Alcohol dependence: Treatment effectiveness and the concept of craving

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ALCOHOL

Treatment effectiveness and DEPENDENCE

the concept of craving

Wencke de Wildt
ALCOHOL

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ALCOHOL DEPENDENCE:
TREATMENT EFFECTIVENESS AND THE CONCEPT OF CRAVING

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CHAPTER 1

GENERAL INTRODUCTION
INTRODUCTION

This chapter provides a general theoretical and empirical background for the studies presented in this thesis. Firstly, alcohol use disorders, as currently classified and conceptualized, are shortly pointed out. Subsequently, an introduction to the treatment of alcohol use disorders is given, followed by an overview of the empirical support on combining pharmacotherapy and psychotherapy. In addition, issues regarding the treatment of alcohol dependence in routine practice are addressed. Next, the role of subjective craving in alcohol use disorders is described. The introduction ends with an outline and the contents of this thesis.

ALCOHOL USE DISORDERS: DIAGNOSTIC CRITERIA

In the DSM-IV, the general applied classification system of psychiatric disorders, two different alcohol use disorders are distinguished: alcohol abuse and alcohol dependence (American Psychiatric Association, 1994). Alcohol abuse refers to a maladaptive pattern of alcohol use with at least one of the following problems: 1) failure to fulfil major role obligations, 2) recurrent use in hazardous situations, 3) recurrent legal problems, and 4) continuing despite social or interpersonal harm. A diagnosis of alcohol dependence requires fulfilment of at least three of the seven diagnostic criteria for dependence, occurring at any time in the same 12-months period, including 1) tolerance, 2) withdrawal, 3) more or longer use than intended, 4) persistent desire or unsuccessful efforts to cut down, 5) much time spent on obtaining, using alcohol or recovering, 6) important activities are given up or reduced, and 7) continuing use despite physical or psychological harm. Although clinicians generally consider the phenomenon of craving (e.g. the strong and overwhelming desire to drink) an important aspect of dependence, it is absent in the formal criteria of DSM-IV. In ICD-10 the criterion ‘a strong desire or sense of compulsion’ relates to the idea of craving for alcohol (WHO, 1992).

ALCOHOL DEPENDENCE: CURRENT THEORIES ON ADDICTION

Alcohol dependence or addiction is generally conceptualized as a multifactorial disease with biological, psychological and social determinants. Social context and environment serve both as a risk factor and protective factor for substance use, playing an important role in substance use initiation (Gifford & Humphreys, 2007). It is also clear that there is a genetic component to many aspects of alcohol drinking and that there are genetic
influences at different stages in the development of addiction, next to the substantial role of environmental factors (WHO, 2004; Crabbe, 2002). Psychological learning theories have tried to explain the interactions between environment and addictive behaviour, using the two major theories of learning; instrumental conditioning and Pavlovian conditioning. Alcohol is associated with rewarding effects. It induces positive feelings (like the “high” or the “rush”) or reduces negative emotional states. These rewarding effects enhance the likelihood that substance use occurs through the process of instrumental conditioning. It is thought to explain the initiation of substance use and the transition to abuse. Pavlovian conditioning refers to the process in which alcohol-related cues, after repeatedly being paired with alcohol consumption, become conditioned stimuli. As a result, it is believed that exposure to these cues can induce cue reactivity: psychophysiological reactions (e.g. increase in heart rate, salivation) which can be experienced as craving and might lead to continued substance use and relapse.

Scientific advances over the last decades have emphasized the position that addiction is a chronic brain disease (Leshner, 1997), which is characterized by an intermittent course of recovery and relapses. Likewise, the current theories on the development and persistence of addictive behaviours are dominated by neurobiological research and findings, clarifying the biological basis of the behavioural and psychological factors that contribute to dependence. For example, research has shown that the neurobiological basis of the described learning processes appears to be dopamine signals in the nucleus accumbens (WHO, 2004). Recently also the glutamate system has been shown to play an important role in cue-induced reactivity and probably craving (van den Oever et al., 2008). Specific brain processes and circuits are thought to be involved in addiction. Based on the results of functional imaging studies, Goldstein and Volkow (2002) provided an integrated model that attempts to explain the loss of control and compulsive substance use that characterize addiction. The model proposes a network of four brain circuits involved with 1) reward (nucleus accumbens), 2) motivation/drive (orbitofrontal cortex), 3) memory (amygdala and hippocampus), and 4) control (prefrontal cortex and cingulate gyrus). The saliency value of the drug and drug-related stimuli is enhanced at the expense of natural reinforcers. This is a consequence of conditioned learning and of the resetting of the reward thresholds as an adaptation at the high levels of stimulation induced by the substance of abuse. In this model, during exposure to the substance or substance-related cues, the memory of the expected reward results in overactivation of the reward and motivation circuits while decreasing the activity in the cognitive control circuit. This contributes to an inability to inhibit the drive to seek and consume the specific substance and results in compulsive consumption. It is currently believed that drugs are reinforcing not just because they are pleasurable but because, by increasing dopamine, they are being processed as salient stimuli that will
motivate the procurement of more drugs (regardless of whether the drug is consciously pleasurable or not) (Volkow et al., 2009).

**TREATMENT OF ALCOHOL USE DISORDERS: METHODS AND EMPIRICAL SUPPORT**

In the treatment of alcohol use disorders a distinction can be made between psychosocial interventions and pharmacological treatments. In this paragraph an overview is given of the empirically supported interventions in alcohol treatment.

**Psychosocial treatment of alcohol use disorders**

In the last decades a large number of randomized controlled trials (RCT) has been conducted on the efficacy of different psychosocial treatment approaches for alcohol dependent patients. In reviews, brief interventions and motivational enhancement therapy consistently head the list of empirically supported interventions (Miller & Wilbourne, 2002). Brief interventions include some form of advice-giving, usually in combination with other interventions and delivered in one or two sessions. Motivational enhancement therapy (MET) aims at enhancing the patients’ motivation to change his drinking behaviour and includes the application of Motivational Interviewing (MI; Miller & Rollnick, 1991; 2002). MI is a person-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving the ambivalence that often exists in patients with alcohol problems (Miller & Rollnick, 2002). In MI, motivation to change drinking behaviour is assumed to be an interpersonal process, the product of the interaction between the therapist and the patient. Brief interventions and MET have primarily proven their efficacy in people who are not actively seeking treatment for alcohol problems (e.g. identified in health-care settings as at-risk drinkers), having mild or moderate alcohol problems.

A second category of empirically supported treatments consist of interventions based on cognitive behavioural therapy (CBT). From a cognitive-behavioural perspective, alcohol dependence is defined as a habitual, maladaptive method for attempting to cope with the stresses of daily living. This maladaptive way of coping is triggered by internal and external cues and reinforced by positive rewards and/or avoidance of punishment (Monti et al., 1989). As opposed to MI, in which the responsibility for change methods is left with the patient and natural problem-solving processes are elicited from the patient,
CBT focuses on teaching new strategies and skills for more effectively coping with antecedents of alcohol use. Specific empirically supported components of CBT are behavioural contracting and self-monitoring (Miller & Wilbourne, 2002). There is also substantial evidence for the efficacy of cognitive behavioural treatments that pay particular attention to the patients social support network: social skills training, community reinforcement approach and behavioural couple therapy (Miller & Wilbourne, 2002; Powers, Vedel & Emmelkamp, 2008). Treatment methods designed to educate, confront, shock or foster insight regarding the nature and causes of alcoholism have shown to be ineffective in changing drinking behaviour. Also relaxation training, milieu therapy, mandatory Alcoholics Anonymous attendance and poorly specified counselling are at the bottom of the list of empirically supported treatments.

In sum, effective psychosocial treatment of alcohol use disorders aims at enhancing the motivation to change drinking behaviour and consists of several cognitive behavioural interventions, paying attention to the patient’s social support network.

**Pharmacotherapy of alcohol use disorders**

The three best known and most widely used agents in the treatment of alcohol use disorders are disulfram, naltrexone and acamprosate.

Disulfram, historically the first agent for alcohol treatment, prevents the metabolism of alcohol causing an accumulation of acetaldehyde levels and subsequently an aversive experience when alcohol is consumed. As such disulfram functions as a psychological deterrent to prevent the patient from drinking. Although the literature on disulfram is substantial, the number of controlled clinical trials is limited yielding inconsistent results (Mann, 2004). Several reviews have concluded that unsupervised disulfram is of limited utility but endorse supervised disulfram (Anton, 2001; Hughes & Cook, 1997). There is modest positive evidence that disulfram reduces the number of drinking days without enhancing abstinence rates (Garbutt et al., 1999). Giving the physiological impact of acetaldehyde intoxication and potential associated risks, alcohol dependent patients treated with disulfram should be monitored carefully (Mann, 2004).

In the nineties two new medications were introduced in the field of alcohol treatment; naltrexone and acamprosate. Naltrexone is an opiate receptor antagonist and is thought to reduce the positive reinforcing effects of alcohol and to reduce craving. From a review (Kranzler & Van Kirk, 2001), several meta-analyses (Bouza et al., 2004; Rösner et al., 2008; Streton & Whelan, 2001) and a Cochrane review (Srisurapanont & Jarusuraisin, 2005) it can be concluded that naltrexone has a significant positive effect on the proportion of patients relapsing into heavy drinking, as well as on drinking
frequency and alcohol consumption. However, results on its effect on enhancing abstinence rates are inconsistent.

Although its precise mechanism of action remains to be elucidated, acamprosate is believed to modulate glutamatergic transmission and to reduce the negative craving that alcohol dependent patients experience in the absence of alcohol (Mann, 2004). A substantial amount of reviews and meta-analyses conclude that acamprosate effectively maintains complete abstinence in detoxified alcohol dependent patients and reduces drinking frequency (Mann, 2004; Mann, Lehert & Morgan, 2004; Scott, Dennis & Foss, 2005; Rösner et al., 2008).

RCTs which directly compare the efficacy of these medications are scarce. Recently, supervised disulfiram appeared to be superior to naltrexone and acamprosate when combined with a brief cognitive behavioural therapy (Laaksonen et al, 2008). Also, in two open randomized trials disulfiram showed to be superior to acamprosate and naltrexone (De Sousa & De Sousa, 2004; 2005). Compliance was enhanced by asking a family member to observe the patient when taking the medication. Rubio et al. (2001) conducted an open randomized trial to compare the efficacy of naltrexone and acamprosate in daily clinical practice. Naltrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at one time and reducing craving, compared to acamprosate.

A few studies have been conducted on the efficacy of combining different pharmacotherapies. Kiefer et al. (2003) conducted a controlled study comparing and combining naltrexone and acamprosate. Comparing the course of non-relapse rates between naltrexone and acamprosate, the naltrexone group showed a tendency for a better outcome regarding time to first drink and time to relapse, i.e. maintenance of abstinence. The combined medication was significantly more effective than acamprosate, but not than naltrexone. This finding was replicated by Feeney et al. (2006) in a matched samples study. However, in the large COMBINE study (Anton et al., 2006), data did not support the combined use of acamprosate and naltrexone. It must be noted that in this study acamprosate was not effective as compared to placebo, and naltrexone was only slightly more effective than placebo. In comparing and combining acamprosate and disulfiram (Besson et al., 1998), both agents had similar efficacy, but the combination was more effective than either drug alone for maintaining alcohol abstinence.
COMBINING PHARMACOTHERAPY AND PSYCHOSOCIAL INTERVENTIONS IN THE TREATMENT OF ALCOHOL USE DISORDERS: THEORY AND EMPIRICAL SUPPORT

The introduction of naltrexone and acamprosate in the field of alcohol treatment substantially broadened the range of treatment options and, in addition, raised the question whether and how to combine these agents with psychosocial treatments. In this paragraph the theoretical background on this issue and the empirical research up to 2002 (when our first results were published) is summarized. The recent literature on this issue will be discussed in the final chapter of this thesis together with the results of our own study. A distinction is made between three research questions:

- Does pharmacotherapy add to the efficacy of psychosocial treatment in alcohol use disorders?
- Does psychosocial treatment add to the efficacy of pharmacotherapy in alcohol use disorders?
- Do certain psychosocial interventions add more to the effectiveness of pharmacotherapy than other psychosocial interventions in the treatment of alcohol use disorders?

Theoretical background

In general, in the field of alcohol treatment it has been recommended that medication should be prescribed in combination with psychosocial treatment (Garbutt et al., 1999; APA, 1995; Swift, 1999). Several assumptions are underlying this recommendation (Caroll, 1997; Onken & Blaine, 1995). One of the potential benefits of integrated treatments is that improvement over a broader range of symptoms is to be expected. Combining different forms of treatment which are likely to work on different sets of symptoms may be an effective strategy for treating the broad and variable range of symptoms and problems alcohol abusers face. Second, no single form of treatment is effective for all patients. By combining psychotherapy and pharmacotherapy to match treatment to the needs of the specific patient, treatment outcomes might be enhanced. Last, each form of treatment may offset drawbacks of the other. One important limitation of pharmacotherapy is low medication compliance. This is well demonstrated with the prescription of naltrexone (Volpicelli et al., 1997): compliance with naltrexone played an important role in the increased efficacy in naltrexone over placebo. Psychosocial interventions may be used to reduce the impact of side effects of pharmacotherapy and
to enhance medication compliance. On the other hand, stabilization through prescription of medication might be necessary to provide the conditions under which effective psychotherapy can be delivered. Pharmacotherapies may effectively address short-term and comparatively circumscribed areas (e.g. reduction of craving), which, if unaddressed, would severely undercut the effectiveness of treatment. Psychotherapies, while requiring more time to exert their effects, may be more effective at addressing the range of the patients’ problems and do so much more durable than pharmacotherapies.

Does pharmacotherapy add to the effectiveness of psychosocial treatment in alcohol use disorders?

In all placebo-controlled trials with acamprosate, medication was prescribed in the context of psychosocial treatment, i.e. active medication and placebo were always added to some psychosocial intervention. Research usually involved psychosocial treatment as usual, as was the case in, for example, the Benelux placebo-controlled study on the efficacy of acamprosate (Geerlings, Ansoms & van den Brink, 1997). All studies on the efficacy of naltrexone except two (Latt et al., 2002; O’Malley et al., 2003) have delivered naltrexone in the context of formal psychosocial intervention (e.g., supportive therapy, CBT). In naltrexone studies more specific or manual-based treatments were delivered, as compared to acamprosate trials. Given the fact that, overall, prescription of active medication was more effective than placebo (Garbutt et al., 1999), we can conclude that both acamprosate and naltrexone add to the effectiveness of psychosocial treatment. Also, in some studies on the efficacy of disulfiram, supervised medication was added to treatment-as-usual, for example in Chick et al. (1992) and Fuller and Roth (1986). We can conclude that there is evidence that supervised disulfiram adds to the effectiveness of psychosocial treatment. However, the number of studies is limited.

Does psychosocial treatment add to the effectiveness of pharmacotherapy in alcohol use disorders?

The first RCT investigating the added value of psychosocial treatment on pharmacotherapy was conducted by Azrin et al. in 1982. A total of 43 alcoholic patients were randomized to 1) a traditional disulfiram treatment with education and sympathetic listening by the counsellor; 2) a socially motivated disulfiram assurance group with specific training in adhering to the medication regime; and 3) a disulfiram assurance group combined with behavioural skills training based on the Community Reinforcement
program. About five sessions were given in each program. The results indicated that the traditional treatment was the least effective, the disulfiram assurance more effective and the combination with behavioural skills training the most effective. This rank order of effectiveness was found for all outcome measures. The difference between the treatment groups became greater with each passing month. Marital status was found to be associated with the effectiveness of the treatment. For married patients the disulfiram assurance program was as effective as the combined assurance program and behavioural therapy.

Monti et al. (1991) investigated the effects of combining naltrexone, communications skills training (CST) and cue exposure therapy (CET) with urge-specific coping skills training. In a 2x2 design alcohol abusing or dependent patients were randomized to receive either the CET/CST package or a control treatment (n= 165) followed by randomization to 12 outpatient weeks of natrexone or placebo (n=128). The control treatment consisted of education and relaxation. Natrexone showed to reduce the severity of relapses only in patients with some degree of compliance. Patients who received CET/CST reported fewer relapses and fewer heavy drinking days at 6 and 12 months follow-up than patients in the control treatment. Interactions of medication with behavioural treatments were not significant, indicating independent effects, with naltrexone neither helping nor impeding the effectiveness of the CET/CST approach and vice versa.

O'Malley et al. (1992) systematically varied the nature of the additional psychotherapy in a randomized, placebo-controlled trial of naltrexone. Naltrexone or a placebo was provided for 12 weeks along with weekly psychotherapy. Patients receiving naltrexone in combination with supportive psychotherapy showed higher abstinence rates than patients receiving naltrexone in combination with coping skills training. However, if drinking was re-initiated the latter group was found to be less likely to experience relapse to heavy drinking than the former group. The results of this study indicate that additional psychosocial intervention may indeed be of great relevance for effective pharmacotherapy in alcohol dependent patients and that there may be differential effects for different psychosocial approaches, depending on the phase of treatment, the selected outcome measure and the aim of treatment. Heinälä et al. (2001) investigated the efficacy of naltrexone or placebo in combination with cognitive coping skills or supportive therapy, delivered in group sessions, in a design comparable to O'Malley et al (1992). However, the patient was instructed to take naltrexone or placebo only when craving for alcohol occurred (targeted or as-needed medication). Naltrexone showed to be effective over placebo, but only when used in conjunction with coping skills training.
Do certain psychosocial interventions add more to the effectiveness of pharmacotherapy than other psychosocial interventions in the treatment of alcohol use disorders?

In the studies of Azrin et al. (1982), O’Malley et al. (1991) and Heinälä et al. (2001) various psychosocial interventions were added to medication in order to investigate whether certain psychosocial interventions add more to the effectiveness of pharmacotherapy than others. Results indicate that indeed differential effects exist, depending on treatment phase, outcomes measures (O’Malley et al., 1992), and subgroups of patients (Azrin et al., 1982). Heinälä et al. (2001) showed that the effectiveness of naltrexone over placebo could only be established in conjunction with a specific psychosocial intervention, illustrating the relevance of this type of research. Up to 2002, no studies on acamprosate were conducted addressing this question. Also, no studies on the efficacy of time-limited medication compliance strategies were available, with the exception of Azrin’s study on disulfiram.

