acceptance, efficacy and safety of a robust dose of 60 mg/day SR dexamfetamine were investigated. As was described in Chapter 1, this trial was

different from the previous two trials and consisted of a multicentre, randomised, double-blind, placebo-controlled design.

Seventy-three chronic crack-cocaine and heroin dependent patients in heroin-assisted treatment were randomly assigned to receive either 12 weeks of daily supervised 60 mg oral SR dexamfetamine (n=38) or 12 weeks of daily supervised identical placebo (n=35) in addition to daily co-prescribed pharmaceutical heroin and methadone. The primary outcome measure was the number of self-reported days of cocaine use during study treatment. Secondary outcomes were medication adherence, tolerability and safety, self-reported and urine-based cocaine use-related outcomes (e.g. longest period of consecutive abstinence), cocaine craving, physical and mental health, social functioning, and patient satisfaction.

Medication adherence was high (92%) with no differences between the dexamfetamine and placebo groups. Study blinding was successful, given that in the dexamfetamine group only 54% of the patients correctly identified their medication compared with only 60% in the placebo group.

SR dexamfetamine treatment resulted in significantly fewer days of cocaine use, a longer period of consecutive cocaine abstinence, a higher proportion of participants who achieved a period of at least 21 days of abstinence, and a higher proportion of cocaine-negative urines than placebo treatment. In addition, on days that patients used crack-cocaine, their mean number of cocaine hits decreased, with larger reductions in the dexamfetamine group than in the placebo group. SR dexamfetamine was not superior to placebo on other secondary outcomes.

One or more adverse events were reported by 74% of the patients in the dexamfetamine group and by 46% of the patients in the placebo group. Most adverse events were transient and well-tolerated. One serious adverse event occurred in the placebo group.

It was concluded that SR dexamfetamine is a well-accepted, effective, and safe agonist treatment for comorbid treatment-refractory cocaine dependence in heroin dependent patients in heroin-assisted treatment.

Results in an updated context

Since the start of the CATCH project, several other studies on the effects of pharmacological treatment with topiramate, modafinil and SR dexamfetamine in crack-cocaine dependent patients have been conducted. In this section, our conclusions regarding these treatments will be positioned within the context of more recent findings.

Topiramate

In our first trial, topiramate was not efficacious in the treatment of cocaine dependence, and findings from other studies that were published prior and during the execution of our trial were equivocal. Therefore, we concluded in Chapter 2 that the evidence for topiramate's efficacy was inconsistent and limited at best.

Since then, two additional 12-week randomised controlled trials (RCTs) were conducted, again with inconsistent results. Umbricht and colleagues (2014) investigated the efficacy of 15 weeks 300 mg/day topiramate versus placebo with and without contingency management in 171 American cocaine dependent patients in methadone maintenance treatment. They found that treatment retention was 72% and did not differ between patients receiving topiramate and those receiving placebo. In addition, topiramate was not different from placebo in reducing cocaine use. They therefore concluded that topiramate is not efficacious for increasing cocaine abstinence in methadone patients (Umbricht et al., 2014). In contrast, in the most recent placebo-controlled RCT on 200 mg/day topiramate treatment in 60 Brazilian crack-cocaine dependent men without comorbid substance or psychiatric disorders, clear efficacy of topiramate was demonstrated (Baldaçara et al., 2016). Treatment compliance was excellent (97%), significantly more topiramate-treated patients achieved cocaine-abstinence during treatment, and the quantity and frequency of cocaine use was significantly lower in the topiramate compared with the placebo group (Baldaçara et al., 2016).

Despite this recent positive study, the overall evaluation of topiramate's efficacy in the treatment of cocaine dependence still tends to be negative. In line with our conclusions, a Cochrane review on anticonvulsants (Minozzi et al., 2015b) and a systematic review and meta-analysis specifically on topiramate (Singh et al., 2016) both concluded that there is no current evidence for the efficacy of topiramate, but it has to be mentioned that the study of Baldaçara

(2016) was not included. However, even though the outcomes of this latter trial indicate that there might be potential for topiramate, it remains unclear which factors are important contributors to this positive evaluation of topiramate, and to date, no clear explanations have been found for the inconsistency of the findings. Therefore, we still conclude that, to date, the evidence for topiramate's efficacy in the treatment of cocaine dependent patients is insufficient.

Modafinil

Concerning modafinil, we concluded in Chapter 3 that our negative study findings were in line with two randomised controlled trials of Schmitz et al. (2014; 2012). In addition, we concluded that the positive results of modafinil in the treatment of cocaine dependence found by Dackis et al. (2005) had never been replicated so far, because positive modafinil-related results from subsequent trials were only observed in secondary outcomes or in post hoc defined subgroups (Anderson et al., 2009; Dackis et al., 2012). Nevertheless, we emphasised that further research on the potential of modafinil treatment in cocaine dependence was warranted, given the positive indications of modafinil-related cocaine use reductions in high adherent patients in our study.

Two additional randomised placebo-controlled studies on the efficacy of modafinil in the treatment of cocaine dependence were published since the execution of our trial and both studies reported positive results on cocaine-related outcomes. In a recent trial by Kampman et al. (2015), 8 weeks treatment with modafinil (300 mg/day) showed good compliance (75%) and resulted in significantly higher cocaine abstinence rates than placebo among cocaine dependent patients without comorbid alcohol dependence. In another recent trial in cocaine dependent patients, 6 weeks treatment with modafinil (400 mg/day) showed excellent retention (95%) and resulted in significantly higher abstinence rates in the modafinil compared to the placebo group (Morgan et al., 2016). In both trials, the simultaneous use of contingency management may have been responsible for the high medication adherence. These recent studies are the first studies after the trial of Dackis et al. (2005) that convincingly demonstrated efficacy of modafinil in cocaine dependence. Altogether, we conclude that modafinil might be efficacious in the treatment of cocaine dependence if good medication adherence can be achieved.

