The handle http://hdl.handle.net/1887/48025 holds various files of this Leiden University dissertation.

Author: Nuijten, M.A.A.
Title: CATCH: New pharmacological treatment options for crack-cocaine dependence. Results from three randomised controlled trials
Issue Date: 2017-04-19
Chapter 1

General introduction*

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 serotonin, 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.