Conclusion and focus of this thesis

It can be concluded that there is ample evidence that pharmacotherapy (naltrexon and acamprosate) adds to the effectiveness of psychosocial treatment of patients with alcohol use disorders. In contrast, the amount of research on the additional effect of psychosocial treatment on pharmacotherapy is very limited, but the few available studies indicate that this combination might be beneficial. Questions concerning the necessity, nature and intensity of such psychosocial interventions and the efficacy of particular treatment combinations need to be addressed (Garbutt et al., 1999). The main RCT in this thesis investigates the additional value of two forms of evidence-based psychosocial treatment on the effect of acamprosate (chapter 2).

TREATMENT OF ALCOHOL DEPENDENCE IN ROUTINE PRACTICE

The RCT on the added value of psychotherapy on the prescription of acamprosate in the treatment of alcohol dependent patients, starting in 1997 (chapter 2), was the first large scale multicentre trial in substance use disorder patients in the Netherlands using manual-based treatments. As such, this trial appeared to be important in the introduction of cognitive-behavioural interventions and motivational interviewing. In the same period Dutch substance abuse treatment centres were starting a major national-wide
reorganization called “Resultaten Scoren” (“To Score Results”: GGZ Nederland, 1998; Schippers, Walburg & Schramade, 2002). The program included the development of treatment manuals, based on the existing empirical support of cognitive behavioural therapy and motivational interviewing, and dissemination of these interventions. A second key issue in this project was the development of outcome monitoring. One of the main reasons for the reorganization was the notion that many empirically supported behavioural and pharmacological treatments were rarely used in the daily practice of Dutch substance abuse treatment centres. Conversely, treatments were used that had not undergone any evaluation of efficacy. The gap between research and practice is generally considered a major issue facing virtually all areas of clinical psychiatry (Carroll & Rounsaville, 2003). In addition, limited research is conducted on the merits of science driven treatments in routine practice.

**Efficacy versus effectiveness research**

Randomized controlled trials (RCTs) are the gold standard for establishing efficacy of interventions in medicine. This is also true for the test of new treatments in alcohol use disorders. RCTs evaluate efficacy, i.e. whether a given treatment improves outcomes relative to a control or a comparison condition. This requires testing treatments under ideal conditions. As such, RCTs often entail substantial deviations from usual practice conditions, by eliminating treatment preferences, using specialized providers and settings, maintaining high treatment compliance and excluding patients with major comorbid conditions (Wells, 1999). Treatment is delivered by highly skilled, rigorously trained, and closely supervised therapists, using standardized treatment protocols. Exclusion criteria are used to maximize homogeneity. For example, in Project MATCH and the COMBINE study, two large RCTs in the field of alcohol use disorders, more than 60% of the patients presenting for alcohol treatment was not eligible to the study as a result of exclusion criteria (Project MATCH, 1997; Anton et al., 2006). Overall, internal validity is giving high priority in RCTs, thereby facilitating the evaluation of efficacy (i.e. how well a treatment works under ideal conditions). As a consequence, efficacy trials are often criticized as having limited generalizability to issues and problems in daily practice.

Effectiveness studies evaluate effects of treatments under conditions approximating usual care. As opposed to efficacy studies, in effectiveness research external validity is improved at the expense of internal validity. As such these studies often lack design features required to definitely answer basic issues regarding treatment effectiveness or to rule out alternative explanations for findings. However, effectiveness studies are a necessary addition to RCTs in order to test the ecological validity and to
provide information how well a treatment works in routine clinical practice. In pharmacotherapy research these so-called phase IV studies are part of the testing process, but this is less common in psychotherapy research.

**Bridging the gap**

It is proposed to use effectiveness research as a strategy for bridging the gap between research and practice (Institute of Medicine, 1998; Carroll & Rounsaville, 2003). The National Institute on Drug Abuse developed a stage model of behavioural therapies research as an attempt to conceptualize the transition from initial development of a new treatment intervention to ultimate community utilization (Rounsaville, Caroll & Onken, 2001). It distinguishes three progressive stages that roughly parallel those for the development of pharmacological treatments. Stage I consists of initial development and pilot or feasibility testing of new and untested treatments. Stage II consists of RCTs to evaluate efficacy of treatments that have shown promise in initial studies. In stage III, which corresponds with phase IV research for pharmacological trials, issues of transportability of treatments whose efficacy has been demonstrated in at least two stage II trials are addressed. However, a limitation of this model is the currently underdeveloped stage III.

**Conclusion and focus of this thesis**

At the moment there are no large-scale studies available on the effectiveness of empirically proven psychosocial treatments in alcohol use disorders in routine practice. In this thesis the treatment outcomes of manual-based cognitive behavioural therapy for patients with an alcohol use disorder are investigated (chapter 3).

**THE ROLE OF SUBJECTIVE CRAVING IN ALCOHOL USE DISORDERS**

In early theories, based on clinical observations, craving was seen as a key substrate of addiction and the driving force behind the continued use of a drug despite the negative consequences. As from the 1970s more research was conducted on the concept of craving, it became apparent that not only different definitions were used, but also that disagreement existed on the function, nature and relevance of craving and the assumed
relationship between craving and relapse. The development of new medications for the treatment of alcohol dependence, acamprosate and naltrexone, which are supposed to achieve their effect through reductions of craving, has led to growing interest in the concept of craving and the development of instruments to measure craving (Drummond, 2001; Anton, 1999). However, at present, the phenomenon of craving is still a puzzle and opinions remain divided.

**The definition and concept of craving**

The term craving is used to mean various things including liking, wanting, urges, desires, needs, intentions or a compulsion to use (Kozlowski & Wilkinson, 1987). Sometimes the autonomic and behavioural correlates of subjective craving (cue-reactivity) have been included in definitions of craving. It is stated that a proper definition of craving for alcohol should be restricted to subjectively experienced desires or urges to drink alcohol and, for the sake of conceptual clarity and the construct’s usefulness as a predictor of relapse, should exclude potential precipitating and consequential factors (Verheul, van den Brink & Geerlings, 1999). In general, craving is taken to be the ‘conscious experience of a desire to take a drug’ (Drummond, 2001). Some argue that the term should be used only to refer to strong desires or urges to drink alcohol (Kozlowski & Wilkinson, 1987). Others argue that this restriction is artificial and results in a dichotomous representation of the concept, which is not analogous to other psychological phenomena such as depression and anxiety (Franken, 2003a). Most authors agree that craving possesses both cognitive and emotional aspects. Most authors also agree that physiological reactions (e.g. heart rate, skin conductance) are part of the craving concept and that these reactions do occur in response to alcohol-related cues (Niaura et al., 1988).

**Theories of craving**

The main theoretical models of craving can be classified broadly in: 1) phenomenological, 2) conditioning, and 3) cognitive models (Drummond, 2001). Phenomenological models are derived from clinical observation and are descriptive rather than explanatory. Craving is considered a symptom of an underlying addictive disorder. Phenomenological models have been influential in classification systems of addictive disorders and in the development of pharmacological therapies. Conditioning models are based on the theories of classical conditioning, whereas cognitive models are based on the assumption
that responses to alcohol and alcohol-related cues involve various cognitive processes, such as expectations regarding the pleasant effects, and the person’s belief in his own ability to cope with the desire to drink (Singleton & Golerick, 1998). Cognitive approaches consider craving the product of higher order mental functions (Tiffany, 1999). Conditioning as well as cognitive theories of craving have been important in the development of behavioural and cognitive therapies of substance use disorders. The last decade several integrated models are proposed that integrate conditioning theories with cognitive and neurobiological approaches.

Anton (1999), for example, developed a neuroadaptive model of craving. It proposes that chronic alcohol exposure leads to changes in brain cell function (i.e. sensitization, or neuroadaptation). In turn, neuroadaptation leads to an imbalance in brain function which results in subjective feelings of discomfort and, subsequently, craving. Neuroadaptation can contribute to the development of a reward memory, i.e. memory of the importance of alcohol or alcohol-related stimuli. During prolonged abstinence conditioned stimuli may activate this reward memory, thereby also inducing craving. Craving, in turn, may result in relapse to drinking.

Verheul, van den Brink & Geerlings (1999) postulated a psychobiological three-pathway model of craving in alcoholics, which was hypothesized to be helpful in unravelling the mechanisms of anti-craving compounds and, therefore, holds promise for a better match between certain patients and specific pharmacotherapies. A reward pathway, a relief pathway and an obsessive craving pathway were distinguished with each pathway comprising a biological and a psychological component. However, so far, the matching hypotheses derived from this model could only be partly confirmed (Ooteman et al., 2009).

Franken (2003a; 2003b) postulated an integrated model in which attentional bias is assumed to be central. Attentional bias refers to the empirically proven enhanced attentional processing of drug- or alcohol-related stimuli in dependent persons. In his cognitive psychopharmacological model of craving, the presence of attentional bias is responsible for the enhanced likelihood to detect and become aware of alcohol cues in the environment. The perception of alcohol cues is related to increased dopaminergic activity and conditioned responses (e.g., craving) that may trigger relapse. Attention-related cognitive processes such as memory-bias may contribute to increased craving. Because of the limited capacity of attention the automatic focusing on alcohol-related cues would result in a subsequent failure in the processing of competitive cues. Several hypotheses derived from this model were confirmed in a series of studies (Franken, 2003b).
Craving and relapse

One of the key reasons for the continuing study of craving is its potential role in relapse to drinking behaviour following a period of abstinence in alcoholics (Drummond, 2000). At the moment its relation to drinking behaviour and relapse is not well established. Although it is often assumed that craving is predictive of relapse, neither studies of craving and alcohol consumption in the laboratory nor studies of craving and relapse in the real world have provided strong evidence that craving is directly responsible for alcohol use in alcoholics (Tiffany & Conklin, 2000). Clinicians have noted that some alcoholic patients do not experience craving. Studies of relapse episodes indicate that addicts rarely identify craving as a major direct trigger for alcohol use (e.g. Miller & Gold, 1994; Tiffany & Carter, 1998). Also, craving does not inevitably lead to relapse (Tiffany, 1990). The results regarding the role of craving in treatment outcomes are inconsistent, with craving predicting less drinking in some studies and more drinking in others (Rothenow & Monti, 1999).

The inconsistent findings regarding the predictive value of craving on relapse might be attributed to inadequate measurements (Drummond, 2000). None of the available measures is appropriate across all settings, and awareness of the limitations and strengths of different measures is needed (Sayette et al., 2000). Also, craving may vary considerably over time, and, hence, the temporal dynamics of craving may influence its predictive value depending on how and when it is measured. The timing of craving measurement may prove to be a critical determinant of its predictive validity (Drummond, 2000). Alternatively, it is possible that craving is only predictive under certain conditions. For example, Niaura (2000) suggested that both craving and low self-efficacy need to be present for relapse to occur. Finally, it might be that autonomic and/or behavioural correlates of craving or the determinants or mediators of craving might be predictive for relapse in stead of the subjective experience of craving itself.

Conclusion and focus of this thesis

The concept and structure of craving is not completely clear and its predictive validity is not well established. In this thesis, therefore, two studies are included that address a) the underlying model of alcohol craving (chapter 4), and b) the predictive validity of subjective craving (chapter 5).
PRESENT THESIS

This thesis is primarily based on the results of a RCT testing the additional value of two proven-effective psychosocial interventions to the prescription of acamprosate in patients with alcohol problems: motivational enhancement therapy and cognitive behavioural therapy. In chapter 2, the outcomes of the RCT are reported at post-treatment and six months follow-up. Based on the literature reviewed above it is hypothesized that the addition of a psychosocial intervention to the prescription of acamprosate will significantly reduce treatment drop-out, enhance medication compliance, and both maintain abstinence and prevent relapse. In the light of the broad spectrum of behaviours and issues addressed by cognitive behavioural therapy, it is also expected that such supplemental treatment will significantly reduce psychological distress.

Motivational Interviewing and Cognitive Behavioural Therapy are efficacious in treatment of alcoholic patients. However, the effectiveness in routine practice has, until now, not been assessed in large samples. Naturalistic outcome studies are a necessary addition to RCTs to provide information on the merits of these interventions in a routine treatment environment. In chapter 3, the effectiveness of manual-based cognitive behavioural therapy in routine alcohol treatment is investigated. The study examines the outcomes of two evidence based interventions for alcoholic patients in routine clinical practice and assesses whether patient characteristics are predictive of treatment outcome.

There is no agreement between researchers on the definition of alcohol craving and its underlying theoretical model. The study in Chapter 4 aims to elucidate the structure of alcohol craving using the Obsessive Compulsive Drinking Scale (Anton, 1996). Data from four studies, including the main RCT, are pooled to obtain a large, heterogeneous and multinational sample. The factor structures of the OCDS previously found are evaluated and compared with alternative causal models based on modern theories of craving.

In addition to the lack of agreement about the theoretical model of craving, the relationship between subjective craving and relapse to drinking in abstinent alcohol dependent patients is not well established. Instruments applied in prediction studies, time windows of the predictive validity of craving scores, and the definition of treatment outcome may have a decisive effect on the predictive power of craving. Chapter 5 aims to establish the effect of instrument variation, variations in time window and the type of outcome in the relationship between subjective craving and treatment outcome in abstinent alcoholics, using OCDS data from the RCT.

In the general discussion (chapter 6), the major findings in this thesis are discussed in the context of recent research. Limitations and recommendations for future
research are pointed out. The relevance of the results for clinical practice is discussed and remaining research questions are described in relation to recent topics in alcoholism research.

Finally, in chapter 7, a summary of this thesis is presented.
CHAPTER 2

DOES PSYCHOSOCIAL TREATMENT ENHANCE THE EFFICACY OF ACAMPROSATE IN PATIENTS WITH ALCOHOL PROBLEMS?

This chapter is published as:
ABSTRACT

Aims: Acamprosate in combination with psychosocial treatment has been shown to be effective for the treatment of alcohol dependence. The goal of the present study was to determine whether the addition of psychosocial intervention to the medical prescription of acamprosate contributes to treatment outcome.

Methods: Patients (n=248) meeting DSM-IV criteria for alcohol dependence or abuse were recruited in 14 outpatient treatment centres and randomized into one of three treatment conditions: acamprosate; acamprosate plus minimal intervention aimed at motivational enhancement (3-weekly sessions of 20 min); and acamprosate plus brief cognitive behavioral therapy (7-weekly sessions of 60 min). Acamprosate was prescribed for 28 weeks, medically monitored by a physician on six occasions lasting 10 min. Drinking behavior, medication compliance and psychological distress were assessed throughout the treatment period. Follow-up assessment was undertaken 6 months after termination of pharmacological treatment.

Results: Of 241 patients with intention to treat (ITT), 114 (47.3%) remained in treatment for the full 28 weeks; 169 of the ITT population (70.1%) were seen for follow-up. No statistically significant differences were found between treatment groups for any of the drinking outcomes either at the end of the 28 weeks of treatment or at 6-months follow-up. There were no statistically significant differences in medication compliance, drop-out rates, or psychological distress. However, a significant interaction effect was observed between treatment centre and treatment group, indicating that brief interventions were differentially effective in different treatment centres.

Conclusions: A clear supplemental value of minimal and brief psychosocial interventions to the prescription of acamprosate was not demonstrated. The widely held belief that pharmacotherapy for alcohol dependence should always be combined with psychosocial intervention is debatable and merits further research.
INTRODUCTION

There is an increasing interest in pharmacotherapy for alcohol dependence. In a systematic review of the scientific literature on the efficacy of different agents for the treatment of alcohol dependence, both acamprosate and naltrexone were judged to be quite promising (Garbutt et al., 1999; Swift, 1999). It is generally recommended that such agents be prescribed in combination with some form of psychosocial intervention to provide emotional support, address any psychological or social problems, and increase compliance with the medication (Garbutt et al., 1999). In fact, psychosocial treatment is presently considered an essential component of any treatment programme for substance misuse disorders (American Psychiatric Association, 1995). With recent developments in pharmacotherapy, however, new questions concerning the necessity, nature, and intensity of such psychosocial interventions and the efficacy of particular treatment combinations are arising (Garbutt et al., 1999).

O’Malley et al. (1992) systematically varied the nature of the additional psychotherapy in a randomized, placebo-controlled trial of naltrexone. Naltrexone or a placebo were provided for 12 weeks along with weekly psychotherapy. Patients receiving naltrexone in combination with supportive psychotherapy showed higher abstinence rates than patients receiving naltrexone in combination with coping skills training. If drinking was re-initiated, however, the latter group was found to be less likely to experience a relapse to heavy drinking than the former group. The results of this study indicate that additional psychosocial interventions may be of great relevance for effective pharmacotherapy in alcohol dependent patients.

In studies of the efficacy of acamprosate, medication was added to the counseling or psychotherapy that was the routine practice of the participating centres. The effectiveness of acamprosate without psychosocial support is unknown, and it is therefore generally recommended that the medication be prescribed in combination with psychosocial support. Studies are nevertheless needed to assess the actual necessity, nature, and intensity of the psychosocial intervention.

The purpose of the present study was therefore to examine whether the addition of psychosocial intervention to the medical prescription of acamprosate enhances treatment outcomes. Two psychosocial interventions of known clinical effectiveness (Miller et al., 1995), motivational enhancement and brief cognitive behavioural therapy, were tested. It was hypothesized that the addition of a psychosocial intervention to the medical prescription of acamprosate would significantly reduce treatment drop-out, enhance medication compliance, and both maintain abstinence and prevent relapse. In light of the broad spectrum of behaviours and issues addressed by cognitive behavioural
therapy, it was also expected that such supplemental treatment would significantly reduce psychological distress.

**Patients and methods**

**Study design**
A total of 248 patients was randomized into one of three treatment conditions: acamprosate; acamprosate plus minimal intervention aimed at motivational enhancement; or acamprosate plus brief cognitive behavioural therapy. A placebo group was not included in the study. Although in clinical practice it is generally recommended to prescribe acamprosate for a period of 1 year, pharmacotherapy was provided for 28 weeks.

Patients were assessed during the selection and inclusion visit (baseline). They were then assessed during weeks 2, 4, 10, 16, 22, and 28 of treatment. Follow-up assessment was undertaken 6 months after termination of the pharmacological treatment.

The patients were recruited from 14 outpatient addiction treatment centres in The Netherlands. Two of the 14 participating centres provided < 10 patients, nine of the centres provided 10-25 patients, and three of the centres provided > 25 patients. Sealed envelope randomization with balancing by blocks of 15 was used to obtain equal numbers of patients per treatment group from each centre.

All of the patients provided their written informed consent. The trial was performed in compliance with Guidelines for Good Clinical Practice (I.C.H. Expert Working Group, 1996).