SR dexamfetamine

Regarding SR dexamfetamine in the treatment of cocaine dependence, both positive and negative results have been reported in previous research and in Chapter 5 we concluded that, taken together, our study most convincingly showed the benefits of SR dexamfetamine in cocaine use reductions, albeit in a specific study population. We also concluded that "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".

Only one trial with an amphetamine-analogue comparable to SR dexamfetamine has been published in cocaine dependent patients since our SR dexamfetamine study was conducted and the results of this study were thus not included in the discussion of Chapter 5. In a randomised placebo-controlled trial among patients with cocaine dependence and co-occurring attention-deficit/ hyperactivity disorder (ADHD), 12 weeks treatment with extended-release mixed amphetamine salts (MAS-ER; 60 or 80 mg/day) was significantly more effective than placebo in the reduction of cocaine use and in the reduction of ADHD symptoms (Levin et al., 2015). In the most recent Cochrane review on the effectiveness of psychostimulants in the treatment of cocaine dependence, dexamfetamine was (again) identified as a promising agonist treatment, particularly in patients with dual heroin and cocaine dependence (Castells et al., 2016). Therefore, we see no reasons to deviate from our positive conclusion about SR dexamfetamine in Chapter 5.

Overall

In sum, findings from the CATCH project concerning the pharmacotherapeutic potential of topiramate, modafinil and SR dexamfetamine, are in line with findings from other studies, which show great promise for agonist therapy with SR dexamfetamine, some promise for modafinil, but no convincing evidence for topiramate in the treatment of patients with (crack-) cocaine dependence.

Medication adherence

In all three CATCH trials, patients' willingness to participate in pharmacotherapy was assessed during the eligibility phase, either before study inclusion (dexamfetamine trial) or before providing second informed consent pertaining to pharmacological treatment participation (topiramate and modafinil trial). In the topiramate and modafinil trials, the vast majority (i.e. 82% and 94%, respectively) gave second consent. Notwithstanding their initial willingness, however, medication adherence was low in these two trials and most patients prematurely discontinued treatment. In the modafinil trial, some patients indicated that medication-related adverse events contributed to their non-adherence, but in general reasons for non-adherence remained unknown.

Medication non-adherence and treatment discontinuation are well-known problems in medication research (Servick, 2014) and in the treatment of chronic diseases, with average adherence rates in developed countries reaching about 50% only (World Health Organization, 2003). For example, in physical illnesses, medication non-adherence rates vary from 30% in diabetes (Iglay et al., 2015) to 50% in hypertension (Krousel-Wood et al., 2004) and in mental illnesses, non-adherence rates were estimated to be more than 40% in psychosis and ADHD (Colizzi et al., 2016; Frank et al., 2015) and 50% in depression (Sansone and Sansone, 2012). In addiction care, it was demonstrated that one third to half of the alcohol dependent patients prematurely discontinue their medications (Blodgett et al., 2014; Stout et al., 2014). Non-adherence rates in our topiramate and modafinil trials were even higher, 86% and 90%, respectively (Nuijten et al., 2014, 2015), which is comparable to the high non-adherence (>80%) to oral naltrexone in patients with opiate dependence (Bart, 2012). In contrast, non-adherence rates are relatively low in various agonist replacement therapies: less than 40% in methadone maintenance or buprenorphine treatment (Bart, 2012), around 20% in heroin-assisted treatment (Blanken et al., 2010b), and even less than 10% in our dexamfetamine trial (Nuijten et al., 2016a).

Poor adherence to long-term therapies severely compromises the potential effectiveness of treatment, resulting in poor treatment outcomes, decreased quality of life and increased health care costs (World Health Organization, 2003). In clinical trials, adherence is essential, given that the real potential of medication,

as well as the implication of its side effects, can only be demonstrated when medication intake is optimal (Servick, 2014).
Reasons for non-adherence in our trials were mostly not clear, but from a review on medication adherence, examples of major predictors of low adherence are side effects of medication, disbelief in the benefit of treatment, missed appointments, and complexity of treatment (Osterberg and Blaschke, 2005). Also, insufficient benefits from pharmacotherapy, which might be reflected in continued or increased substance use, can contribute to non-adherence (Stout et al., 2014), as well as inappropriate dosing (Faggiano et al., 2003; Salamina et al., 2010).

Strategies to optimize medication adherence include enhancing motivation, providing information, monitoring of adverse events and dosing, involving patients in treatment decisions when possible, sending reminders, and providing social support (Brown and Bussell, 2011; Corneli et al., 2015; Hollands et al., 2015; Weiss, 2004). Obviously, a good doctor-patient relationship with effective communication between the two is essential to improve adherence (Brown and Bussell, 2011; Weiss, 2004; World Health Organization, 2003). Administration of extended-release formulations can also improve compliance, as has been demonstrated in opiate dependence treatment with extended-release naltrexone provided as intramuscular injections lasting about four weeks or subcutaneous implants lasting three to six months (Kunøe et al., 2014; Larney et al., 2014), and with subcutaneous buprenorphine implants lasting six months (Ling et al., 2010; Rosenthal et al., 2013; Rosenthal et al., 2016).

Medication management interventions can also be helpful to support and optimise the use of medications in the treatment of patients with substance use disorders (Weiss, 2004). An example in the addiction field is the BRENDA-approach, which is a motivation and treatment-compliance enhancing support strategy with the following elements: Biopsychosocial evaluation; Report to the patient; Empathy; Needs collaboratively identified; Direct advice; and Assessment of outcomes (Volpicelli et al., 2001). BRENDA facilitates both therapeutic alliance and treatment compliance and, thus, improves clinical outcomes (Starosta et al., 2006). Another strategy is behavioural reinforcement or contingency management using incentive- or voucher-based interventions to improve medication adherence (DeFulio and Silverman, 2012; Petry et al., 2012).

Finally, the measurement of medication adherence deserves attention since there are large differences in medication adherence rates depending on measurement method, ranging from approximately 30% with a medication event monitor to 80% with a urine-based biochemical tracer (e.g. riboflavin) and nearly 90% with self-report (Mooney et al., 2004). This suggests that medication adherence can be overestimated and medication event monitoring should be used additionally to other methods for measuring adherence (El Alili et al., 2016; Mooney et al., 2004).

In sum, medication adherence is an overall problem in chronic disease management, including that of patients with substance use disorders, but with agonist treatment, particularly for opiates, being an important exception. However, even in some of the dexamfetamine trials in cocaine dependent patients, medication adherence and treatment retention were low (Grabowski et al., 2001; Grabowski et al., 2004a; Schmitz et al., 2012). Therefore, medication management and contingency management interventions should be implemented to promote adherence. Finally, medication adherence has to be carefully monitored in order to accurately assess actual adherence.

Agonist treatment

Substitution treatment with the agonist SR dexamfetamine clearly showed the most positive effects on cocaine use in our trials. This finding is in accordance with the increasing evidence that agonist therapy might be the most promising strategy in cocaine dependence (Mariani and Levin, 2012). The goal of (supervised) agonist therapy is to replace uncontrolled and harmful substance use by the use of an agonist medication, that can be used more safely in terms of dose, route of administration, and adverse effects, resulting in reduced intoxication, withdrawal, and illicit substance use (Herin et al., 2010; Mariani and Levin, 2012; Shearer, 2008). Given that abstinence is not always an acceptable or feasible treatment goal for chronic crack-cocaine users, it might be more appropriate to reduce cocaine use-related harms by the use of (partial) substitution of cocaine by an agent with similar neurotransmitter targets (i.e. dopaminergic, serotonergic and noradrenergic receptors) and comparable – but less harmful – neurochemical and behavioural effects (Herin et al., 2010). This approach fits into the more general strategy of harm reduction, in which recovery

in other life domains, such as health and social functioning, is more important than reducing or quitting substance use per se (Marlatt, 1996).

There are numerous positive results of harm reduction strategies using substitution pharmacotherapy, albeit not (yet) in crack-cocaine dependence. For instance, an average of four years of heroin-assisted treatment was associated with stable physical, mental and social health and with absence of illicit heroin use (Blanken et al., 2010a); prescribed heroin along with methadone was associated with a decrease in the use of illicit substances, a decrease in criminal activities and incarcerations, a possible reduction in mortality, and an increase in treatment retention (Ferri et al., 2011). In addition, a treatment regimen targeted at maintenance and harm reduction with emphasis on retaining low adherent patients was found to be one of the main predictors of the effectiveness of opioid substitution therapy (Kourounis et al., 2016).

Potentially effective agonist substitution therapy for cocaine dependence concerns a wide range of agents. They share some of their effects with cocaine, mostly by increasing extracellular dopamine levels, but they have different pharmacological profiles in terms of both their mechanism of action and their neurotransmitter targets. It is important to understand why some of the dopamine agonists seem to be more effective in treating cocaine dependence than others.

The efficacy of dopamine agonists might be related to the presence of a psychostimulant working mechanism. In a Cochrane review, direct dopamine agonists without psychostimulant characteristics (i.e. amantadine, bromocriptine, levodopa/carbidopa, pergolide, cabergoline, hydergine and pramipexole) were not effective in the treatment of cocaine dependence (Minozzi et al., 2015a). In contrast, indirect dopamine agonists that function as cocaine-like drugs, particularly bupropion and dexamfetamine, were identified as promising agonist substitution treatments for cocaine dependence (Castells et al., 2016). These reviews thus suggest that only indirect dopamine agonists with psychostimulant properties produce positive outcomes.

However, not all indirect agonists (psychostimulants) seem to be equally effective. Some authors argue that amphetamine-analogues like methamphetamine and dexamfetamine, which cause a direct release of monoamines, in particular dopamine and norepinephrine (dela Peña et al., 2015),

are more effective than monoamine/dopamine reuptake inhibitors like modafinil, methylphenidate, and bupropion (Stoops and Rush, 2013). Sustained-release methamphetamine, which causes a massive release of multiple neurotransmitters, including dopamine and norepinephrine (Herin et al., 2010), was convincingly superior to placebo in reducing cocaine use (Mooney et al., 2009), and several trials have now provided support for the efficacy of dexamfetamine in the treatment of cocaine dependence, albeit mostly among patients with comorbid ADHD (Levin et al., 2015) or comorbid heroin dependence in opioid maintenance treatment (Grabowski et al., 2004a; Nuijten et al., 2016a). Moreover, dosing seems to be related to efficacy, with a tendency of higher dexamfetamine doses (e.g. ≥60 mg/day) being more effective than lower doses (e.g. 30 mg/day) (Grabowski et al., 2001; Grabowski et al., 2004a; Levin et al., 2015). Hence, the efficacy of amphetamine-analogues might be restricted to certain subpopulations and/or adequate dosing.