**Patients**
The patients were between the ages of 18 and 65 years. They all met the DSM-IV criteria for alcohol dependence or alcohol abuse (American Psychiatric Association, 1994), had achieved 3-17 days of abstinence, and were clearly motivated to attain long-term abstinence. The criteria for exclusion were renal insufficiency, an antisocial personality disorder, psychotic symptoms, a serious illness unrelated to alcoholism, a history of treatment for epileptic seizures, and current dependence on psychoactive substances other than nicotine and alcohol. Women were required to use a reliable method of birth control and pregnant and lactating women were excluded from the study. Patients were also excluded from participation if they were currently receiving treatment with a non-registered drug, participating in another clinical trial, or had undergone previous treatment with acamprosate.
Treatments

*Prescription and monitoring of acamprosate.* All patients were prescribed a daily dose of 1332 or 1998 mg (four or six tablets) of acamprosate according to body weight (<60 or >60 kg respectively). The total duration of the pharmacological treatment period was 28 weeks. The patients in each condition were seen by a physician of the addiction treatment centre in weeks 2, 4, 10, 16, 22, and 28 in order to monitor the acamprosate treatment. The appointment was limited to 10 min visits with a focus on the assessment of drinking behaviour and the monitoring of vital signs and other medically relevant aspects of the treatment. Physicians were instructed to not reinforce the patient’s abstinence, not to attempt to increase the patient’s motivation, and not discuss high-risk situations.

*Minimal intervention (MI):* This group of patients was monitored as described above and also received minimal intervention consisting of three sessions of 20 min each with the physician in weeks 2, 3, and 4. The overall goal of the intervention was to increase the patient’s motivation using motivational interviewing strategies (Miller & Rollnick, 1991; Miller et al., 1992). In the first session, the costs and benefits of the patient’s drinking behavior were specified. The physician provided personal feedback about the blood test (γ-glutamyltransferase: γ-GT) and emphasized the need for abstinence. In the second and third sessions, the progress of the patient was discussed together with situations in which the patient was tempted to drink, but succeeded in not doing so. Any lapses were also discussed in a non-judgmental manner and, when necessary, the physician helped renew the patient’s motivation for change by asking what he or she recalled as the most important reason for changing his or her drinking behaviour. The physician also affirmed, complimented, and reinforced the patient in order to enhance self-responsibility and self-esteem. Special attention was paid to medication compliance in every session.

*Brief cognitive behavioural therapy (BCBT):* This group of patients was monitored by the physician as described above and also received brief cognitive behavioural therapy from a social worker or psychologist. The BCBT consisted of five standard and two elective weekly sessions of 60 min in weeks 2-8. The overall goal of the therapy was to increase the person’s ability to cope with high-risk situations that could precipitate relapse. The therapy was modelled after Monti et al. (1989) and the coping skills therapy manual from Project MATCH (Kadden et al., 1992). During the first 15 min of each session, the drinking behaviour of the patient was reviewed. Medication compliance and motivation for change were enhanced using motivational interviewing strategies. The remainder of the session was devoted to one or more of the topics mentioned below. The patient was asked to bring a significant other to the first session. To build the patient’s motivation for change, several components of the Dutch elaboration of Miller’s Drinker’s
Check-Up (Miller, Sovereign & Krege, 1988) were used (Schippers, Brokken & Otten, 1994). The patient was also encouraged to monitor good and bad daily moments. In session two, the therapist provided instructions and trained the patient on problem-solving skills. Cognitive restructuring was addressed in sessions three and four. To meet the individual needs of the patient to the greatest extent possible, the patient and therapist jointly selected two of the eight elective topics as most appropriate. The array of elective sessions was as follows: increasing pleasant activities, managing negative mood and depression, awareness of anger, anger management, assertiveness, drink refusal skills, enhancing social support networks, and couples involvement. The final intervention session was devoted to relapse prevention and supposed to be conducted with all patients.

Treatment integrity
Both psychosocial interventions were manual-guided. The medical prescription and monitoring of the acamprosate was based on a case report form and a number of guidelines. To promote the consistency and quality of treatment delivery, the physicians and therapists participated in a centralized training seminar. All of the contacts with the patients were audio-taped. The adherence of the therapists and physicians to the guidelines for the specific types of intervention and their competence were monitored by reviewing the audiotapes and supervision by a psychologist.

Coding systems were developed to rate adherence to the treatment manuals during medical consultation, MI and BCBT. Three categories of items were constructed: items essential to the intervention, items proscribed in the intervention and items considered compatible with, but not essential to, the intervention (Waltz et al., 1993). A total of 43.3% of the medical consultations, 47.8% of MI sessions, and 38.1% of the BCBT sessions were rated. Overall the adherence to the manuals and the guidelines was judged good to very good (Disveld, 1997).

Assessment
At baseline, alcohol abuse or dependence was diagnosed using the Composite International Diagnostic Interview for DSM-IV (CIDI 2.1: World Health Organization, 1997). Socio-demographic information and the patient's medical and alcohol history were obtained. A physical examination and laboratory tests (γ-GT, alanine aminotransferase, aspartate aminotransferase, mean cell volume and creatinine) were performed. The patient completed a questionnaire to assess current psychological distress (SCL-90 or Symptom Checklist-90: Arrindell & Ettema, 1986).

During treatment, the physician, who was not blind to the treatment group, assessed the patient on six occasions: during week 2, week 4, and every 6 weeks thereafter.
(weeks 10, 16, 22, and 28). The patient was asked to report on drinking behaviour in the period since the previous visit. Conservative definitions were chosen: abstinence was defined as complete abstinence between two visits and relapse as the use of any amount of alcohol between two visits. In cases of relapse, the number of drinking days and the number of drinks per drinking day were assessed. Data on concomitant medication and attendance at self-help groups or other treatment agencies for alcohol problems were collected. The occurrence of any adverse events was documented. Compliance with the medication was checked by counting the number of tablets returned by the patient. Psychological distress was assessed in weeks 2, 10, and 28. At the end of the treatment period, physical examination and laboratory analyses were repeated.

Six months after termination of the pharmacological treatment, the subjects were invited for a follow-up visit. Drinking behaviour and psychological distress were assessed.

**Statistical analysis**

Sample size calculation was based on the two-sided confirmatory test between continuous abstinence proportions in each group. The abstinence rate for the acamprosate-alone group was assumed to be close to 20%; a difference as large as 20% compared with the two other groups (without Bonferroni correction) should be detected under an α of 0.05, with at least 80% power. The primary outcome criteria for drinking behaviour included total number of abstinent days, rates of continuous abstinence, abstinence rate for the last 6 weeks of treatment, time to first relapse, number of drinks per drinking day and laboratory values. The final sample consisted of 241 patients (97.2 %) receiving at least one dose of the medication and thus providing at least one key data point after baseline: the intention-to-treat (ITT) sample. Patients who missed a visit or prematurely withdrew from the study were considered non-abstinent for that particular data collection point. In addition, a per protocol analysis (PP) was performed. All of the patients who completed 28 weeks of treatment and attended all of the additional psychosocial treatment sessions were included in the per protocol sample (n=97).

Two-tailed testing with the level of significance set at 5% was used throughout the study. Time to the first relapse was evaluated with survival analysis and log-rank test. χ²-Tests were used for analysing abstinence rates during the last 6 weeks of treatment. Total number of abstinent days, level of psychological distress, and γ-GT were examined using the Kruskal-Wallis test. Number of drinks per drinking day was examined with the Cochran-Mantel-Haenszel test.

In a post hoc analysis, the influence of subjects’ baseline characteristics and the role of differences between centres was investigated by analyzing the variance of the residual variability in the main outcome measure using both centre and the interaction between centre and treatment, by applying a general non orthogonal analysis of
variance, calculated through a General Linear Model (sum of squares decomposition type III).

RESULTS

Sample characteristics
Of the 241 in the ITT sample, 77 (32.0%) were randomized to receive acamprosate alone, 86 (35.7%) to receive acamprosate plus MI, and 78 (32.3%) to receive acamprosate plus BCBT (Figure 1).

Figure 1. Randomization and progress of patients through the trial.

Note: MI = Minimale Intervention. BCBT = Brief Cognitive Behavioral Therapy. ITT = Intention To Treat sample (patients receiving at least one dose of medication and thus providing at least one key point after baseline). PP = Per Protocol sample (patients who completed 28 weeks of pharmacotherapy and completed all of the additional psychosocial treatment sessions).
The data in Table 1 show no statistically significant differences between the treatment groups at baseline in socio-demographic variables, family history of alcohol problems, psychological distress or history and patterns of drinking problems.

Table 1. Baseline socio-demographical and drinking data*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acamprosate (n=77)</th>
<th>Acamprosate + MI (n=86)</th>
<th>Acamprosate + BCBT (n=78)</th>
<th>Total group of patients (n=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>44.3 ± 7.6</td>
<td>44.8 ± 8.7</td>
<td>44.3 ± 9.5</td>
<td>44.5 ± 8.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65 (84.4)</td>
<td>72 (83.7)</td>
<td>63 (80.8)</td>
<td>200 (83.0)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (15.6)</td>
<td>14 (16.3)</td>
<td>15 (19.2)</td>
<td>41 (17.0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>74 (96.1)</td>
<td>86 (100)</td>
<td>76 (97.4)</td>
<td>236 (97.9)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3.7)</td>
<td>0 (100)</td>
<td>2 (2.6)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Civil status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>18 (23.4)</td>
<td>19 (22.1)</td>
<td>17 (21.8)</td>
<td>54 (22.4)</td>
</tr>
<tr>
<td>Married / cohabiting</td>
<td>37 (48.1)</td>
<td>52 (60.5)</td>
<td>39 (50.0)</td>
<td>128 (53.1)</td>
</tr>
<tr>
<td>Divorced</td>
<td>20 (26.0)</td>
<td>14 (16.3)</td>
<td>20 (25.6)</td>
<td>54 (22.4)</td>
</tr>
<tr>
<td>Widower</td>
<td>2 (2.6)</td>
<td>1 (1.2)</td>
<td>2 (2.6)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>43 (55.8)</td>
<td>61 (70.9)</td>
<td>36 (46.2)</td>
<td>140 (58.1)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>34 (4.2)</td>
<td>25 (29.1)</td>
<td>42 (53.8)</td>
<td>101 (41.9)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma-GT (U/l)</td>
<td>115.8 ± 194.7</td>
<td>92.9 ± 105.1</td>
<td>127.2 ± 246.8</td>
<td>111.1 ± 188.2</td>
</tr>
<tr>
<td>No. of drinks per drinking day</td>
<td>15.7 ± 8.3</td>
<td>14.2 ± 8.2</td>
<td>16.1 ± 9.6</td>
<td>15.3 ± 8.7</td>
</tr>
<tr>
<td>Years of alcohol problems</td>
<td>11.1 ± 7.5</td>
<td>11.8 ± 8.7</td>
<td>12.0 ± 8.2</td>
<td>11.6 ± 8.1</td>
</tr>
<tr>
<td>Family member with alcohol problems</td>
<td>43 (55.8)</td>
<td>43 (50.0)</td>
<td>40 (51.3)</td>
<td>126 (52.3)</td>
</tr>
<tr>
<td>Meeting DSM-IV criteria for alcohol dependence</td>
<td>74 (97.4)</td>
<td>84 (97.7)</td>
<td>77 (98.7)</td>
<td>235 (97.9)</td>
</tr>
<tr>
<td>Previous treatment for alcohol problems</td>
<td>46 (59.7)</td>
<td>57 (66.3)</td>
<td>47 (60.3)</td>
<td>150 (62.2)</td>
</tr>
<tr>
<td>Frequency of drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>50 (64.9)</td>
<td>58 (67.4)</td>
<td>54 (69.2)</td>
<td>162 (67.2)</td>
</tr>
<tr>
<td>Weekends</td>
<td>3 (3.9)</td>
<td>1 (1.2)</td>
<td>6.6 (7.7)</td>
<td>10 (4.1)</td>
</tr>
<tr>
<td>Continuous (not daily)</td>
<td>13 (16.9)</td>
<td>16 (18.6)</td>
<td>11 (14.1)</td>
<td>40 (16.6)</td>
</tr>
<tr>
<td>Episodic</td>
<td>11 (14.3)</td>
<td>11 (12.8)</td>
<td>7 (9.0)</td>
<td>29 (12.0)</td>
</tr>
</tbody>
</table>

Note: Values are means ± SD or numbers (%). MI = Minimal intervention; BCBT = Brief Cognitive Behavioral Therapy.
* None of the variables differed significantly across the treatment groups.
Drop-out and treatment compliance

Of the 241 patients, 114 (47.3%) remained in treatment for the 28 weeks. A patient was regarded as a drop-out when he or she stopped the pharmacotherapy before week 28. The drop-out rates and reasons for termination are reported in Figure 1. There were no significant differences in the drop-out rates or reasons for termination across the three treatment conditions.

The mean duration of the treatment was 148.2 days (SD 73.5). There were no significant differences between the three treatment groups in treatment duration [$\chi^2(2)=0.265$, $P=0.876$]. Patients who remained in treatment took between 89 and 100% of the prescribed medication. There were no statistically significant differences in medication compliance across the treatment conditions.

Patients receiving medication plus MI attended a mean number of 2.84 of the intervention sessions (out of three 20-min sessions). Patients receiving medication plus BCBT attended a mean number of 5.32 of the sessions (out of seven 60-min sessions).

Drinking outcomes

Total number of abstinent days: The total number of abstinent days (±SD) was 108.5 ± 71.2 for group 1, 119.1 ± 135.5 for group 2, and 108.1 ± 100.0 for group 3. The total number of abstinent days for the total group of patients was 111.2 ± 72.6 (median 107.0), which is 56.7% abstinent days during 28 weeks of treatment (ITT sample). There were again no statistically significant differences between the treatment groups [$\chi^2(2)=1.501$, $P=0.472$]. For the PP sample, the mean number of abstinent days was 173.9 days (median 183.0) or 88.7% abstinent days. Again, there were no statistically significant differences between the treatment groups [$\chi^2(2)=5.109$, $P=0.078$].

Rates of continuous abstinence: The ITT results show that 13.0% of the patients in group 1, 20.9% of group 2, and 10.3% of group 3 were continuously abstinent across the entire 28-week treatment period (Fig.2). The PP sample yielded the following percentages: 27.0, 40.9 and 18.8% respectively. The differences between the treatment groups for both the ITT and the PP samples were not significant [$\chi^2(2)=4.006$, $P=0.135$; $\chi^2(2)=3.319$, $P=0.190$].
Figure 2. Survival analysis. Continuous abstinence for the treatment period.

Note:

= Acamprosate

= Acamprosate and Minimal Intervention

= Acamprosate and Brief Cognitive Behavioral Therapy
Abstinence rates during the last six weeks of treatment: As already mentioned, the abstinence rates for the periods between visits were recorded at each visit. An overview of the abstinence rates for the last six weeks of treatment is presented in Table 2. Statistical analyses were performed for three categories: abstinent, relapse, and missing. During the last 6 weeks of the 28-week treatment period, 18.2% of the ITT patients in group 1, 24.4% of group 2, and 17.9% of group 3 were abstinent; 37.8, 47.7 and 31.3% of the PP sample groups were abstinent. None of the analyses revealed statistically significant differences [(χ²(4)=2.447, P=0.654; χ²(2)=1.600, P=0.449).

Table 2. Number of patients who were abstinent, relapsed, or missing during the last six weeks of treatment (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Acamprosate (n=77)</th>
<th>Acamprosate + MI (n=86)</th>
<th>Acamprosate + BCBT (n=78)</th>
<th>Total group of patients (n=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT sample *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>14 (18.2)</td>
<td>21 (24.4)</td>
<td>14 (17.9)</td>
<td>49 (20.3)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>23 (29.9)</td>
<td>23 (26.7)</td>
<td>19 (24.4)</td>
<td>65 (27.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>40 (51.9)</td>
<td>42 (48.8)</td>
<td>45 (57.7)</td>
<td>127 (52.7)</td>
</tr>
</tbody>
</table>

| Per protocol sample ** | | | | |
|-----------------------|-------------------------|--------------------------|--------------------------------|
| Abstinent             | 14 (37.8)               | 21 (47.7)                | 5 (31.3)                        | 40 (41.2)                      |
| Relapsed              | 23 (62.2)               | 23 (52.3)                | 11 (68.8)                       | 57 (58.8)                      |

Note:
* ITT sample: P=0.654
** Per protocol sample: P=0.449
For abbreviations, see Table 1

Time to first relapse. Survival analyses were completed to examine the time to first relapse throughout the 28-week treatment period. The mean (±SD) number of days to the first relapse was 53.4 ± 6.5 for group 1, 65.5 ± 7.0 for group 2, and 55.4 ± 6.5 for group 3 (ITT). There were no significant differences between the treatment groups [χ²(2)=0.843, P=0.656]. In the PP sample, the mean number of days to the first relapse was 61.2 ± 9.4, 90.9 ± 9.8, and 41.5 ± 10.3, respectively. Analyses again revealed no statistically significant differences between the PP treatment groups [χ²(2)=4.761, p=0.093].

Number of drinks per drinking day: During the last 6 weeks of treatment, the mean number of drinks per drinking day for those patients who relapsed was 8.0 ± 6.5
for group 1, 6.1 ± 4.1 for group 2, and 5.1 ± 4.1 for group 3. Statistical tests on the differences between week 28 and the start of the treatment did not reveal significant differences between the treatment groups \( \chi^2(2) = 1.971, P=0.373 \).

**Lab values:** The mean \( \gamma\)-GT level for those patients who completed the entire treatment period was 52.0 ± 60.6 in group 1, 49.1 ± 54.1 in group 2, and 50.2 ± 88.7 in group 3. The differences between the mean \( \gamma\)-GT level at the start of the treatment and week 28 did not differ significantly between the treatment groups \( \chi^2(2)=2.520, P=0.284 \).

**Psychosocial outcomes**

In week 28 the mean SCL-90 score (± SD) was 131.6 ± 45.1 for the patients in group 1, 119.0 ± 29.7 for group 2, and 132.7 ± 57.3 for group 3. The level of psychological distress had decreased compared with pretreatment levels, but this decrease was similar in the three treatment groups \( \chi^2(2)=0.884, P=0.643 \). Analysis of the subscales of the SCL-90 questionnaire also revealed no significant differences between the various treatment groups.

Only a few patients attended self help groups (3.4%) and 22.9% of the patients consulted some other professional for alcohol-related problems during the treatment. In almost every case, it was a general practitioner that was consulted by the patient. There were no significant differences in additional treatments between treatment groups.

**Follow-up after treatment ended**

A total of 169 patients from the ITT population (70.1%) were contacted 6 months after the treatment period ended: 52 from group 1 (67.5%), 64 from group 2 (74.4%), and 53 from group 3 (67.9%) (difference between groups were not significant). With regard to the ITT patients, 13.0, 16.3 and 14.1% of the patients in groups 1, 2, and 3 respectively were found to be continuously abstinent from the end of treatment to follow-up \( \chi^2(4) =2.547, P=0.636 \). From the start of the treatment to the end of the follow-up period, 9.9% of the patients in group 1, 12.8% of the patients in group 2, and 8.9% of the patients in group 3 were continuously abstinent. Significant differences between the treatment groups were not detected.

The mean level of psychological distress at follow-up (±SD) was 135.3 ± 49.7. Tests on the difference between follow-up and the start of treatment reveal no significant difference between the treatment groups \( \chi^2(2)=1.376, p= 0.503 \). Thus, none of the analyses reveal significant differences between the treatment groups at 6 months follow-up.
Post hoc analysis

To take into account the other possible effects on outcomes, an additional analysis was applied on the total number of abstinent days (Table 3). Due to expected departures from normality and inequality in variances, the total number of abstinent days was rank-transformed. After sequential backward elimination of non-significant terms, the following terms remained significant predictors: age, total number of DSM-IV alcohol dependence symptoms, and an interaction between treatment group and centre.

Table 3. Analysis of variance in the rank-ordered total number of abstinent days (assessed by general linear model, sum of suares decomposition of type III).

<table>
<thead>
<tr>
<th></th>
<th>d.f.</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSTANT</td>
<td>1</td>
<td>21159.064</td>
<td>21159.064</td>
<td>5.151</td>
<td>.809</td>
</tr>
<tr>
<td>Centre</td>
<td>13</td>
<td>51403.582</td>
<td>3954.122</td>
<td>0.963</td>
<td>.649</td>
</tr>
<tr>
<td>Treatment</td>
<td>2</td>
<td>26072.481</td>
<td>13036.241</td>
<td>3.174</td>
<td>.183</td>
</tr>
<tr>
<td>Centre.trt</td>
<td>26</td>
<td>210741.066</td>
<td>8105.426</td>
<td>1.973</td>
<td>.007</td>
</tr>
<tr>
<td>DSM total</td>
<td>1</td>
<td>18335.892</td>
<td>18335.892</td>
<td>4.464</td>
<td>.039</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>48765.432</td>
<td>48765.432</td>
<td>11.872</td>
<td>.001</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>10174.733</td>
<td>10174.733</td>
<td>2.477</td>
<td>.316</td>
</tr>
<tr>
<td>ERROR1</td>
<td>195</td>
<td>800952.677</td>
<td>4107.450</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: d.f., degrees of freedom; SS, sum of squares; MS, mean square; centre.trt, centre x treatment interaction; DSM total, number of positive answers on the DSM-IV criteria for alcohol dependence.

DISCUSSION

The present study is the first to assess the effectiveness of acamprosate in isolation (i.e., without additional psychosocial intervention). Although the general treatment outcome is lower than in a German acamprosate study (Sass et al., 1996), nevertheless the outcomes for the three treatment groups nevertheless resemble those of patients receiving acamprosate in placebo-control studies with the Dutch population (Geerlings, Ansoms & van den Brink, 1997; Ansoms et al., 2000).

Contrary to our hypotheses, adding a psychosocial intervention to the prescription of acamprosate did not enhance drinking outcomes or compliance with the medication.
There was also no reduction in drop-out rates or the level of psychological distress. Even in those patients who completed the pharmacotherapy and were compliant with the psychosocial interventions, no differences in treatment outcome between the treatment groups were found. Although minimal interventions and brief cognitive behavioural therapy have been shown to be effective for the treatment of alcohol problems (Miller et al., 1998), their supplemental value in combination with pharmacotherapy could not be demonstrated.

It could be argued that the additional psychosocial intervention was not sufficient to produce significant differences in treatment outcome. The patients receiving no psychosocial intervention had, like the other groups, consultation with the physicians six times in 28 weeks. The total contact time with the physician was 1 hour. The minimal intervention group was seen in addition for three sessions of 20 min duration each, which only represents an extension of 1 h of contact beyond that of the acamprosate-only group. Being involved in a research intervention itself might also have had a benefit for the patients. While the minimal intervention was relatively limited in time and frequency, the difference between acamprosate medication alone and acamprosate plus brief cognitive behavioural therapy was quite marked. Total contact time offered was extended by a further 7 h, and a broad spectrum of behaviours and issues was addressed. Interventions aimed at teaching coping skills are strongly supported in reviews of alcohol treatment outcome studies (Miller et al., 1998).

In clinical practice, it is generally recommended to prescribe acamprosate for a period of 1 year. However, we believe that prescription of acamprosate for 1 year would not have given different results. Less than 50% of the patients completed 28 weeks of pharmacological treatment. In addition, an extended treatment duration would have made the supplemental value of psychosocial treatment even less marked in relative terms. This suggests that yet another explanation for the lack of any supplemental treatment effect must be sought.

A potential explanation for the present findings may lie in biased sample selection. Although the demographic and alcohol-related baseline characteristics of the subjects in this study shows closely resemble those of the population of patients with alcohol problems seen in the outpatient addiction centres in The Netherlands, it is possible that another bias may have entered: patients with a clear interest in psychosocial treatment might have refused to participate in the study for fear of not being referred to a therapist. This may have influenced the outcomes of the psychosocial interventions in a negative manner.

The integrity and consistency of the different treatments undertaken in the present study were carefully controlled for. The adherence of the therapists and physicians to the manuals and guidelines was good. Only a few protocol violations
occurred. In addition, the patients treated in groups 2 and 3 received, as intended, more psychosocial intervention in total, which means that the independent variable was successfully manipulated and that the lack of significant differences between the treatment groups is not a consequence of poor internal validity. The internal validity was also not jeopardized by patients attending psychosocial treatment outside the interventions provided in the study. Few patients attended self-help groups or consulted other professionals for alcohol problems, and numbers of these were not significantly different between treatment groups.

Since the assessing physicians were not blind to the treatment conditions of the patients, it is possible that they might have been biased in their assessments in one way or the other. However, we have no indications as to which way, if at all, they might have been biased.

We believe the study was powerful enough to detect differences in outcome between the treatment groups. Also, the outcome measures for drinking behaviour that we used were shown in previous studies to be sensitive enough to detect differences between treatment groups. However, since we found a significant interaction between centres and treatment conditions, we cannot rule out the possibility that, although the general results show no supplemental value of extra psychosocial intervention, in some centres there was a positive effect of additional psychosocial intervention, while in others there was a negative or no effect of such intervention.

We conclude that the supplemental value of minimal and brief psychosocial interventions to the prescription of acamprosate could not be demonstrated in the current study. It is possible that more intensive psychosocial intervention is needed to really improve treatment results. Conversely, one can argue that the medical prescription of acamprosate without additional psychosocial intervention is a realistic and sufficient treatment option for at least a particular group of patients. The general assumption that pharmacological treatment for alcohol dependence should always be accompanied by some form of psychosocial intervention is thus open to debate. Further research is, therefore, needed in order to develop evidence-based guidelines regarding the combination of pharmacotherapy and psychosocial intervention for alcohol problems.
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CHAPTER 3

EFFECTIVENESS OF MANUAL-BASED
COGNITIVE BEHAVIORAL THERAPY IN
ROUTINE OUTPATIENT ALCOHOL
TREATMENT

Koeter, W. van den Brink (* both authors contributed equally)

Submitted for publication
ABSTRACT

Aims: Motivational interviewing and cognitive behavioural therapy have proven efficacy in the treatment of alcoholic patients. However, the effectiveness in routine practice has, until now, not been assessed in large samples. Naturalistic outcomes studies are a necessary addition to RCTs to provide information on the merits of these interventions in a routine treatment environment. The present study examined the outcomes of two evidence-based interventions for alcoholic patients in routine clinical practice and assessed whether patient characteristics are predictive of treatment outcome.

Methods: A total of 599 alcoholic patients admitted for outpatient treatment in two addiction centres were allocated, based on a stepped care protocol, to a brief cognitive behavioural therapy (BCBT) or to a standard cognitive behavioural therapy (SCBT). Treatments were manual-based. Drinking behaviour was assessed at nine months follow-up.

Results: In accordance with the stepped care protocol, patients in SBCT were more severe in terms of addiction severity, social problems and psychiatric problems. Also, BCBT and SCBT showed to differ in treatment intensity. Almost half of the patients (49.2%) were treated according to the prescribed sessions. In BCBT 59.0% completed treatment, in SCBT 40.8%. At nine months follow-up, 25.2% of the patients achieved abstinence, 18.0% were drinking in a controlled way, 56.8% were drinking heavily. Several variables were predictive for treatment outcome, but the overall variance accounted for by the predictors was small.

Conclusion: Findings indicate that treatment outcomes of alcohol RCTs are preserved in routine practice. Outcomes might be further improved by additional relapse prevention strategies and post-treatment telephone-based evaluations, identifying patients who are in need of more intensive treatment.
INTRODUCTION

Randomized controlled trials (RCTs) are the methodological gold standard for establishing efficacy of interventions in medicine. This is also true for the test of new treatments in alcohol use disorders. In RCTs, treatments are tested under ideal conditions with specially trained and supervised therapists in order to evaluate whether they improve outcomes as compared to control or other treatments. Exclusion criteria are used to maximize homogeneity. In Project MATCH and the COMBINE study more than 60% of patients presenting for alcohol treatment were not eligible for the study as a result of exclusion criteria (Anton et al., 2006; Project Match Research Group, 1997). As such, internal validity is given high priority in RCTs, thereby facilitating the evaluation of efficacy (i.e. how well a treatment works under ideal conditions). As a consequence, most RCTs suffer from low external validity and do not necessarily offer a realistic estimate of effectiveness (i.e., how well a treatment works in the real world of day-to-day clinical practice). In summary, internal validity is improved at the expense of external validity and thus clinical relevance. Naturalistic outcome studies, observing the effectiveness of interventions in routine practice, are a necessary addition to RCTs in order to test the ecological validity and to provide information on the merits of these interventions in a routine treatment environment. In pharmacotherapy research these so-called phase IV studies are part of the testing process, but this is less common in psychotherapy research.

In the field of drug use disorders several large-scale naturalistic outcome studies have been conducted (Gossop, Marsden, Stewart, & Kidd, 2003; Hubbard, Craddock, & Anderson, 2003). In the field of alcohol use disorders, naturalistic studies evaluating the effectiveness of treatments are scarce. A few studies have focused on relapse and mortality rates in treated alcoholics followed over periods of eight years and more (Finney & Moos, 1991; Mann, Schafer, Langle, Ackermann, & Croissant, 2005). These studies reveal the course of alcoholism, but give no insight into outcomes of treatment programs because, due to the long follow-up duration, the relation between treatment and patient’s drinking behaviour is weak. Some naturalistic pharmacotherapy studies are available. For example, acamprosate studies have been conducted on the combination of pharmacotherapy and psychosocial interventions in naturalistic conditions (Pelc et al., 2002; Soyka, Preuss, & Schuetz, 2002). The available naturalistic studies on treatment outcome of psychotherapeutic interventions for alcohol use disorders, some with limited sample sizes, focus on intensive and long-term interventions consisting of a mixture of psychotherapeutic methods (f.e. Bottlender & Soyka, 2005; Gual, Ligon, & Colom, 1999; Ojehegen, Berglund, & Moberg, 1994; Ojehegen, Skjaerries, & Berglund, 1988). However, it is unclear whether these treatments were evidence based. In general, non-
randomized studies are more likely than randomized studies to examine broad or unspecified treatments (Moyer & Finney, 2002).

Motivational interviewing (Miller & Rollnick, 1991, 2002) and cognitive behavioral skills training (Marlatt & Gordon, 1985; Monti, Abrams, Kadden, & Cooney, 1989) have proven efficacy in outpatient treatment of patients with alcohol use disorders (Miller & Wilbourne, 2002). However, the effectiveness of these interventions in a routine treatment environment has, until now, not been assessed in large samples. Therefore, the present follow-up study aims to provide information on the merits of motivational interviewing and cognitive behavioral skills training in alcoholic patients in routine practice. A brief cognitive behavioral therapy (BCBT) and a standard cognitive behavioral therapy (SCBT), modeled after the Project MATCH manuals for motivational enhancement therapy and cognitive behavioral coping skills therapy (Kadden et al., 1994; Miller, Zweben, DiClemente, & Rychtarik, 1994), were described in manuals and implemented according to a stepped care protocol (Merkx et al., 2007; Sobell & Sobell, 2000) in two substance abuse treatment centers. In addition, routine outcome monitoring was implemented by conducting telephone-based interviews at nine months follow-up (Oudejans et al., 2009).

The following research questions are investigated in routine clinical practice:

1) Do baseline characteristic of patients in BCBT differ from patients in SCBT?
2) What is the treatment consumption of treatment-seeking, alcohol-dependent patients in manual-based BCBT and SCBT?
3) Do BCBT and SCBT differ in treatment intensity when applied in routine practice?
4) What is the effectiveness of manual-based BCBT and SCBT in treatment seeking alcohol dependent patients in terms of drinking behavior and polysubstance abuse at 9 months follow-up?
5) Which pre-treatment patient characteristics are predictive of treatment consumption of BCBT and SCBT?
6) Which pre-treatment patient characteristics and process variables (i.e. treatment consumption) are predictive of treatment outcome (i.e. drinking behavior) of BCBT and SCBT at 9 months follow-up?

**METHODS**

**Sample**
The study population consisted of patients admitted for alcohol use disorders to outpatient treatment in the period June 2003 – October 2004 in two regional Dutch substance abuse treatment centers, one in a large city and one in a suburban area.
As shown in Figure 1, from all 3,118 patients admitted, 523 patients (16.8%) did not show up for treatment after intake. A total of 1,013 patients (32.5%) started more intensive treatments like inpatient treatment. Patients that needed detoxification in a day treatment or inpatient facility prior to or during outpatient treatment were also considered inpatients. The remaining 1,582 patients (50.7%) started outpatient treatment. Of these, 477 (30.2%) started BCBT, 684 (43.2%) started SCBT and 421 (26.6%) were referred to other forms of outpatient treatment (like group CBT, not taken into account here).

![Flow-chart sampling](image)

**Figure 1.** Flow-chart sampling

**Note:** BCBT = brief cognitive behavioural therapy, SCBT = standard cognitive behavioural therapy.

All patients were informed at intake that they would be approached routinely by phone after nine months for a follow-up interview, as was standard procedure within the ROM system employed in both treatment centers. Of the 1,161 patients in the two treatment
modalities a total of 599 patients (51.6%) were successfully interviewed at follow-up. In a previous study of our research group on the feasibility of the method of telephonic follow-up interviews within this ROM system, detailed figures on non-response reasons became available. Main reasons for non-responds data were mostly inability to contact the patient (35.1%), and the percentage of refusals was small (3.3%). Other reported reasons for non-response include language problems, patients that turned out to be deceased, deaf or hearing-impaired patients, and intoxicated patients. (Oudejans et al, 2009).

The group of 599 respondents comprised the study sample. Treatment centers did not differ in percentage of patients referred to BCBT and SCBT.

**Follow-up attrition**

Overall, 51.6% of the patients were successfully interviewed at follow-up, which took place nine months after intake. There was no significant difference in follow-up rate between the treatment centers. However, follow-up rates differed significantly between BCBT (58.3%) and SCBT (46.9%) ($\chi^2_{(1)} = 16.97; p=0.00$). To assess selection bias due to follow-up attrition, differences between non-respondents and respondents were analyzed using t-tests and $\chi^2$-tests. As shown in Table 1, patients who were successfully followed-up were slightly older. In BCBT, non-respondents were more likely to be living alone and to have more severe alcohol problems. In SCBT, non-respondents were less likely to be Dutch and employed. In addition, they were having less family problems and less heavy drinking days than non-respondents.
### Table 1: Follow-up attrition: patient baseline socio-demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Brief Respondents (n = 278)</th>
<th>CBT Non-respondents (n = 199)</th>
<th>Standard Respondents (n = 321)</th>
<th>CBT Non-respondents (n = 363)</th>
<th>Δ respondents - nonrespondents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>45.0 ± 11.9</td>
<td>42.8 ± 11.6³</td>
<td>45.8 ± 11.3</td>
<td>43.0 ± 10.4³ **</td>
<td>³ T(145)=2.0; p=0.045 **</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>** T(562)=3.4; p=0.001 **</td>
</tr>
<tr>
<td><strong>Ethnicity</strong> Dutch</td>
<td>226 (90.0)</td>
<td>154 (85.1)</td>
<td>273 (74.1)</td>
<td>274 (83.5)³</td>
<td>³ χ²(1) = 10.03; p=0.002</td>
</tr>
<tr>
<td><strong>Civil status</strong> Alone</td>
<td>160 (60.6)</td>
<td>145 (74.7)³</td>
<td>232 (74.1)</td>
<td>264 (75.2)</td>
<td>³ χ²(1) = 10.05; p=0.002</td>
</tr>
<tr>
<td><strong>Source of income</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>** χ²(3) = 11.68; p=0.009</td>
</tr>
<tr>
<td>Employment</td>
<td>178 (66.9)</td>
<td>118 (61.5)</td>
<td>178 (57.6)</td>
<td>175 (49.4)³</td>
<td></td>
</tr>
<tr>
<td>Unemployment</td>
<td>57 (21.4)</td>
<td>48 (25.0)</td>
<td>102 (33.0)</td>
<td>132 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Pension</td>
<td>14 (5.3)</td>
<td>9 (4.7)</td>
<td>13 (4.2)</td>
<td>8 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>17 (6.4)</td>
<td>17 (8.9)</td>
<td>16 (5.2)</td>
<td>39 (11.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drinking days in last 30 days</td>
<td>15.1 ± 11.7</td>
<td>14.5 ± 11.4</td>
<td>15.8 ± 11.7</td>
<td>17.4 ± 11.2</td>
<td></td>
</tr>
<tr>
<td>Number of drinking days &gt; 4 glasses in last 30 days</td>
<td>12.5 ± 11.3</td>
<td>13.5 ± 11.6</td>
<td>14.7 ± 11.6</td>
<td>17.2 ± 11.0³³</td>
<td>** χ²(3) = 11.68; p=0.009</td>
</tr>
<tr>
<td><strong>Psychiatric problems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of psychiatric problems (ASI)</td>
<td>2.5 ± 1.8</td>
<td>2.7 ± 1.9</td>
<td>3.4 ± 2.0</td>
<td>3.6 ± 2.0</td>
<td></td>
</tr>
<tr>
<td><strong>Family and Social Problems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of family and social problems (ASI)</td>
<td>1.9 ± 1.6</td>
<td>2.0 ± 1.7</td>
<td>2.5 ± 1.8</td>
<td>2.9 ± 1.7³³</td>
<td>** χ²(3) = 11.68; p=0.009</td>
</tr>
<tr>
<td><strong>Treatment consumption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>164 (59.0)</td>
<td>95 (47.7)</td>
<td>131 (40.8)</td>
<td>154 (42.4)</td>
<td></td>
</tr>
<tr>
<td>Over-treated</td>
<td>62 (22.3)</td>
<td>54 (27.1)</td>
<td>63 (19.6)</td>
<td>75 (21.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Values are means ± SD or numbers (%). CBT = cognitive behavioral therapy; ASI = Addiction Severity Index

### Procedure

Each patient participated in a treatment intake interview, consisting of two or three one-hour sessions. The first interview addressed socio-demographic background, reasons for admission, treatment history and pattern of substance use. In the second interview, the...
European version of the Addiction Severity Index (Kokkevi & Hartgers, 1995) was administered by staff of the intake team (mainly social workers and psychologists). If indicated, a medical or psychiatric examination was performed. Data was entered into the Electronic Patients Records (EPRs).