The positive results of modafinil that we referred to in a previous section (Kampman et al., 2015; Morgan et al., 2016), suggest that not only monoamine releasers but also (certain) dopamine reuptake inhibitors may be effective in the treatment of cocaine dependence. This also applies to the norepinephrine-dopamine reuptake inhibitor bupropion, an antidepressant and anti-smoking medication (Castells et al., 2016). Methylphenidate, another dopamine reuptake inhibitor, showed inconsistent findings in a review of Dürsteler and colleagues (2015), with generally positive results in open-label studies and case-reports, but negative results in randomised controlled trials (Dürsteler et al., 2015). As with dexamfetamine, methylphenidate's efficacy may be dependent on dosing or restricted to subpopulations. In the trials reviewed by Dürsteler et al. (2015), doses did not exceed 90 mg/day, but in a trial among amphetamine dependent patients with comorbid ADHD doses up to 180 mg/day showed better treatment outcomes than placebo (Konstenius et al., 2014). Dopamine agonists may also reduce cocaine use through their positive effect on cognitive functions due to increases in dopamine levels in other regions than the reward system, such as the prefrontal cortex (e.g. Sofuoglu et al., 2013; Volkow et al., 2010; Wood et al., 2014). However, the evidence for this mechanism of action is currently still limited.

Finally, despite the promising status of agonist treatment for cocaine dependence, there are also concerns about its use, including the lack of specific receptors to target, the cardiovascular and psychosis inducing risk (Darke and Farrell, 2015), and the risk for abuse (Mariani and Levin, 2012). Indeed, when psychostimulants are used in substitution treatment in cocaine dependent patients, this has to be done with caution. To determine the most appropriate agonist medication, severity of cocaine use should be taken into account, for instance a dopamine reuptake inhibitor such as modafinil to patients with low-to-moderate cocaine dependence, and a dopamine releaser such as dexamfetamine to highly severe cocaine dependent patients (Herin et al., 2010). In addition, risks can be reduced by establishing a good therapeutic relationship, the use of sustained-release preparations, distribution of small amounts of medication, pill counts, regular health check-ups, frequent patient visits, and supervised intake (Mariani and Levin, 2012). At the same time, however, despite the potential health risks of agonist substitution therapy, one has to realise that ongoing compulsive (crack-)cocaine use, with its illegal status and its unknown purity and adulterants, is likely to be more harmful than agonist medication.

To summarize, with regard to agonist substitution treatment for cocaine dependence, indirect dopamine agonists with psychostimulant effects seem to be most effective, with most of the evidence pointing to amphetamine-analogues. However, so far there are too many unknown associations with dosing, comorbidity and cognitive performance to determine which agonists are most effective. Hence, both mechanistic and efficacy studies are needed to identify the most effective agonist treatment(s) in cocaine dependence. This will be discussed in more detail in the next paragraph.

Conclusions & future directions

The aim of the CATCH project was to investigate the feasibility, efficacy and safety of topiramate, modafinil, and SR dexamfetamine in the treatment of crack-cocaine dependent patients. Based on our findings and previous research, we conclude that topiramate should not be recommended as a medication for the treatment of crack-cocaine dependence, whereas the potential efficacy of modafinil needs to be further explored. Agonist therapy with SR dexamfetamine currently seems to be the best option for patients with chronic crack-cocaine

dependence. This implies that the focus of treatment is moved from abstinence to harm reduction, in which recovery and improvement of quality of life are at least as important as abstinence from cocaine.

Given the diversity of agonist agents, each with a specific pharmacological profile, future research should be aimed at finding the most efficacious agonist treatment for cocaine dependence, taking into account target populations, dosing strategies, effects on cognitive functions and side effects. Mechanistic studies should be conducted in order to further understand the neurobiological and neurocognitive processes involved in cocaine dependence and its treatment. Imaging techniques can contribute to the identification of new receptor targets and to the development of individualised treatment strategies (Ghitza et al., 2010; Gould et al., 2014; Gould et al., 2013; Hu et al., 2015). This might also result in the discovery of new, promising agonists, such as atypical dopamine transporter (DAT) inhibitors (e.g. CTDP-32 476 (Xi et al., 2016)) or long-acting dopamine uptake inhibitors (Velazquez-Sanchez et al., 2013) that are associated with inhibited cocaine self-administration in rats. In addition, the agonistic compounds that are currently investigated in humans should be further explored with respect to their neurotransmitter targets (Crunelle et al., 2013), cognitive effects (Moeller et al., 2014), and mechanisms of action (Konova et al., 2013). Given that certain psychostimulants enhance cognitive functioning (e.g. improve inhibitory control), most likely by increasing cortical excitability (Bisagno et al., 2016), mechanisms of actions of cognitive enhancers, as well as their specific effects in relation to clinical outcomes are important targets for future studies (Nuijten et al., 2016b; Sofuoglu et al., 2013).

Efficacy studies should be performed in which agonist treatments with different mechanisms of action are studied in placebo-controlled head-to-head comparisons, e.g. placebo versus dexamfetamine and versus modafinil or versus methylphenidate. Moreover, the superiority of specific agonist treatments within different target populations, such as in cocaine versus other stimulant dependent patients, with and without ADHD or comorbid heroin dependence, should be investigated. Different dose levels and treatments of longer duration than investigated in our trials (i.e. >12 weeks) should be considered, with a proper balance between desirable and adverse effects.

Apart from agonist pharmacotherapy as 'stand-alone' treatment, combined agonist therapy and psychological treatment deserves attention in future research. Although dexamfetamine was superior to placebo in reducing cocaine use in our study, patients in the dexamfetamine group still used cocaine on more than half of the study treatment days and in the last month of treatment the percentage of cocaine-negative urine samples was rather low (11%). Additional psychological treatments, in which patients learn to adequately cope with their addiction and related problems may enhance the efficacy of agonist treatment. Cognitive behavioural treatment (CBT) is a treatment targeted at improving coping and social skills, but as described in Chapter 1, CBT is associated with rather low retention rates in cocaine dependent patients (Dutra et al., 2008; Shearer, 2007). To improve retention, contingency management (CM) interventions might be most useful. CM as an add-on to CBT has been shown to improve treatment retention (Fitzsimons et al., 2015; Miguel et al., 2016; Schierenberg et al., 2012), and enhance cocaine abstinence, both factors that are likely to result in a greater impact of CBT treatment (Petitjean et al., 2014; Schierenberg et al., 2012; Vocci and Montoya, 2009). Also, when post-treatment effects of CM are waning, sustained effects of CBT might still be present (Carroll and Onken, 2005).

When treatment is aimed at harm reduction instead of abstinence, this will require adaptation of treatment goals and reinforcement procedures in CM. For instance, vouchers might be earned when benzoylecgonine (BE) concentrations, indicating the presence of cocaine-metabolites, are reduced in subsequent urine samples until predefined stabilised levels are achieved, or when urine samples are BE-negative on pre-specified days of the week. To date, the literature on this topic is scarce, but one randomised controlled study described the differences between CM for cocaine-abstinence compared with CM for shaping cocaine abstinence (Preston et al., 2001). The authors found that reinforcement of behaviour that patients will readily engage in (i.e. BE-concentrations ≤25% compared with previous urine sample) increased compliance with behaviours that patients will not readily engage in (i.e. complete abstinence).

In the context of combined agonist pharmacotherapy and psychological treatment, it is also worthwhile to investigate cognitive outcomes, and the relation between these cognitive outcomes and reductions in cocaine use and

improvements in quality of life. Previous research showed improvements in various executive functions after sustained (≥2 weeks) cocaine-abstinence (Schulte et al., 2014), and small but consistent cognitive improvements in attention, working memory, declarative memory and executive functions were related to reduced cocaine use within one year (Vonmoos et al., 2014). In addition, improved cognitive functioning was found to be related to better treatment retention (Aharonovich et al., 2008) and to better learning, practicing, and implementation of new cognitive skills (Sofuoglu et al., 2013).

To conclude, our study on new pharmacological treatment options for cocaine dependent patients is an important contribution to the addiction research field, with negative findings pertaining to the efficacy of topiramate, ambiguous findings for modafinil, and promising findings for agonist substitution treatment with SR dexamfetamine. The latter finding is a major step towards an effective pharmacotherapy for cocaine dependence and an encouragement for future research, that should be focused on extending the results to other chronic cocaine/ stimulant dependent patients, and on improving and maintaining the effects of dopamine agonist therapy in the treatment of cocaine dependence.

Nederlandse samenvatting
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Nederlandse samenvatting

Introductie

Compulsief cocaïnegebruik, met name van crack-cocaïne (de rookbare variant van cocaïne, ook wel 'basecoke' genoemd) gaat gepaard met een grote belasting voor zowel de gebruiker zelf als voor de samenleving, zoals op het gebied van lichamelijke en psychische gezondheidsproblemen en sociale marginalisatie. In de Nederlandse verslavingszorg heeft ongeveer de helft van alle cocaïnegerelateerde hulpvragen betrekking op het gebruik van crack-cocaïne, en de meerderheid van de cocaïneafhankelijke patiënten heeft een relatief lange behandelduur en keert regelmatig terug in zorg. Ook gebruiken zij vaak andere middelen naast cocaïne, zoals heroïne en alcohol.

Het meest gebruikelijke behandelaanbod in de verslavingszorg is een psychosociale behandeling, vaak in de vorm van cognitieve gedragstherapie, maar de effectiviteit hiervan is bij (crack-) cocaïneafhankelijkheid gering en er zijn tot op heden geen bewezen effectieve farmacologische behandelingen, ondanks de vele onderzoeken die reeds gedaan zijn op dit vlak. Kortom, crack-cocaïneafhankelijkheid is een serieus en complex probleem waarvoor geen adequate behandeling beschikbaar is.

De CATCH-studie (CATCH is een acroniem voor "*Cocaine Addiction Treatments to improve Control and reduce Harm*") werd geïnitieerd om nieuwe farmacologische behandelmogelijkheden te onderzoeken voor de behandeling van crack-cocaïne afhankelijkheid in Nederland. In drie aparte, gerandomiseerde, gecontroleerde haalbaarheidsstudies met parallelle groepen werden drie veelbelovende medicamenten onderzocht op acceptatie, effectiviteit en veiligheid bij de behandeling van crack-cocaïneafhankelijkheid: (1) topiramaat, (2) modafinil, en (3) vertraagde afgifte dexamfetamine. Het doel van het onderzoek was om uit deze drie medicamenten een of meer kandidaten te selecteren om in toekomstig onderzoek in een grotere studie verder te bestuderen. De selectie van deze medicamenten en het ontwerp van de onderzoeken worden beschreven in **Hoofdstuk 1**.