According to a stepped care protocol (Merkx et al., 2007; Sobell & Sobell, 2000) each patient was referred to one of the following levels of care: (1) brief outpatient treatment, (2) standard outpatient treatment, (3) day treatment or residential treatment, and (4) long-term psychosocial care. Patients were referred to the first level of care if they had a maximum of one previous treatment episode in the last 5 years, and severity of alcohol problems, psychopathology and social problems were low or moderate. If patients did not fulfill the criteria for brief outpatient treatment, they were referred to the second level of care. Or, where severe social problems (e.g. being homeless) were present, or a treatment history of more than two treatment episodes, patients were referred to more intensive or longer types of treatment (e.g. day or residential treatment, long-term psychosocial care). The present study focuses on patients referred to manual-based individual CBT on one of the first two levels of care (i.e. BCBT and SCBT).

**Treatment**

BCBT consisted of four 45 minutes sessions in a period of two months. SCBT consisted of ten 45 minutes sessions in a period of six months. Both interventions were manual-based (Leefstijltraining 1: de Wildt, 2000; Leefstijltraining 2: de Wildt, 2001).

In BCBT, motivational enhancement was more dominant than behavioral interventions. In order to enhance motivation for change, the techniques of motivational interviewing were used (Miller & Rollnick, 1991, 2002). Coping skills training and relapse prevention techniques were administered to reach abstinence or controlled drinking and to prevent patients from relapse (Marlatt & Gordon, 1985; Monti et al., 1989). Patients were helped to identify high-risk situations, cope with urges and craving and were trained in refusal skills. An individual emergency plan was developed to prevent a relapse when a lapse occurred. In SCBT more sessions were available to apply motivational interviewing and to teach the coping skills as described in BCBT. In addition, extra topics could be selected (e.g. managing depressive mood, enhancing social support, increasing pleasant activities). In both treatments a significant other was invited to support the patient in changing his or her behavior.

Both treatments were performed by social workers, psychologists and psychiatric nurses. Implementation of these interventions took place in the year 2000, i.e. 3-4 years before the start of the current study. Due to turn over of staff the range of clinical
experience with the interventions varied from a few months to four years. However, every staff member received intensive training.

**Measurements**
Data on pretreatment socio-demographic, clinical characteristics and type and amount of treatment sessions was collected through the EPR. EuropASI severity scores on the sections alcohol and drug use, gambling, psychiatric problems and family and social relations represented severity of drinking and co-morbid problems. Drinking behavior was further specified with the ASI items on age of onset, years of alcohol use and number of (heavy) drinking days. For the presence of polysubstance abuse we relied on the EPRs. The routinely administered 9-month follow-up interview provided data on treatment outcomes. Independent (not overlapping with intake staff or treatment providers) and specially trained interviewers re-contacted patients by phone. The interview focused on patient satisfaction, quality of life and the eight EuropASI problem sections. Each section comprised of questions about the 30 days preceding the follow-up interview. In this study, only the items from the alcohol, drugs and gambling sections of the EuropASI were used to assess treatment outcome.

**Treatment consumption**
To evaluate treatment consumption we quantified the number of actual attended treatment sessions registered in the EPRs. Three levels of treatment consumption were distinguished: 1) patients who were under-treated; 2) patients who completed treatment according to the manual and 3) patients who were over-treated.

In BCBT patients were considered to be under-treated if they attended less than three of the four sessions, completers if they attended three to five sessions, and over-treated if they attended six or more sessions. SCBT patients were considered under-treated when attending less than six sessions, completers if they attended six to eleven sessions, and over-treated if they attended twelve sessions or more. In addition, the mean number of attended sessions was calculated.

**Treatment effectiveness**
Primary outcome measure was self-reported alcohol use in the 30 days preceding the follow-up interview. Three outcome categories were distinguished:
- current complete abstinence (no alcohol use in the last 30 days);
- current controlled drinking (up to 21 days in the last month for men, up to 14 days for women and no days with more than 4 glasses),
- current harmful/heavy drinking (more than 21 days for men and more than 14 days for women in the last month, or days with more than 4 glasses).
In order to further specify drinking behavior for the patients who were categorized as controlled drinkers or heavy drinkers, we calculated their mean number of (heavy) drinking days in the 30 days prior to follow-up.

Secondary outcome measure was self-reported use of concurrent substances and gambling (polysubstance abuse). Patients were categorized as completely abstinent from concurrent substances when they refrained from substance(s) in the last 30 days. Controlled use of concurrent substances was defined as up to 6 days of use in the last 30 days. Harmful use was defined as more than 6 days of use in the last 30 days.

Data-analysis
The study sample consisted of 599 patients receiving at least one therapy session and providing follow-up information. Baseline differences between both treatment groups were analyzed using t-tests and \( \chi^2 \)-tests, to evaluate whether the stepped care allocation indeed resulted in different patient groups. Difference in number of attended sessions between BCBT and SCBT were evaluated using a t-test in order to determine whether BCBT and SCBT indeed differed in treatment intensity.

To assess which patients or process characteristics were predictive of treatment consumption and treatment effectiveness, the following potential predictors were used: type of treatment, treatment center, socio-demographic characteristics, pre-treatment characteristics of drinking pattern, polysubstance abuse and severity of co-morbid problems. The outcome measures treatment consumption and effectiveness were dichotomized. Treatment consumption was dichotomized into “not completed” and “completed”, where the “completed” group represented all patients who completed the treatment and patients who were “over-treated” as described above. Effectiveness was dichotomized as “success” (complete abstinence and controlled drinking) and “no success” (harmful/heavy drinkers). Univariate associations between potential predictors for treatment completion were calculated with type of treatment as a covariate and we established possible interaction effects. To establish independent predictors for treatment consumption we entered all variables in a multiple logistic regression using a likelihood ratio procedure (backward elimination). The same statistical procedure was conducted to assess predictors for treatment success.

RESULTS

Sample
Table 2 describes the baseline characteristics of the patients at intake. The mean (± SD) age of the study sample was 45.4 ± 11.6. Men composed 68.8% of the sample. In the
30 days prior to treatment, patients reported a mean of more than 15 drinking days, and a mean of more than 13 heavy drinking days. The mean alcohol use severity score on the ASI was 4.8 ± 1.1. On average patients had a 13-year history of alcohol problems. 21.9% also used other substances, mainly cannabis and cocaine. In accordance with the stepped care paradigm, the SCBT group was more severe in terms of addiction severity, social problems and psychiatric problems.

Table 2: Patient baseline socio-demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>BCBT (n = 278)</th>
<th>SCBT (n = 321)</th>
<th>Total (n = 599)</th>
<th>Statistical tests Δ BCBT - SCBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n = 599)</td>
<td>45.0 ± 1.9</td>
<td>45.8 ± 1.3</td>
<td>45.4 ± 1.16</td>
<td></td>
</tr>
<tr>
<td>Sex (n = 599)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>193 (69.4%)</td>
<td>219 (68.2%)</td>
<td>412 (68.8%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (n = 548)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td>226 (90.0%)</td>
<td>273 (91.9%)</td>
<td>499 (91.1%)</td>
<td></td>
</tr>
<tr>
<td>Civil status (n = 577)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>160 (60.6%)</td>
<td>232 (74.1%)</td>
<td>392 (67.9%)</td>
<td></td>
</tr>
<tr>
<td>Source of income (n = 575)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>178 (66.9%)</td>
<td>178 (57.6%)</td>
<td>356 (61.9%)</td>
<td>x²(1) = 12.01; p=0.001</td>
</tr>
<tr>
<td>Unemployment/social security</td>
<td>57 (21.4%)</td>
<td>102 (33.0%)</td>
<td>159 (27.7%)</td>
<td></td>
</tr>
<tr>
<td>Pension</td>
<td>14 (5.3%)</td>
<td>13 (4.2%)</td>
<td>27 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>17 (6.4%)</td>
<td>16 (5.2%)</td>
<td>33 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drinking days in last 30 days (n = 451)</td>
<td>15.1 ± 1.17</td>
<td>15.8 ± 1.17</td>
<td>15.4 ± 1.17</td>
<td></td>
</tr>
<tr>
<td>Number of drinking days &gt; 4 glasses in last 30 days</td>
<td>12.5 ± 1.3</td>
<td>14.7 ± 1.6</td>
<td>13.7 ± 1.15</td>
<td></td>
</tr>
<tr>
<td>Age of onset (drinking) (n = 463)</td>
<td>19.1 ± 6.3</td>
<td>19.2 ± 7.0</td>
<td>19.1 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Alcohol use severity (ASI) (n = 581)</td>
<td>4.4 ± 1.0</td>
<td>5.2 ± 1.0</td>
<td>4.8 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Polysubstance abuse or gambling (n = 599)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No polysubstance abuse</td>
<td>236 (84.9%)</td>
<td>232 (72.3%)</td>
<td>468 (78.1%)</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>19 (6.8%)</td>
<td>30 (9.3%)</td>
<td>49 (8.2%)</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>6 (2.2%)</td>
<td>27 (8.4%)</td>
<td>33 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Gambling</td>
<td>0 (0.0%)</td>
<td>4 (1.2%)</td>
<td>4 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>17 (6.1%)</td>
<td>28 (8.7%)</td>
<td>45 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Drug use severity (ASI) (n = 545)</td>
<td>0.4 ± 1.2</td>
<td>1.1 ± 1.9</td>
<td>0.8 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Psychiatric problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of psychiatric problems (ASI) (n = 524)</td>
<td>2.5 ± 1.8</td>
<td>3.4 ± 2.0</td>
<td>3.0 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Family and social problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of family and social problems (ASI) (n = 521)</td>
<td>1.9 ± 1.7</td>
<td>2.5 ± 1.9</td>
<td>2.2 ± 1.8</td>
<td></td>
</tr>
</tbody>
</table>

Note: Values are means ± SD or numbers (%). BCBT = brief cognitive behavioral therapy; SCBT = standard cognitive behavioral therapy. ASI = Addiction Severity Index.
Treatment consumption

Table 3 shows that half of the total group completed treatment (49.2%). In BCBT 59.0% of the patients completed treatment. In SCBT 40.8% completed treatment. On average, patients in BCBT attended about 4.5 ± 2.8 sessions, whereas patients in SCBT attended about 7.7 ± 5.2 sessions (t(507.5)=9.2; p=0.00). This significant difference indicates that the two treatment modalities indeed represent two levels of care in routine practice.

Table 3: Treatment consumption

<table>
<thead>
<tr>
<th>No. (%) of patients</th>
<th>Brief CBT (n = 278)</th>
<th>Standard CBT (n = 321)</th>
<th>Total group (n = 599)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under-treated</td>
<td>52 (18.7)</td>
<td>127 (39.6)</td>
<td>179 (29.9)</td>
</tr>
<tr>
<td>Completed treatment</td>
<td>164 (59.0)</td>
<td>131 (40.8)</td>
<td>295 (49.2)</td>
</tr>
<tr>
<td>Over-treated</td>
<td>62 (22.3)</td>
<td>63 (19.6)</td>
<td>125 (20.9)</td>
</tr>
</tbody>
</table>

Note: CBT = cognitive behavioral therapy

Treatment effectiveness

As shown in Table 4, 25.2% of the total group of patients reported to be completely abstinent of alcohol during the last 30 days preceding follow-up, 18.0% were categorized as controlled drinkers, leaving 56.8% drinking heavily or harmfully. Patients in the controlled drinking group (according to our definition having no heavy drinking days) were drinking on average 7.5 ± 4.8 days. The number of drinking days in the heavy/harmful drinking subgroup was 17.3 ± 10.0 whereas the number of heavy drinking days was 10.2 ± 10.0.

As regards to polysubstance abuse, a small proportion of the patients were categorized in the harmful category (7.3%).

Table 4: Treatment effectiveness at follow-up: current alcohol use in the last 30 days

<table>
<thead>
<tr>
<th>No. (%) of patients</th>
<th>Brief CBT (n = 278)</th>
<th>Standard CBT (n = 321)</th>
<th>Total group (n = 599)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current complete abstinence</td>
<td>64 (23.0)</td>
<td>87 (27.1)</td>
<td>151 (25.2)</td>
</tr>
<tr>
<td>Current controlled drinking</td>
<td>59 (21.2)</td>
<td>49 (15.3)</td>
<td>108 (18.0)</td>
</tr>
<tr>
<td>Current harmful / heavy drinking</td>
<td>155 (55.8)</td>
<td>185 (57.6)</td>
<td>340 (56.8)</td>
</tr>
<tr>
<td>Polysubstance abuse (harmful)</td>
<td>14 (5.0)</td>
<td>30 (9.3)</td>
<td>44 (7.3)</td>
</tr>
</tbody>
</table>

Note: CBT = cognitive behavioral therapy
**Prediction**

*Treatment consumption*

Table 5 shows the multiple logistic regression model with independent predictors for treatment completion. No interaction effects for type of treatment, socio-demographic and clinical variables were found. Strongest independent predictors for treatment completion were type of treatment, treatment site, sex and educational level; with patients in BCBT, at the urban treatment site, being female and having middle or higher education having the best prognosis for treatment completion. Nagelkerke’s R square for this model is 0.188, indicating that the percentage of variance explained by this model is modest.

**Table 5: Multiple logistic prediction for treatment completion, final model**

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCBT vs. BCBT</td>
<td>0.32</td>
<td>0.00</td>
<td>0.19, 0.54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Site</th>
<th>OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban vs. Suburban</td>
<td>1.65</td>
<td>0.05</td>
<td>1.00, 2.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs. Male</td>
<td>2.26</td>
<td>0.01</td>
<td>1.24, 4.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational Level</th>
<th>OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No education/low</td>
<td>1.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1.61</td>
<td>0.13</td>
<td>0.87, 2.98</td>
</tr>
<tr>
<td>High</td>
<td>3.15</td>
<td>0.00</td>
<td>1.63, 6.09</td>
</tr>
</tbody>
</table>

| Constant           | 1.63 | 0.14    |          |

Nagelkerke $R^2 = 0.188$

*: Backward Stepwise elimination (likelihood ratio; p in = 0.05, p out = 0.10) method from SPSS 13.0 for MacOSx; variables not in the equation: age, ethnic origin, civil status, source of income, age of onset > 4 glasses, years of alcohol use > 4 glasses, no. of drinking days last 30 days > 4 glasses, polysubstance abuse, severity score family and social problems, severity score psychiatric problems.

*Treatment effectiveness*

As the multiple logistic regression model in Table 6 shows, age, ethnic origin and the number of heavy drinking days serve as independent predictors for treatment success together with the interaction effect of the presence of polysubstance abuse and type of treatment. Treatment success is more likely in older patients, and in non-Dutch patients, and less likely with increasing days of heavy drinking at intake and the combination of secondary substance and SCBT. Treatment consumption was not related to treatment.
success. The percentage of variance explained by these predictors is modest (Nagelkerke’s R square = 0.149).

Table 6: Multiple logistic prediction for treatment success, final model

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCBT vs. BCBT</td>
<td>1.39</td>
<td>0.19</td>
<td>0.85, 2.26</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1.04</td>
<td>0.00</td>
<td>1.02, 1.06</td>
</tr>
<tr>
<td><strong>Ethnic Origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Dutch vs. Dutch</td>
<td>2.74</td>
<td>0.01</td>
<td>1.24, 6.08</td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drinking days in last 30 days &gt; 4 glasses</td>
<td>0.97</td>
<td>0.00</td>
<td>0.95, 0.99</td>
</tr>
<tr>
<td><strong>Drug use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polysubstance abuse (yes)</td>
<td>1.43</td>
<td>0.53</td>
<td>0.47, 4.35</td>
</tr>
<tr>
<td><strong>Interaction effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polysubstance abuse (yes) * Type of treatment (SCBT)</td>
<td>0.24</td>
<td>0.04</td>
<td>0.06, 0.92</td>
</tr>
</tbody>
</table>

Nagelkerke R² = 0.149

* Backward Stepwise elimination (likelihood ratio; p in = 0.05, p out = 0.10) method from SPSS 13.0 for MacOSx; variables not in the equation: treatment completion, treatment site, sex, civil status, educational level, source of income, age of onset (drinking) > 4 glasses, years of alcohol use > 4 glasses, severity score family and social problems, severity score psychiatric problems.

**DISCUSSION**

In this study treatment consumption and effectiveness of evidence based treatment for alcoholic patients in routine practice was investigated. In accordance with the stepped care protocol, patients referred to SBCT were more severe in terms of addiction severity, social problems and psychiatric problems. Data showed a significant difference in the number of sessions attended between BCBT and SCBT (4.5 vs. 7.7 sessions) indicating that in routine practice treatment modalities indeed differed in level of care. Almost half of the patients (49.2%) were considered to be treated according to the prescribed sessions in the manuals. However, in this study, treatment consumption was not related to post-treatment drinking behavior, which is in contrast with other studies (Fiorentine &
Anglin, 1996; Moos & Moos, 2003a, 2003b). Probably, this is a consequence of the fact that treatments were brief en time-limited: the contrast between undertreated patients and patients treated according to the protocol was therefore limited.