Farmacotherapie met topiramaat

Topiramaat is een anti-epilepticum met gamma-aminoboterzuur (GABA) versterkende en glutamaat tegenwerkende eigenschappen, wat van invloed is op

het beloningssysteem. Twee eerdere onderzoeken die voorafgaand aan de CATCH-studie werden uitgevoerd onder cocaïneafhankelijke patiënten, toonden aan dat topiramaat bijdroeg aan (langdurende) cocaïne-abstinentie en hunkering naar cocaïne verminderde, waardoor topiramaat als een veelbelovend medicament werd beschouwd.

Tegen deze achtergrond werd in het eerste deelonderzoek van de CATCH-studie topiramaat bestudeerd als aanvulling op cognitieve gedragstherapie (CGT) bij crack-cocaïneafhankelijke patiënten (**Hoofdstuk 2**). Vierenzeventig crack-cocaïneafhankelijke patiënten namen deel aan dit open-label, gerandomiseerd haalbaarheidsonderzoek. Zij werden gerandomiseerd naar ofwel een behandeling bestaande uit 12 weken CGT plus 200 mg/dag topiramaat (n=36) ofwel een behandeling bestaande uit alleen 12 weken CGT (n=38). De primaire uitkomstmaat was CGT behandelretentie. Secundaire uitkomsten betroffen topiramaat innametrouw, veiligheid, cocaïne- en ander middelengebruik, cocaïne hunkering, gezondheid, sociaal functioneren en patiënttevredenheid.

De innametrouw van topiramaat was laag: slechts 14% van de deelnemers nam gedurende de volledige studieperiode van 12 weken hun medicatie. Redenen voor het niet-innemen van topiramaat bleven grotendeels onbekend. Uit de '*intent-to-treat*' analyses bleek dat topiramaat de CGT behandelretentie niet verbeterde, en evenmin het cocaïne- en ander middelengebruik verminderde. Post hoc exploratieve analyses lieten een moderatie-effect zien van opiaatafhankelijkheid: topiramaat leidde alleen tot een vermindering van het cocaïnegebruik bij crack-cocaïneafhankelijke patiënten met een bijkomende opiaatafhankelijkheid. Uit een exploratieve vergelijking tussen patiënten die hun topiramaat meer of minder dan 6 weken hadden ingenomen bleek geen verschil in het cocaïnegebruik. Topiramaat-inname ging gepaard met bijwerkingen, vooral tintelingen, maag/darmklachten en vermoeidheid, maar deze waren vaak mild en van voorbijgaande aard. Er waren geen ernstige ongewenste medische gebeurtenissen.

Geconcludeerd werd dat topiramaat een veilig en goed getolereerd medicament is voor deze groep crack-cocaïneafhankelijke patiënten, maar dat de effectiviteit niet aangetoond werd, waarschijnlijk door de lage medicatietrouw.

Farmacotherapie met modafinil

Klinische uitkomsten

Modafinil is een medicament dat de waakzaamheid vergroot en stimulerende effecten heeft als gevolg van het vertragen van dopamine-heropname. Het vermoeden bestaat dat deze effecten de chemie in de hersenen van verslaafde mensen normaliseren en het middelengebruik verminderen. Voorafgaand aan de start van de CATCH-studie werden er veelbelovende resultaten van modafinil gerapporteerd ten aanzien van de vermindering van het cocaïnegebruik en de hunkering naar cocaïne. In **Hoofdstuk 3** zijn de acceptatie, effectiviteit en veiligheid van modafinil (400 mg/dag) als aanvulling op cognitieve gedragstherapie (CGT) bij crack-cocaïneafhankelijke patiënten onderzocht.

Vijfenzestig crack-cocaïneafhankelijke patiënten namen deel aan een open-label, gerandomiseerde haalbaarheidsstudie. Deelnemers werden gerandomiseerd naar ofwel een 12 weken durende behandeling met individuele CGT plus 400 mg/dag modafinil (n=30), ofwel een 12 weken durende behandeling met alleen individuele CGT (n=35). De primaire uitkomstmaat was CGT behandelretentie. Secundaire uitkomstmaten bestonden uit modafinil innametrouw, tolerantie en veiligheid, cocaïne- en overig middelengebruik, cocaïne hunkering, gezondheid, sociaal functioneren en patiënttevredenheid.

De modafinil innametrouw was laag: slechts 10% van de deelnemers maakte hun modafinil-behandeling af. Bij 20% van de deelnemers aan de modafinil-behandeling had het voortijdig stoppen met modafinil te maken met ongewenste medische gebeurtenissen. De '*intent-to-treat*' groepsanalyses lieten zien dat modafinil de CGT behandelretentie niet verbeterde en ook niet positief bijdroeg aan de secundaire cocaïnegerelateerde uitkomsten. Beide groepen hadden vergelijkbaar grote verminderingen in het cocaïnegebruik gedurende de studieperiode. In exploratieve analyses die onder de deelnemers aan de modafinil-behandeling werden uitgevoerd, werd gevonden dat het cocaïnegebruik tussen het begin en einde van de studie sterker verminderde bij patiënten die hun modafinil minimaal 8 weken hadden ingenomen dan bij patiënten die hun modafinil minder trouw (<8 weken) hadden ingenomen. De tevredenheid over de ontvangen behandeling verschilde niet tussen de groep die CGT plus modafinil ontving en de groep die alleen CGT kreeg. De CGT plus modafinil groep rapporteerde de meeste ongewenste medische gebeurtenissen, en de meest

genoemde klachten waren hartkloppingen, agitatie en hoofdpijn. Er vonden twee ernstige medische ongewenste gebeurtenissen plaats, maar deze waren niet gerelateerd aan de modafinil-behandeling.

Geconcludeerd werd dat de acceptatie en de effectiviteit van modafinil niet aangetoond konden worden in de huidige studie, en dat dit waarschijnlijk te wijten was aan de lage innametrouw. Echter, in exploratieve analyses werden substantiële verminderingen in het cocaïnegebruik gevonden in een subgroep met een hoge innametrouw van modafinil.

Cognitief functioneren

Hoge impulsiviteit en een aandachtsbias komen vaak voor bij cocaïneafhankelijke patiënten en in eerdere studies is aangetoond dat dit tot slechte behandelresultaten leidt. Het is aangetoond dat modafinil cognitieve functies verbetert en dit zou kunnen bijdragen aan een verbetering van de klinische uitkomsten bij crack-cocaïne afhankelijke patiënten. In **Hoofdstuk 4** onderzochten we: (1) of impulsiviteit en een aandachtsbias bij aanvang van de behandeling voorspellend was voor de behandeluitkomsten; (2) of modafinil als aanvulling op cognitieve gedragstherapie (CGT) impulsiviteit en aandachtsbias verminderde; en (3) of veranderingen in impulsiviteit en aandachtsbias gerelateerd waren aan verbeteringen in behandeluitkomsten.

Dit onderzoek was een uitbreiding op de hoofdstudie met modafinil en daarom bestond deze onderzoeksgroep uit dezelfde 65 crack-cocaïneafhankelijke patiënten die gerandomiseerd waren naar 12 weken CGT plus modafinil, of alleen CGT. Zelfgerapporteerde impulsiviteit werd bij aanvang van de behandeling gemeten met de Barratt Impulsiviteitsschaal (BIS-11). Bij de beginmeting en in week 12 werden ‘inhibitie controle’ als een gedragsmaat van impulsiviteit, in termen van cognitieve interferentie (Stroop taak) en respons inhibitie (‘stop signaal taak’), en aandachtsbias met de verslavingsvariant van de Stroop taak, vastgesteld. Klinische uitkomsten waren CGT behandelretentie en crack-cocaïnegebruik.

Een lage zelfgerapporteerde impulsiviteit bij de beginmeting voorspelde een betere CGT behandelretentie, terwijl een lage impulsiviteit, gebaseerd op zelfrapportage en op de gedragstaken, en een lage aandachtsbias bij de beginmeting minder cocaïnegebruik op week 12 voorspelden. Cognitieve

prestaties verbeterden tijdens de onderzoeksbehandeling, maar deze verbeteringen konden niet worden toegeschreven aan de modafinil-behandeling, vooral vanwege de lage innametrouw. Exploratieve vergelijkingen binnen de modafinilgroep suggereerden dat de patiënten met een hoge modafinil-innametrouw (≥8 weken) sterker verbeterden op cognitieve interferentie dan patiënten met een lage modafinil-innametrouw (<8 weken). Verbeteringen in impulsiviteit of aandachtsbias hingen niet samen met CGT behandelretentie of veranderingen in cocaïnegebruik.

Er werd geconcludeerd dat impulsiviteit en aandachtsbias bij het begin van de behandeling de CGT behandelretentie en klinische uitkomsten voorspellen bij crack-cocaïne afhankelijke patiënten, maar er waren geen aanwijzingen dat modafinil de impulsiviteit of aandachtsbias verminderde in deze groep. Toekomstige onderzoeken met cognitief-versterkende medicijnen zouden strategieën moeten includeren om de medicatietrouw te optimaliseren, zodat beter bepaald kan worden of de medicamenten het cognitief functioneren verbeteren en daarmee uiteindelijk het cocaïnegebruik verminderen.

Farmacotherapie met dexamfetamine

De behandeling met heroïne op medisch voorschrift (HMV) is effectief voor methadonresistente, heroïneafhankelijke patiënten, maar hun bijkomende cocaïneafhankelijkheid blijft problematisch. Vertraagde afgifte dexamfetamine is een veelbelovende agonistische farmacotherapie voor de behandeling van (bijkomende) cocaïneafhankelijkheid. In **Hoofdstuk 5** werden de acceptatie, effectiviteit en veiligheid van een robuuste dosering van 60 mg/dag vertraagde afgifte dexamfetamine onderzocht. Zoals beschreven in Hoofdstuk 1, was het design van dit deelonderzoek anders dan dat van de eerste twee deelonderzoeken, en het betrof een multicenter, gerandomiseerd, dubbelblind, placebogecontroleerd design.

Drieënzeventig chronische crack-cocaïne- en heroïneafhankelijke patiënten, die een HMV-behandeling ontvingen, werden random toegewezen aan een 12 weken durende gesuperviseerde behandeling met 60 mg/dag vertraagde afgifte dexamfetamine (n=38) of een identiek lijkend placebo (n=35) als aanvulling op hun dagelijkse behandeling met methadon en diacetylmorfine. De primaire uitkomstmaat was het aantal zelfgerapporteerde dagen waarop cocaïne werd

gebruikt gedurende de onderzoeksperiode. Secundaire uitkomsten waren medicatie-innametrouw, tolerantie en veiligheid, cocaïnegebruik-gerelateerde uitkomsten, gebaseerd op zelfrapportage en urinetesten (bijv. de langste periode van aaneengesloten cocaïne-abstinentie), cocaïne hunkering, lichamelijke en psychische gezondheid, sociaal functioneren, en patiënttevredenheid.