In the 30 days preceding the 9 months follow-up, 25.2% of patients were abstinent, 18.4% were drinking in a controlled way, and 56.4% were still drinking heavily. We conclude that treatment was successful in 43.6% of the patients. Taking into account a mean duration of alcohol problems of 13 years in this study sample, indicating a chronic nature, these results are satisfying (Dennis & Scott, 2007). Due to differences in patient characteristics, outcome measures and follow-up window, it is difficult to compare the treatment outcomes of our study with RCTs on the efficacy of alcohol interventions. However, a comparison with Project MATCH is interesting because BCBT and SCBT were modeled after two of the three treatments of Project MATCH. In this study 23.3% of patients in motivational enhancement therapy and 20.8% of patients in cognitive behavioural coping skills therapy achieved abstinence (Project Match Research Group, 1997) which is comparable to our results. However, primary outcome in Project MATCH was the percentage of patients who were completely abstinent in the 90 days prior to 9 months follow-up. In our study, patients submitted information about the 30 days prior to follow-up. On the other hand, in Project MATCH several exclusion criteria were used. For example, patients who used other substances besides marijuana or could not identify a significant other could not participate in Project MATCH, whereas in the current naturalistic study these patients were not excluded. In addition, a substantial number of patients in our study succeeded in controlling their drinking behaviour. Analysis shows that, indeed, those patients were drinking on a relatively small number of days and these outcomes can therefore be considered treatment success.

Several variables were predictive for treatment consumption and treatment effectiveness. However, overall explained variance is relatively small. One explanation is the application of the stepped care protocol, resulting in a rather homogeneous patient group per treatment condition. On the other hand, our findings are in line with recent studies that indicate that self-reported measures, for example on personality dimensions or craving, are less predictive of relapse than neurocognitive functions and physiological measures (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008; Kosten et al., 2006). This suggests that future research will benefit from the inclusion of endophenotypic indicators such as neuropsychological, neurophysiological, neuroimaging and biochemical functions.

The strengths of the current effectiveness study are its large sample size, the use of manual-based empirically proven treatments and the broad range of clinical predictors. In many effectiveness studies, treatments are more of a “black box” than in efficacy studies, which typically rely on treatment protocols (Wells, 1999). The strength of our
study is that treatments were standardized while preserving usual-care conditions. Moreover, a large and unselected sample was used. As such, this study provides valuable information on the merits of cognitive behavioural intervention for alcohol use disorders in a routine treatment environment. However, some limitations must be acknowledged. First, treatment outcome was assessed with self-report measures that were not corroborated with information collected from collateral informants. However, self-reported substance use appears to be reasonably valid, especially when obtained independently from treatment providers as was the case here (Babor, Steinberg, Anton, & Del Boca, 2000; Babor, Stephens, & Marlatt, 1987). Second, only 51.6% of the total group of patients in BCBT and SCBT were successfully followed-up as opposed to the 80% regularly recommended. Non-responders were younger at baseline; less socially integrated and had more severe alcohol problems. These variables are potentially negatively related to treatment effectiveness. Our treatment outcomes might therefore be an over-estimation of the real treatment success.

This is the first large naturalistic study investigating the effectiveness of time-limited, evidence based outpatient psychotherapeutic interventions for alcohol use disorders in routine practice. We conclude that treatment outcomes of alcohol RCTs are preserved in a naturalistic setting and that the use of treatment manuals contributed to this result. However, the proportion of relapsing patients is high. Although this is a feature of a chronic disease, outcomes might be improved by additional relapse prevention strategies. For example, addition of contingency management to CBT might enhance treatment outcomes. This intervention is among the more effective treatments for substance use disorders (Lussier, Heil, Mongeon, Badger, & Higgins, 2006; Prendergast, Podus, Finney, Greenwell, & Roll, 2006). Also prescription of proven effective pharmacotherapy, acamprosate and naltrexone (Miller & Wilbourne, 2002), especially in the more severe SCBT patients, could further improve treatment effectiveness. Next, strategies in routine outcome monitoring (ROM) yield promising results. During-treatment measurements and feedback initiated at the beginning and at multiple times throughout the course of out-patient treatment support decision making and are proven to enhance outcome in outpatient psychotherapy (Brown & Jones, 2005; Lambert, Harmon, Slade, Whipple, & Hawkins, 2005). A similar approach was proposed by McLellan as Concurrent Recovery Monitoring (CRM) in outpatient addiction treatment (McLellan, McKay, Forman, Cacciola, & Kemp, 2005). In addition, multiple post-treatment telephone contacts, also referred to as “Extended Case Monitoring” and “Recovery Management Check-Ups” are an effective way to reduce relapse rates and to identify patients who relapse early after treatment (Dennis, Scott, & Funk, 2003; Scott, Dennis, & Foss, 2005; Stout, Rubin, Zwick, Zywiak, & Bellino, 1999). As such, telephone-based
monitoring can be an essential part of a stepped care approach, identifying patients who are in need of a more intensive treatment.

ACKNOWLEDGEMENTS

The Jellinek (part of Arkin, Amsterdam) and Brijder Substance Abuse Treatment Division (part of Parnassia Bavo Group) have made it possible for us to conduct this study.
CHAPTER 4

INVESTIGATING THE STRUCTURE OF CRAVING USING STRUCTURAL EQUATION MODELLING IN THE ANALYSIS OF THE OBSESSIVE COMPULSIVE DRINKING SCALE: A MULTINATIONAL STUDY

This chapter is published as:
ABSTRACT

Background: Currently, there is no agreement among researchers on the definition of craving and its underlying theoretical model. The Obsessive Compulsive Drinking Scale (OCDS) seems to measure certain aspects of craving, but its theoretical basis remains unclear. The aim of this study was to investigate the structure of alcohol craving, using OCDS data.

Methods: OCDS data from four studies were pooled to obtain a large and heterogeneous sample of 505 participants. All participants were treatment-seeking alcoholics meeting DSM-IV criteria for alcohol dependence. The factor structures of the OCDS previously found were evaluated using confirmatory factor analyses. The goodness of fit of these solutions was compared with those of alternative causal models: an obsessive-compulsive disorder model, an inhibition model and a cognitive-behavioral model. These alternative models were based on modern theories about craving and tested in the OCDS data, using structural equation modeling. In this way, the current study replaced simple correlational analysis by a more sophisticated causal way of analyzing the underlying structure of the OCDS items. The best fitting model was selected by comparing the mean discrepancy between the implied and observed matrices of the models.

Results: The data showed that the previously reported factor structures had to be rejected. Also, the inhibition model and obsessive-compulsive disorder model did not fit the data. The cognitive-behavioral model showed encouraging fit. Optimizing strategies were applied to further improve the fit of this model, which resulted in a model with close fit to the data.

Conclusions: The causal cognitive-behavioral model showed to be superior. It showed that the OCDS contains many items that do not represent the core concept of craving, but instead are indicators for the consequences of craving. From this model, it seems that craving, in the narrow sense, can be reliably assessed with only five items of the OCDS.
INTRODUCTION

Craving is frequently considered a central phenomenon in addiction. It has been conceptualized in a variety of ways. The term has been used to refer to phenomena such as recurrent and persistent thoughts about alcohol, the struggle to control these drives, withdrawal symptoms, anticipation of positive outcome, relief from negative affect, lack of control over use, cue-induced autonomic responses, and others (Verheul, Geerlings & van den Brink, 1999). Some argue that the term craving should be used only to refer to strong desires or urges to drink alcohol. However, many definitions include possible mechanisms that might underlie craving experiences or include precipitating and consequential factors (Verheul, Geerlings & van den Brink, 1999). During the past decades, several theoretical models have been used to explain alcohol craving. Currently, there is no agreement among researchers on its underlying theoretical model. Similarly, there is no single accepted measure of alcohol craving. Self-report measures are very popular in alcohol research, but most of these questionnaires are non-validated single-item scales (Tiffany, Carter & Singleton, 2000). In the last decade, several multi-item craving instruments have been developed, which allow us not only to measure craving, but also to examine the structure of craving. One of these instruments is the Obsessive Compulsive Drinking Scale (OCDS) (Anton, Moak & Latham, 1996) (see appendix).

The OCDS is a 14-item, self-report questionnaire developed to measure alcohol-associated thoughts and compulsions to drink. The instrument is based on the assumption that the drive to consume alcohol, the recurrent and persistent thoughts about alcohol, and the struggle to control these drives and thoughts are similar to the thought patterns and behaviors of patients with obsessive compulsive disorder (OCD) (Modell et al., 1992a; Modell et al., 1992b). However, research has not identified the existence of the two factors, obsessions and compulsions, which were originally thought to be present in the OCDS.

To investigate the structure of craving, confirmatory factor analysis of the OCDS was performed by Bohn, Barton and Barron (1996). They showed that the factor structure was more complex than the original two dimensions of obsessions and compulsions related to drinking. In fact, four factors emerged: (1) drinking obsessions, (2) alcohol consumption, (3) automaticity of drinking, and (4) interference associated with drinking. In contrast to the results of Bohn et al., Kranzler et al. (1999) reported a three-factor structure: (1) obsessions, (2) control and consequences, and (3) alcohol consumption. According to the authors these different results may be attributable to the different rotation method applied in the factor analysis and to differences in the clinical characteristics of the samples.
In an exploratory factor analysis, the OCDS developers (Roberts, Anton, Latham & Moak, 1999) identified three factors: (1) resistance / control impairment, (2) obsessions, and (3) interference. The authors concluded that the items from the factors “alcohol consumption” and “automaticy” obtained by Bohn et al. were represented in the resistance / control impairment factor. According to the authors this distinction was, apart from slight differences in item assignments, the major difference between the two studies.

Although no consensus seems to exist with regard to the underlying structure of the OCDS, the instrument has shown its practical benefits in alcohol research. Several studies suggest that the OCDS is predictive of relapse during active treatment (Anton, Moak & Latham, 1996; Roberts et al., 1999) and it was also found to be sensitive to change during anticraving treatments (Anton, Moak & Latham, 1996; Kranzler, Mulgrew, Modesto-Lowe, & Burleson, 1999). The OCDS seems to measure certain aspects of craving, but its theoretical basis remains unclear.

The aim of the current study is to investigate the structure of alcohol craving, using OCDS data from a large and heterogeneous sample, moving away from a pure correlational analysis and introducing a causal way of analyzing the underlying structure of the OCDS items. Until now, analyses on the OCDS were based on correlational (factor-analytic) techniques only. In this study, however, the causal relations between the items will be investigated using structural equation modeling. The factor structures of the OCDS previously found are evaluated using confirmatory factor analyses. The goodness of fit of these solutions is compared with those of alternative causal models. These alternative models are based on modern theories about craving and alcohol dependence and tested in the data using structural equation modeling. Finally, we assess whether the best fitting model is invariant over age, gender and language.

METHODS

Participants
Obsessive Compulsive Drinking Scale data from four studies were pooled to obtain a large and heterogeneous sample.

Two hundred forty-eight participants were recruited from 14 outpatient addiction treatment centers in the Netherlands from a 28-week, randomized clinical trial evaluating the supplemental value of psychosocial interventions to the prescription of acamprosate (Wildt et al., 2002). Treatment-seeking patients in these 14 centers who met the criteria for the clinical trial were invited to participate. The OCDS was administered during the inclusion visit, when the patient was at least three and at most 17 days abstinent from alcohol. All participants in this clinical trial met DSM-IV (American Psychiatric Association,
1994) criteria for alcohol dependence (95.6%) or alcohol abuse (4.4%). For the current study, only the alcohol-dependent patients were selected.

Thirty-nine participants from The Netherlands and Belgium were enrolled in three outpatient alcohol treatment centers from a cross-sectional study to evaluate the psychometric characteristics of a Dutch translation of the OCDS (Schippers et al., 1997). A random group of participants was recruited on the basis of their availability in a 2-week study period. All participants met DSM-IV criteria for alcohol dependence and received ongoing supportive treatment. The maximum period between the last acute weaning treatment and this study was not restricted, the mean period being 3.8 ± 8 months.

Fifty participants from the French-speaking countries Belgium, France and Switzerland were enrolled in a cross-sectional study to evaluate the psychometric characteristics of the translated French version of the OCDS (Annsseau et al., 2000). Patients meeting the DSM-IV criteria for alcohol dependence who had undergone weaning treatment within the past 3 months were selected.

Two hundred six participants were enrolled in two long-term inpatient treatment programs in Germany. All subjects met DSM-IV criteria for alcohol dependence. The aim of the study was to assess the psychometric characteristics of the translated German version of the OCDS (Mann & Ackerman, 2000). In the years 1996 and 1997, the OCDS was administered in the first week of treatment as a standard part of the clinical intake assessment.

From a total of 543 participants in the four studies, we selected a sub-sample of 505 participants (94.7%), all meeting the DSM-IV criteria for alcohol dependence and with data available on the variables age, gender and country (table 1): 78% males, mean age of 45 years (SD =9.12), 50% married, 78% completed at least middle education level, and 53% having a full time job. For all these variables, there was a similar distribution across gender, except for employment: only 37% of the women were employed full time as compared with 57% of the men. Further details regarding the sample can be found in Table 1.

**Table 1.** Sociodemographic data of the subjects (N=543)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>248</td>
<td>39</td>
<td>50</td>
<td>206</td>
</tr>
<tr>
<td>In- / outpatient</td>
<td>Outpatient</td>
<td>Unknown</td>
<td>Inpatient</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Language</td>
<td>Dutch</td>
<td>Dutch</td>
<td>French</td>
<td>German</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>83.0</td>
<td>79.5</td>
<td>64</td>
<td>73</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>44.5 (8.6)</td>
<td>45 (6.8)</td>
<td>50.22 (9.56)</td>
<td>42.8 (9.5)</td>
</tr>
<tr>
<td>Civil status (% married)</td>
<td>53.1</td>
<td>28.0</td>
<td>48.0</td>
<td>51.0</td>
</tr>
<tr>
<td>Employment status (% employed)</td>
<td>58.1</td>
<td>Unknown</td>
<td>40.0</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
**Procedure**

Before statistical analyses were performed, clinically relevant theory-based craving models covering all OCDS items and using a causal way of thinking were constructed by three of the authors (WAJMDW, GMS, WVDB) and one of their colleagues (P. Geerlings). All of them are Dutch speaking. Three different models were proposed.

*The Obsessive Compulsive Disorder model.* Conceptually, the OCDS is derived from the clinical similarity between alcohol dependence and obsessive-compulsive disorders. Brain imaging studies in patients with obsessive-compulsive disorders and alcoholics suggest that the resemblance between both patient groups is not only limited to the phenomenology of the two disorders, but is also revealed in shared anatomical structures and brain functions between certain aspects of obsessive-compulsive states and addiction (Anton, 2000; Volkow & Fowler, 2000). However, previous research has not detected the two factors, obsessions and compulsions, which were originally thought to be present in the OCDS (Bohn et al., 1996; Kranzler et al., 1999; Roberts et al., 1999). Our causal model of craving using the OCDS-items, presented in Figure 1, differs from the model of Anton in two ways: (1) obsessions and compulsions are causally related to interference and (2) self-efficacy is introduced as an effect modifier of this relationship because it is assumed that the extent to which the obsessions and compulsions interfere with the patient’s functioning depends on his or her level of self-efficacy (e.g. Franzblau et al., 1995).

![Diagram](image)

**Fig 1.** Obsessive-compulsive disorder model. The numbers in the boxes correspond with the original OCDS items.

*Inhibition model.* Inspired by neurobiological considerations, a model of alcohol craving was constructed, in which alcohol related cues simultaneously elicit drug-seeking behavior and (unsuccessful) attempts to prevent these behaviors (inhibition). Alcohol dependence is therefore conceptualized as a syndrome of impaired response inhibition...
(Goldstein & Volkow, 2002). As opposed to the obsessive-compulsive disorder model, thoughts about drinking are classified as consequences ("interference") instead of causal factors. The inhibition model is shown in Figure 2.

![Inhibition model](image)

**Figure 2.** Inhibition model. The numbers in the boxes correspond with the original OCDS items

*Cognitive Behavioral model.* This model follows the concepts of the Health Action Process Approach (Schwarzer, 1992) and relapse prevention approaches (Marlatt and Gordon, 1985). In these approaches self-efficacy is a central concept. The importance of self-efficacy has been confirmed in numerous studies of behavioral change (Bandura, 1994). Marlatt and Gordon (1980) postulated that those with high self-efficacy are less likely to relapse and more likely to use coping strategies than those with low self-efficacy. Schwarzer (1992) argues that the patient’s self-efficacy expectation is the most powerful predictor of intention and subsequent behavior. Accordingly, in the constructed cognitive-behavioral model, a distinction is made between behavioral intention and actual behavior. Thoughts and feelings, in relapse prevention approaches called internal high-risk situations (Dimeff & Marlatt, 1995), are assumed to precede behavioral intention and actual alcohol consumption. This behavior interferes with work and social life. The cognitive behavioral model is depicted in Figure 3.
Fig 3. Cognitive-Behavioral model. The numbers in the boxes correspond with the original OCDS items

The three causal models were compared with the four- and three-factor correlational models derived by confirmatory factor analysis according to Bohn et al. (1996). A graphical presentation of this model is presented in Figure 4. The three-factor model is identical to the four-factor model, except that the automaticity and interference items are constrained to load on a single common factor.
Figure 4. Four-structure model (Bohn et al., 1996). The numbers in the boxes correspond with the original OCDS items.

Statistical analyses
The following steps were taken in the analyses of the data.

Step 0. The statistical modeling approach assumes multivariate normality of the data. The assumption was tested for the pooled data, as well as for each country. No marked departure of the normal distribution was found.

Step 1. The four- and three-factor models found by Bohn et al. were tested using confirmatory factor analysis in a random sub-sample of 150 participants in order to
replicate the original study using similar statistical power. Then, the four- and three- 
factor structures were tested in the entire sample (n=518).

Step 2. The fit of the three alternative theory-based models was evaluated in the entire sample. Because the alternative models do not only include correlations on latent 
variables, but also causal relations, a general algorithm of structural equation modeling 
was used. In steps 1 and 2, the Goodness of Fit Index (GFI) of the five models was 
assessed with the maximum likelihood technique assuming multivariate normality of the 
data. Because the different models represent different levels of complexity, the Adjusted 
Goodness of Fit Index (AGFI) was used as a second and preferred criterion (Marsh & 
Hocevar, 1985).

Step 3. Next, the goodness of fit of the five models was compared. The power of 
these comparisons was calculated considering each competing model as both null and 
alternative hypothesis for sample size n=150 and n=518, using the approximate 
technique of Satorra and Saris (1992). The power was sufficient (1-β > 0.80) for all 
comparisons using n=518, but not for comparisons using n=150.