De innametrouw van de onderzoeksmedicatie was hoog (92%) in zowel de dexamfetamine- als placebogroep. De blindering van de studiemedicatie was succesvol aangezien slechts 54% van de patiënten in de dexamfetaminegroep en 60% in de placebogroep correct kon aangeven welke studiemedicatie zij hadden ontvangen.

De behandeling met vertraagde afgifte dexamfetamine leidde tot significant minder dagen cocaïnegebruik, een langere periode van aaneengesloten cocaïne-abstinentie, een hoger percentage deelnemers dat minimaal 21 dagen aangesloten cocaïne-abstinent kon blijven, en een hoger percentage cocaïne-negatieve urinetesten dan de behandeling met placebo. Op de dagen dat patiënten wel crack-cocaïne gebruikten, nam het gemiddeld aantal 'basejes' af, waarbij de vermindering groter was in de dexamfetaminegroep vergeleken met de placebogroep. Behandeling met vertraagde afgifte dexamfetamine was niet beter dan behandeling met een placebo op andere secundaire uitkomstmaten. Een of meerdere medische ongewenste gebeurtenissen werden gerapporteerd door 74% van de deelnemers in de dexamfetaminegroep en door 46% van de deelnemers in de placebogroep. De meeste medische ongewenste gebeurtenissen waren van voorbijgaande aard en werden goed getolereerd. Er vond één ernstige medische ongewenste gebeurtenis plaats bij een patiënt in de placebogroep.

Er werd geconcludeerd dat vertraagde afgifte dexamfetamine een goed geaccepteerde, effectieve en veilige agonistische farmacotherapie is voor behandelresistente cocaïne- en heroïneafhankelijke patiënten in HMV-behandeling.

Conclusie

Het doel van de CATCH-studie was om de haalbaarheid, effectiviteit en veiligheid van topiramaat, modafinil en vertraagde afgifte dexamfetamine te onderzoeken in de behandeling van crack-cocaïneafhankelijke patiënten. Op basis van onze bevindingen en eerder onderzoek concluderen we dat topiramaat niet

aanbevolen wordt als medicamenteuze behandeling van crack-cocaïneafhankelijkheid, terwijl de potentiële effectiviteit van modafinil verder onderzocht zou moeten worden.

Agonistische behandeling met vertraagde afgifte dexamfetamine is voor patiënten met chronische cocaïneafhankelijkheid op dit moment de beste optie. Dat betekent dat de focus van behandeling verschuift van abstinentie naar schadebeperking, waarbij herstel en het verbeteren van de kwaliteit van leven ten minste even belangrijke doestellingen worden als cocaïne-abstinentie.

De veelbelovende bevindingen uit ons onderzoek ten aanzien van een substitutiebehandeling met vertraagde afgifte dexamfetamine is een belangrijke stap naar een effectieve farmacotherapie voor cocaïneafhankelijkheid en is een aanmoediging voor toekomstig onderzoek dat zich zou moeten richten op het uitbreiden van de resultaten naar chronische cocaïne (en andere stimulantia) afhankelijke patiënten, en op het verbeteren en behouden van de effecten van dopamine-agonistische therapie in de behandeling van cocaïneafhankelijkheid.

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Curriculum Vitae

Mascha Nuijten was born on the 19th of July 1975 in Bergen op Zoom, the Netherlands. She completed her pre-university education in 1993 and studied social work at the Social Academy in Breda, which she completed in 1998. After a 5-year working period in the addiction care, she started her study in Clinical and Health Psychology at Leiden University in 2003 where she received her Research Master (cum laude) and Professional Master in 2008. During her research internship she examined the influence of stress on memory in an fMRI-study at the Leiden University Medical Centre. She also was an intern psychologist at the department of Trauma & Dissociation of PsyQ in The Hague. During her study, she kept working in addiction care as a researcher.

After graduation, Mascha worked for two years as a psychologist in addiction care before she started her PhD on new pharmacological treatment options for cocaine dependence in 2010 at the research department of Brijder Addiction Care in The Hague, in collaboration with the Academic Medical Centre of the University of Amsterdam in Amsterdam. The results of this study have been published in international peer-reviewed journals, including Drug and Alcohol Dependence, Journal of Psychopharmacology and The Lancet. For the latter paper on the effectiveness of SR dexamfetamine in crack-cocaine dependence she received the Dr. Peter Moleman Award 2016.

During the completion of her thesis, she was also involved in the planning, organisation and implementation of new addiction research.

Mascha lives in Utrecht together with Onno and their daughter Karlijn.

List of Publications

This thesis

Nuijten, M., Blanken, P., Van de Wetering, B., Nuijen, B., Van den Brink, W., & Hendriks, V. (2016). Sustained- release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled, double-blind trial. *The Lancet*, *387*, 2226-2234.

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Other papers

Nuijten, M., Blanken, P., Van de Wetering, B., Nuijen, B., Van den Brink, W., & Hendriks, V. (2016). Substitutiebehandeling met dexamfetamine SR naast medische heroïne bij chronische cocaïne- en opiaatafhankelijkheid. *Psyfar, 4*, 59-63.

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