Because the classic goodness of fit indicators (e.g. χ², χ²/df, GFI, AGFI) cannot be 
directly compared, and because nested tests were not applicable, the technique of 
Linhart and Zucchini (1986) was used, i.e., each model was evaluated by bootstrapping 
(Bollen & Stine, 1992), comparing the mean discrepancy between the implied and 
observed matrix, and taking into account the calculated SE of this mean.

Step 4. Heuristic strategies were applied to increase the goodness of fit of the best 
model using modification indices. Modification indices are potential links (paths or 
covariances) expected to increase the goodness of fit of the model. Items included in the 
modification indices are generally indicators of more than one latent factor of the model.
If necessary, redundant items were eliminated to optimize the model.

Step 5. Invariant group regressions were performed to assess the invariance of 
the optimized model for the variables country, age, and sexr and the strict invariance (in 
fixing coefficients). In these analyses, the goodness of fit of the optimized model was 
evaluated for subgroups of the relevant variable with structural equation modeling (i.e. 
male and female). In this way the possible influence of the variables country, age, and 
sex could be assessed.

The analyses were carried out with SAS (6.8, SAS Institute Inc, Cary, NC) and 
AMOS (4.0, Arbuckle, Smallwaters, Chicago, IL).
RESULTS

Step 1: Factor structures found by Bohn et al.

First, the three- and four-factor structures were fitted to a random sub-sample of 150 participants using confirmatory factor analysis. We were able to replicate the findings of Bohn et al. However, the fit of the four-factor structure in the random sub-sample of 150 participants was modest at best ($\chi^2=131.23$, df=71, $\chi^2$/df = 1.85, GFI 0.825, AGFI 0.779, p<0.0001). The fit of the three-factor model in this subsample was even worse ($\chi^2=138.18$, df=74, $\chi^2$/df = 1.87, GFI 0.714, AGFI 0.685, p<0.0001). Next, both factor structures were fitted to the total sample of 505 participants. Because of the increased power, the three- and four- factor solutions had to be rejected definitely (three-factor: $\chi^2=612.34$, df=74, $\chi^2$/df = 8.27, GFI 0.715, AGFI 0.735, p<.001; four-factor: $\chi^2=812.63$, df =71, $\chi^2$/df =11.45, GFI 0.815, AGFI 0.747, p<.001).

Step 2: Alternative theory-based models

Next, the alternative models were fitted to the total sample of 505 participants using structural equation modeling. It should be noted that in the obsessive-compulsive disorder model, self-efficacy was assumed to be an effect modifier of the relation between obsessions and compulsions on one hand and interferences on the other hand (Fig 1). However, because effect modifiers can not be modeled in structural equation modeling, two approximations were tested. In the first approximation, self-efficacy was analyzed as separate factor influencing both obsessions/compulsions and interference. In the second approximation, self-efficacy was only directly linked to “interference”. Because the second approximation fit the data slightly better than the first, these data are reported. The obsessive-compulsive disorder model ($\chi^2=717.21$, df=74, $\chi^2$/df=9.69, AGFI 0.642, p<0.001) and the inhibition model ($\chi^2=833.32$, df=75, $\chi^2$/df=11.11, AGFI 0.639, p<0.001) did not fit the data. In contrast, the cognitive-behavioral model showed an encouraging fit ($\chi^2=427.34$, df=69, $\chi^2$/df =6.19, AGFI 0.678, p<0.0001). In Table 2, the measures of fit for each model are reported.
Table 2. Measures of Fit for models of OCDS structure

<table>
<thead>
<tr>
<th>Test model</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$\chi^2$/df ratio</th>
<th>GFI</th>
<th>AGFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-factor (n=150)</td>
<td>131.23</td>
<td>71</td>
<td>1.85</td>
<td>0.825</td>
<td>0.779*</td>
</tr>
<tr>
<td>Three-factor (n=150)</td>
<td>138.18</td>
<td>74</td>
<td>1.87</td>
<td>0.714</td>
<td>0.697*</td>
</tr>
<tr>
<td>Four-factor (n=518)</td>
<td>812.63</td>
<td>71</td>
<td>11.45</td>
<td>0.815</td>
<td>0.747*</td>
</tr>
<tr>
<td>Three-factor (n=518)</td>
<td>612.34</td>
<td>74</td>
<td>8.27</td>
<td>0.715</td>
<td>0.735*</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>717.21</td>
<td>74</td>
<td>9.69</td>
<td>0.813</td>
<td>0.642*</td>
</tr>
<tr>
<td>Inhibition</td>
<td>833.32</td>
<td>75</td>
<td>11.11</td>
<td>0.762</td>
<td>0.639*</td>
</tr>
<tr>
<td>Cognitive-behavioral</td>
<td>427.34</td>
<td>69</td>
<td>6.19</td>
<td>0.811</td>
<td>0.678*</td>
</tr>
</tbody>
</table>

Note: $\chi^2$ = Chi square, df = degrees of freedom, GFI = Goodness of Fit Index, AGFI = Adjusted Goodness of Fit Index. * p < .001

Step 3: Comparison of the models

Comparing the mean discrepancies between the implied and observed matrices and taking into account the calculated SE of this mean (Linhart & Zucchini, 1986), the cognitive-behavioral model seemed to have the smallest mean discrepancy between implied and observed matrices (Table 3). This means that the cognitive-behavioral model has the best fit.

Table 3. Mean Discrepancy of the models by decreasing value

<table>
<thead>
<tr>
<th>Model</th>
<th>Mean Discrepancy (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-factor structure</td>
<td>1365 (5.8)</td>
</tr>
<tr>
<td>Inhibition</td>
<td>1016 (6.1)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>885 (4.9)</td>
</tr>
<tr>
<td>Four-factor structure</td>
<td>846 (3.7)</td>
</tr>
<tr>
<td>Cognitive-behavioral</td>
<td>318 (2.5)</td>
</tr>
</tbody>
</table>

Step 4: Optimized model

Because the cognitive-behavioral model had the best fit, we tested some variations to further improve the fit of this model. The fit improved substantially when adding direct causal paths from behavioral intention to interference and from self-efficacy to feelings/thoughts ($\chi^2$=238.65, df=71, $\chi^2$/df =3.17, AGFI 0.737, p<0.001). However, the goodness of fit remained far from acceptable. Therefore, in addition to adding causal paths, we also tested the fit after removal of ambiguous items, i.e. items appearing in the modification indices. Most of the modification indices included items 3, 11 and 12. No other items were consistently included. The items are probably indicators of more than
one latent factor. In order to suppress the noise created by these ambivalent indicators, these three ambiguous items were deleted (Fig. 5). This considerably improved the goodness of fit ($\chi^2=44.78$, df=38, $\chi^2/df = 1.19$, AGFI= 0.687, p=0.1767), and the optimized cognitive-behavioral model now did much better than any of the other models (mean discrepancy =88, SE=1.2). This optimized model can be considered a close fit to the data (Fig 5).

![Diagram](image)

**Figure 5.** Optimized cognitive-behavioral model. The numbers in the boxes correspond with the original OCDS items.

**Step 5: Invariance of the optimized model**

Invariance of the optimized model was tested using group invariant techniques for sex (male; female), age (<30; 30-45; >45), and language (French, Dutch, German). For each variable, the analysis consisted of testing the associations of the model for each category (e.g. males/females), without equality constraints between corresponding path coefficients. In this way, only the equality of the shape of the model was tested and not the equality of the strength of the paths between the various latent variables within the model. For each separate analysis (age, sex, language), the goodness of fit test did not reject the similarity between the models. However, significant differences were found when equality of the parameters was constrained. Therefore, it can be concluded that the shape of the optimized cognitive-behavioral model can be considered as valid, irrespective of these socio-demographic categories. However, the exact values of the links or paths are
modified by these categories; therefore a strict equivalence including equality of path links across age groups is rejected.

**DISCUSSION**

The goal of this study was to reveal the structure of craving by comparing previously found factor structures of the OCDS with theory-based causal models. The data showed that the previously found factor structures had to be rejected. In addition, we conclude that our theory-based obsessive-compulsive model also has a low level of probability. This corroborates previous factor-analytic research on the OCDS, which did not identify the existence of the obsession and compulsion scales, which were originally thought to be present in the OCDS. The cognitive behavioral model showed to be superior.

In this study, sophisticated statistical analyses were performed on the data, and causal relations were tested. As opposed to confirmatory factor analysis, which detects correlations between concepts, structural equation modeling provides us with the opportunity to test hypothesized causal relations in a model. The tested models were derived from theory and constructed by experts. The large sample size enhanced the statistical power and the likelihood that stable factors could be discovered. The heterogeneity of the sample suggests that these findings are generalizable to the structure of craving of alcoholism patients in general. The participants were representative of alcohol patients receiving professional treatment.

The superior cognitive-behavioral model is, from a theoretical and practical point of view, an attractive model. It supports previous research regarding the important role of self-efficacy in behavioral change and coping behavior (Bandura, 1994). The results of this study match the empirical findings on effective treatment methods for alcohol dependence (Miller et al., 1998) in which techniques of cognitive-behavioral therapy are used and which aim at strengthening the patient’s self-control, coping skills and self-efficacy. Further support of the cognitive-behavioral model for craving can be found in the fact that it proved to be invariant of gender, age and country.

In the statistical analyses, two causal relations were added to the cognitive-behavioral model, and three ambiguous items were deleted in order to optimize the model. The additional causal relations can be well explained from a theoretical point of view. Not only behavior itself but also behavioral intention can interfere with a person’s social life and work functioning. The additional relation between self-efficacy and thoughts/feelings is also plausible: Those with high self-efficacy are likely to use coping
strategies (Marlatt and Gordon, 1980), which might have a direct influence on thoughts/feelings. Item 3 includes the concept of thoughts/feelings as well as the concept of interference, which explains its ambiguity and its deletion in the optimizing strategies. Item 11 asks for a hypothetical situation and item 12 might also be a difficult question to interpret for the patient. However, the latter could also be said about item 5. We have no explanation why item 12 had to be removed and item 5 did not. The question could be raised whether deletion of these items would also improve the other theory-based models. In a post-hoc analysis, we found that goodness of fit of the other models did not improve significantly when the three items were deleted.

Of interest remains the question how to define craving. In our cognitive-behavioral model, the combination of thoughts/feelings (obsessions) and behavioral intention might be considered actual craving (items 1, 2, 4, 5, and 13). In a post hoc analysis, the goodness of fit of this model, in which the items of obsessions and behavioral intention were combined into one latent factor, was assessed. In spite of a slight decrease in goodness of fit, the fit remained acceptable (χ² =38.4, df=24, χ²/df=1.6, AGFI=0.690, p=0.033). This model is more parsimonious and therefore more attractive. In monitoring addicted patients in treatment and assessing treatment outcomes in clinical trials on the efficacy of anticraving medication, the number of items for the measurement of craving could be limited to those of the obsession factor and behavioral intention factor. In the current study, this scale with 5 items showed good reliability (Cronbach’s α=0.814).

A limitation of this study is that probably not all relevant items of craving are included in the OCDS. As a consequence, we might have missed some aspects of craving in our attempt to reveal the underlying structure of craving, e.g. the degree to which craving is elicited by cues. Also, the OCDS is a self-report questionnaire on psychological aspects of craving. Neurobiological aspects, such as lack of inhibition or cue salience, are not explicitly represented or measured. Therefore, on the basis of this study we can not reject the inhibition model as a potential valid theory for alcohol craving. More studies are needed to prove that the cognitive-behavioral model is not specific for the OCDS. Data from other craving questionnaires should be used to further assess the fit of this model. Also, the predictive validity and longitudinal stability of the different concepts remain to be studied.

In summary, we conclude that the OCDS is a useful instrument for the assessment of craving but that craving, in the narrow sense, can possibly be assessed with only five items of the OCDS. Given the invariance of age, sex, and country these items provide a craving measurement that might be applied broadly in alcohol research and treatment.
ACKNOWLEDGEMENT

We thank Peter Geerlings for sharing his scientific knowledge and his clinical experience in the construction of the theoretical models.
APPENDIX. THE OBSESSIVE COMPULSIVE DRINKING SCALE (ANTON, 1996)

1. How much of your time when you’re not drinking is occupied by ideas, thoughts, impulses, or images related to drinking?
2. How frequently do these thoughts occur?
3. How much do these ideas, thoughts, impulses, or images related to drinking interfere with your social or work (or role) functioning? Is there anything you don’t or can’t do because of them? If you are not currently working, how much of your performance would be affected if you were working?
4. How much distress or disturbance do these ideas, thoughts, impulses, or images related to drinking cause you when you’re not drinking?
5. How much of an effort do you make to resist these thoughts or try to disregard or turn your attention away from these thoughts as they enter your mind when you’re not drinking? (Rate your effort made to resist these thoughts, not your success or failure in actually controlling them.)
6. How successful are you in stopping or diverting these thoughts when you’re not drinking?
7. How many drinks do you drink each day?
8. How many days each week do you drink?
9. How much does your drinking interfere with your work functioning? Is there anything that you don’t or can’t do because of your drinking? (If you are not currently working, how much of your performance would be affected if you were working?)
10. How much does your drinking interfere with your social functioning? Is there anything that you don’t or can’t do because of your drinking?
11. If you were prevented from drinking alcohol when you desired a drink, how anxious or upset would you become?
12. How much of an effort do you make to resist consumption of alcoholic beverages? (Only rate your effort to resist, not your success or failure in actually controlling the drinking.)
13. How strong is the drive to consume alcoholic beverages?
14. How much control do you have over the drinking?
CHAPTER 5

IMPROVING THE PREDICTIVE VALUE OF
SUBJECTIVE CRAVING ON RELAPSE IN ALCOHOL
DEPENDENT PATIENTS BY REPEATED MEASURES

W.A.J.M. de Wildt, P. Lehert, G.M. Schippers, W. van den Brink

Submitted for publication
**ABSTRACT**

**Backgrounds:** Research on the relationship between subjective alcohol craving and relapse to drinking has shown inconsistent results. The time window of the predictive validity of subjective craving scores, the applied instrument and subscales that are used in the prediction studies and the definition of treatment outcome may have a serious influence on the predictive power of craving. The present study aimed to establish the effect of instrument variation, variations in time window and type of outcome in the relationship between subjective craving and treatment outcome in abstinent alcoholics.

**Methods:** The predictive value of craving was studied in multi-centre pharmacotherapy trial in 241 alcoholic patients. Craving was measured at baseline and during treatment using different subsets of the Obsessive Compulsive Drinking Scale. Outcome was defined as time to first relapse, cumulative abstinence duration, and abstinence rate at six months follow-up. In a backward regression analysis the additional predictive value of craving on other well known predictors was assessed.

**Results:** Predictive power of baseline craving differed for different types of drinking outcome. No significant differences were found between different subsets of the OCDS. Although baseline measures of subjective craving significantly predicted treatment outcome, craving was a very modest predictor explaining a maximum of 4.2% in the variance of treatment outcome. Other predictors were able to explain 29% of the variance in the total number of abstinence days. Baseline craving was able to independently add a maximum of 3%. The theoretically constructed five-item subset of the OCDS performed best in short term prediction of relapse and when used cumulatively during treatment.

**Conclusions:** Measuring craving at baseline or during treatment is of only limited additional value for predicting relapse. It can be assessed most cost-effectively in routine practice by using the five item subset of the OCDS at baseline and during treatment.
INTRODUCTION

Several studies have explored the relationship between craving and relapse to drinking in abstinent alcohol dependent patients. The results are inconsistent. Although craving is assumed to play a crucial role in the development of addiction and in relapse following a period of abstinence (McKay, 1999), many patients report craving that is not followed by relapse and relapse is often not preceded by craving. Only a small proportion of patients who have relapsed report retrospectively that they experienced craving prior to relapse (Tiffany, 1999; Van den Brink, 1997).

The lack of robust associations between craving and relapse may be attributed to limitations in how craving is measured. There is no single accepted measure of craving. In most clinical trials on the efficacy of pharmacotherapy in alcohol dependence some form of self-report on subjective craving is included, ranging from visual analogue scales and single item scales to multi-item questionnaires. A frequently and widely used self-report questionnaire is the Obsessive Compulsive Drinking Scale (OCDS) (Anton, Moak & Latham, 1996). The OCDS is a 14-item self-report instrument which provides an internally consistent and reliable measure of craving (Anton, Moak & Latham, 1996; Bohn, Barton & Barron, 1996). The instrument is based on the assumption that the drive to consume alcohol, the recurrent and persistent thoughts about alcohol and the struggle to control these drives and thoughts in alcohol dependent patients are similar to the thought patterns and behaviors of patients with obsessive compulsive disorder (OCD) (Modell et al., 1992a; Modell et al., 1992b). However, research has failed to identify the existence of the two factors, obsessions and compulsions, which were originally thought to be present in the OCDS. In a study of Bohn et al. four factors emerged (1996). Kranzler et al.(1999) and Roberts et al. (1999) reported three factors. In our research, we showed that five items of the OCDS have to be considered the core concept of actual craving (de Wildt et al., 2005). A recent study confirmed the stability and reliability of this short 5-item version of the OCDS (Nakovics, Diehl, Croissant & Mann, 2008).

In several clinical trials on the efficacy of pharmacotherapy in alcohol dependence a positive correlation between craving intensity measured by the OCDS and relapse during treatment was found (Anton, Moak & Latham, 1995; Anton, Moak & Latham, 1996; Roberts et al., 1999). For example, in a 12 week treatment trial, Anton et al. (1996) showed that, although patients had similar baseline scores, patients who relapsed or slipped had higher OCDS total scores during treatment than those who maintained continuous abstinence. In addition, scores taken in week 3 of the trial were correlated with alcohol consumption during the rest of the treatment, suggesting that the scale might have predictive validity. However, other studies found that while craving is reduced during treatment, there was no relationship between the decrease in craving and
a reduced probability of relapse (Kiefer et al., 2005; Sass et al., 1996). In a study of Kiefer et al. (2005), the predictive value of several baseline variables were investigated in a placebo-controlled study comparing and combining acamprosate and naltrexone in the relapse prevention of alcoholism. Baseline craving showed no predictive value for the efficacy of treatment with any of the pharmacological interventions. No differences regarding time to first drink and time to relapse appeared between patients with high versus low baseline craving in the total sample.

In a more refined study, Roberts et al. (1999) showed that craving scores were able to predict heavy drinking only in the week directly following the assessment. Kranzler et al. (1999), reported that the OCDS scores obtained at the end of 12 weeks treatment had limited validity in predicting drinking behaviour during a 3-month post-treatment period. Only the alcohol consumption factor, one of the three empirically derived factors in this study, was correlated with drinking behaviour during the follow-up period. These findings may indicate that self-report measures of subjective craving are better in predicting short term drinking outcomes than prolonged outcomes. However, Bottlender and Soyka (2004), using the same factor structure as Kranzler et al. (1999), found that craving measured by the OCDS total score at the end of the treatment was a predictor for relapse in the 12 months after treatment completion. Of the subscales only the obsessions factor was predictive. The previous studies suggest that the predictive power might depend on the subscale that is used. In a study of Flannery, Poole, Gallop and Volpicelli (2003), the pretreatment score on the obsessions subscale of the OCDS showed to be a better positive predictor of weekly drinking during treatment than was the number of pretreatment drinks per week. During treatment the obsessions subscale was also a good predictor of subsequent drinking.

In a study of Morgan, Morgenstern, Blanchard and Labouvie (2004) the OCDS was revised into a 10-item questionnaire, OCDS-R, to assess craving across different substances. Results regarding the predictive validity of the OCDS-R were mixed, depending on the definition of substance use outcome. The OCDS-R baseline score did not predict substance use during treatment. In patients using substances during treatment, the baseline OCDS-R score was not related to the percentage of abstinent days at the end of treatment. However, using the number of days to relapse as outcome measure, the relationship with the OCDS-R score was significant. Participants with OCDS-R scores of 15 were predicted to relapse in 91 days. For every 1-point increase in OCDS-R score there was a 15.7% decrease in expected time to relapse. The findings of this study suggest that in investigating the predictive value of craving on treatment outcome it is important to include different definitions of outcome.

In summary, it seems that the time window of the predictive validity of subjective craving scores, the applied instrument and subscales that are used in the prediction
studies and the definition of treatment outcome may have a serious influence on the predictive power of craving. Differences in these methodological aspects between studies may be responsible for the inconsistent findings. In the present study, the predictive value of craving is studied using the OCDS in a 28 week pharmacotherapy trial in alcohol dependent patients taking into account the potential effects of the time window of prediction, different outcome measures, and the use of different subscales of the OCDS on the relationship between craving and relapse. The following hypotheses are tested:
1. Baseline subjective craving measured with the OCDS differentially predicts treatment outcome in terms of continuous abstinence duration, time to first relapse, and abstinence rates at six months follow-up;
2. Baseline subjective craving measured with the OCDS adds to the predictive power of a series of other well-known predictors of relapse such as addiction severity, age and psychological distress.
3. Subjective craving measured with the OCDS has a higher predictive power on short-term drinking behaviour than on prolonged relapse.
4. Different subscales of the OCDS have different abilities to predict treatment outcome;

MATERIALS AND METHODS

Participants
The present study is based on data obtained from a randomized controlled trial testing the added value of psychosocial intervention to the prescription of acamprosate in outpatients with an alcohol use disorder (De Wildt et al., 2002). Participants were recruited from 14 outpatient addiction treatment centers in the Netherlands. They gave written informed consent to participate in a 28-week clinical trial. All subjects met the DSM-IV criteria for alcohol dependence (97%) or alcohol abuse (3%), had achieved 3-17 days of abstinence, and were motivated to attain long-term abstinence. Subjects were between the ages of 18 and 65 years. Exclusion criteria were renal insufficiency, antisocial personality disorder, psychotic symptoms, serious physical illness unrelated to alcoholism, history of treatment for epileptic seizures, current dependence on psychoactive substances other than nicotine and alcohol, and pregnancy, lactation or refusal to use a reliable method of birth control in women. Patients were also excluded from participation if they were currently receiving treatment with a non-registered drug, participating in another clinical trial, or had undergone previous treatment with acamprosate.
A total of 248 subjects entered the study. The Intention-to-Treat sample (ITT) consisted of 241 subjects receiving at least one dose of the medication and providing at least one key data point after baseline. Baseline craving data were available for all 241 subjects. A total of 114 (47.3%) subjects remained in treatment for the full 28 weeks, and 115 subjects (47.7%) completed all craving assessments during the trial. Of all 241 ITT subjects, 169 patients (70.1%) provided drinking data at the follow-up assessment 6 months after treatment.

Procedures
Subjects were randomized into one of three treatment conditions: acamprosate (n=78); acamprosate plus minimal intervention aimed at motivational enhancement (3 weekly sessions of 20 minutes each) (n=88); or acamprosate plus brief cognitive behaviour therapy (7 weekly sessions of 60 minutes each) (n=82). A placebo group was not included in the study. Pharmacotherapy was provided for 28 weeks. Baseline measures, including assessment of subjective craving and psychological distress, were taken after a minimum of 3 days of abstinence from alcohol. During treatment, craving scores and drinking status data were obtained in weeks 2, 4, 10, 16, 22, and 28. Data were collected by the physician during the medical consultations and based on patient self-report. Follow-up assessment of drinking behavior was undertaken six-months after termination of the pharmacological treatment.

Measurements

Outcome variables
The primary outcome variables for drinking behavior included:
- Cumulative Abstinence Duration (CAD), i.e. the total number of abstinent days during active treatment.
- Time to first relapse (TFR), where relapse was defined conservatively as any alcohol consumption. Time to first relapse is therefore considered the number of days until the first drink.
- Abstinence rate at six months follow-up (ABS6), i.e. the percentage of subjects who were abstinent six months after termination of the pharmacological treatment.

In all outcome criteria drop-outs were considered to be relapses.

Predictor variables
Next to the demographical variables age and gender, a series of predictor variables were chosen from the literature: craving, psychological distress, and addiction severity. In our
original study on treatment outcome of the three treatment conditions a significant
centre by treatment interaction was found (De Wildt et al., 2002). Therefore, centre was
also included as a predictor variable. Assessments of craving, psychological distress, and
addiction severity are described below.

**Craving**
In the present study subjective craving was measured with the Obsessive Compulsive
Drinking Scale (OCDS) (Anton, Moak & Latham, 1996). The Dutch translation of the 14-
item OCDS was used, which has a high psychometric resemblance to the original scale
(Schippers et al., 1997). In the present study the following OCDS-subcales were used to
predict drinking outcomes: (a) total scale excluding items 7 and 8 tapping drinking
behaviour (OBCP), (b) the obsessions subscale (OB; items 1-6), (c) the compulsions
subscales (CP; items 9-14), and (d) a new scale with 5 items representing actual craving
(CRAV; items 1, 2, 4, 5, 13). The latter 5-item subscale is suggested to constitute the
core concept of subjective craving (De Wildt et al., 2005) and has shown to be a stable
and reliable subset of the OCDS (Nakovics et al., 2008). The scale contains the following
items: (1) How much of your time when you’re not drinking is occupied by ideas,
thoughts, impulses, or images related to drinking? (item 1) (2) How frequently do these
thoughts occur? (item 2) (3) How much distress or disturbance do these ideas, thoughts,
imulses, or images related to drinking cause you when you’re not drinking? (item 4) (4)
How much of an effort do you make to resist these thoughts or try to disregard or turn
your attention away from these thoughts as they enter your mind when you’re not
drinking? (item 5) (5) How strong is the drive to consume alcoholic beverages? (item
13).

Craving was assessed several times during the treatment period to investigate the
impact of time-window between craving measurement and outcome on the predictive
validity.

**Psychological distress**
At baseline, data were collected on psychological distress using the Dutch version of the
Hopkins-Symptom-Checklist-90 (Arrindell and Ettema, 1986; Derogatis, Lipman & Covey,
1973), a multidimensional self-report symptom inventory consisting of 90 items. Each
item is measured on a 5-point scale of distress from “not at all” (0) to “extremely” (4).
Current psychopathology is reflected in terms of 9 symptom dimensions: 1) somatic
complaints, 2) anxiety, 3) depression, 4) agoraphobia, 5) obsessions, 6) sensitivity, 7)
hostility, 8) somnolence, and 9) other. The total score reflects the overall level of
psychoneuroticism.
Addiction severity

Several measures of addiction severity were assessed at baseline. Primarily, we used the patients’ number of positive answers on the DSM-IV criteria for alcohol dependence. Alcohol dependence was diagnosed using the Composite International Diagnostic Interview for DSM-IV (CIDI 2.1) (World Health Organization, 1997). Years of existing alcohol problems, number of drinks per drinking day, number of drinking days in the last three months, and number of previous alcoholism treatments were also considered measures of addiction severity. All measures of addiction severity were obtained from the patient self-report by the physician.

Statistical analyses

Randomized patients were considered to be eligible for the analysis when complete OCDS data at baseline were available.

The predictive value of baseline craving, represented by four different subsets of the OCDS, on treatment outcome was estimated by the coefficient of determination ($r^2$) associated with the linear regression between OCDS scores and the considered endpoints (CAD, time to first relapse, and abstinence rate at six months follow-up). To evaluate whether different subscales at baseline have different abilities to predict treatment outcome, a multiple comparison test was carried out.

The additional predictive value of craving was assessed in a statistical model simultaneously taking into account all predictors at once. A type III General Linear model was used to build a multifactor predictive model on Cumulative Abstinence Duration (CAD). Because CAD is not normally distributed, CAD was rank transformed before testing the model. The following potential predictors were used and introduced in a multifactorial backward model: age, gender, treatment centre, treatment condition, number of positive DSM-IV criteria, years of alcohol problems, number of drinks per drinking day, number of drinking days in the last three months, number of previous alcohol treatments, and psychological distress. The coefficient of determination of the resulting model was calculated. Next, OCDS was added to this model to assess the additional predictive value of craving and its effect on the coefficient of determination. Again, the four different subsets of OCDS were tested. The OCDS subset which resulted in the model with the maximum coefficient of determination was considered the best and was also used in testing the third hypothesis on change of predictive value in time.

To assess whether the OCDS has a higher predictive power on short term drinking behaviour than on prolonged relapse, the OCDS measurements during treatment were used in two ways. First, the predictive value of individual OCDS scores at each measurement point were related to the final drinking behaviour (Point Abstinence Prevalence) at 6 months
follow-up. Next, the cumulative OCDS values (calculated as the sum of every OCDS value from baseline until the considered period, e.g. the cumulative value for period 3 should be $\Sigma_{i=1,3}\text{ocds}(i)$) were used to assess whether the pattern of craving during treatment is predictive of treatment outcome at 6 months follow-up. These latter analyses were carried out on the subjects who provided OCDS data on all measurement points during the trial (n=115).

**RESULTS**

**Sample characteristics**
The sample was primarily male (83%), white (97.9%), married (53.1%), and employed (58.1%). Mean ($\pm$ SD) age was 44.5 $\pm$ 8.6. 97.9% of the patients met DSM-IV criteria for alcohol dependence and 2.1% met DSM-IV criteria for alcohol abuse. Patients had an alcohol problem for an average of 11.6 $\pm$ 8.1 years. More than half of the patients (52.3%) had a family member with alcohol problems. 67.2% of the patients drank every day during the year prior to the study. The mean number of standard drinks per drinking day was 15.3 $\pm$ 8.7. The mean level of psychological distress, measured by SCL-90, was 172.2 $\pm$ 58.5.

**Prediction of baseline craving on treatment outcome**
In Table 1 the coefficients of determination between all different outcome measures for drinking behaviour and all OCDS subscales are shown. As hypothesized, there is a negative relationship between baseline craving and treatment outcome. All coefficients, except the correlation between CRAV and abstinence rate at six months follow-up, are significant ($p<.05$). However, the predictive value is very small in all cases. Coefficients of determination vary between 0.9% (CRAV and TFR) and 4.2% (OBCP and CAD). A multiple comparison test was carried out to evaluate differences in predictive value of the different subsets of the OCDS at baseline. No significant differences were found.
Table 1. Coefficients of determination of baseline OCDS on different drinking outcome measures

<table>
<thead>
<tr>
<th>Subset of OCDS</th>
<th>CAD</th>
<th>TFR</th>
<th>Abst₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP₀</td>
<td>0.0378 *</td>
<td>0.0326 *</td>
<td>0.0276 *</td>
</tr>
<tr>
<td>OB₀</td>
<td>0.0334 *</td>
<td>0.0202 *</td>
<td>0.0227 *</td>
</tr>
<tr>
<td>CRAV₀</td>
<td>0.0213 *</td>
<td>0.0093 *</td>
<td>0.0178</td>
</tr>
<tr>
<td>OBCP₀</td>
<td>0.0419 *</td>
<td>0.0314 *</td>
<td>0.0291</td>
</tr>
</tbody>
</table>

Notes: OB = Obsessions, CP=Compulsions, CRAV=five-item index of craving, OBCP=OB + CP. CAD = Cumulative Abstinence Duration, TFR=Time to First Relapse, Abst₆= rate of abstinence at six months follow-up *p<.05.

Additional predictive value of craving on drinking outcome

To assess the additional predictive value of baseline craving on other well known predictors of treatment outcome, first a General Linear Model with a backward selection strategy of potential predictors was used excluding craving as a potential predictor with CAD as the outcome variable. The resulting model (Table 2) detected significant effects of the centre by treatment interaction, initial addiction severity (summed score of DSM criteria), and age. We did not find any evidence for the predictive value of gender, or interaction of the treatment with age or gender or other measures of addiction severity. The coefficient of determination of this model is modest (r²=0.29).

Table 2. Analysis of variance in the rank ordered total number of abstinent days (assessed by general Linear model, Sum of Squares decomposition of type III).

<table>
<thead>
<tr>
<th></th>
<th>DF</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSTANT</td>
<td>1</td>
<td>21159.064</td>
<td>21159.064</td>
<td>5.151</td>
<td>.809</td>
</tr>
<tr>
<td>Centre</td>
<td>13</td>
<td>51403.582</td>
<td>3954.122</td>
<td>0.963</td>
<td>.649</td>
</tr>
<tr>
<td>Treatment</td>
<td>2</td>
<td>26072.481</td>
<td>13036.241</td>
<td>3.174</td>
<td>.183</td>
</tr>
<tr>
<td>Centre * Treatment</td>
<td>26</td>
<td>210741.066</td>
<td>8105.426</td>
<td>1.973</td>
<td>.007</td>
</tr>
<tr>
<td>DSM total</td>
<td>1</td>
<td>18335.892</td>
<td>18335.892</td>
<td>4.464</td>
<td>.039</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>48765.432</td>
<td>48765.432</td>
<td>11.872</td>
<td>.001</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>10174.733</td>
<td>10174.733</td>
<td>2.477</td>
<td>.316</td>
</tr>
<tr>
<td>ERROR1</td>
<td>195</td>
<td>800952.677</td>
<td>4107.450</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>

Note: DF=degrees of freedom, SS=sum of squares, MS=Mean Square, centre * treatment = centre x treatment interaction; DSM total = number of positive answers on the DSM-IV criteria for alcohol dependence.
Second, the various subscales of the OCDS were added to assess the independent, additional predictive value of baseline craving on this model and to assess the effect of these variables in the coefficient of determination. For every subset (OBCP, OB, CP, and CRAV), the added effect on CAD was statistically significant ($p$ varied from 0.002 to 0.029). The maximum coefficient of determination was with the CP subscale ($r^2 = 0.32; \ p = 0.002$), showing CP to have the most significant additional value. As compared to the initial model of other predictors, $r^2$ increased 3%, which is quite comparable with the univariate predictive value. This indicates that baseline craving is an independent, although rather weak, predictor of relapse.

**Predictive power on short term treatment outcomes and prolonged relapse**

Since the CP subset resulted in the model with the highest coefficient of determination, this subset was used in testing the hypothesis regarding the change of the predictive value of craving over time with the abstinence at 6 month follow-up as the outcome. Table 3 shows that that the predictive value of CP craving did not substantially increase during the course of treatment (range 2.4% at baseline till 3.1% at week 28). Separate craving values measured during treatment had even a lower predictive validity than craving measured at baseline. As such, the CP subset did not perform better in predicting shorter or more long-term abstinence. Cumulative CP craving experiences over time also did not increase the predictive power on drinking behaviour.

Because in our previous study the CRAV subset was suggested to constitute the core concept of subjective craving (De Wildt et al., 2005), the same analyses were applied on this subset. In contrast to the CP subset, the predictive power of CRAV did increase over time (range 0.2% at baseline till 7.9% at week 28). The corresponding predictive value of the cumulative CRAV craving experience also increased from 0.2% at baseline to 14.7% at week 28; a significant increase of 14.5% [95%CI: 4.4, 24.3, $p = .023$].
**Table 3.** Coefficients of determination for current craving for each period and for cumulative craving on abstinence on point prevalence at six months follow up

<table>
<thead>
<tr>
<th>OCDS assessment periods</th>
<th>6 month FU</th>
<th>6 month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Each period</td>
<td>Cumulative</td>
</tr>
<tr>
<td>0 (Baseline)</td>
<td>0.024</td>
<td>0.024</td>
</tr>
<tr>
<td>1 (week 2)</td>
<td>0.013</td>
<td>0.023</td>
</tr>
<tr>
<td>2 (week 4)</td>
<td>0.002</td>
<td>0.018</td>
</tr>
<tr>
<td>3 (week 10)</td>
<td>0.005</td>
<td>0.026</td>
</tr>
<tr>
<td>4 (week 16)</td>
<td>0.006</td>
<td>0.034</td>
</tr>
<tr>
<td>5 (week 22)</td>
<td>0.012</td>
<td>0.037</td>
</tr>
<tr>
<td>6 (week 28)</td>
<td>0.031</td>
<td>0.031</td>
</tr>
</tbody>
</table>

**Note:** CP=Compulsions, CRAV=five-item index of craving.

**DISCUSSION**

In the present study, the predictive value of subjective craving was studied using the OCDS in a 28 week pharmacotherapy trial in alcohol dependent patients taking into account the potential effects of the time window of prediction, different outcome measures and the use of different subscales of the OCDS. It was hypothesized that baseline subjective craving differentially predicts treatment outcome in terms of continuous abstinence duration, time to first relapse, and abstinence rate at six months follow-up and adds to the predictive power of a series of other well-known predictors of relapse such as addiction severity, age and psychological distress. We expected subjective craving to have a higher predictive power on short-term drinking behaviour than on prolonged relapse. In addition, it was hypothesized that different subscales of the OCDS have different abilities to predict treatment outcome.

Our first hypothesis was confirmed: predictive power of baseline craving differed for different types of drinking outcome. However, no significant differences were found between different subsets of the OCDS. Baseline craving showed to be a very modest predictor explaining only 1-4% of the variance depending on subscale and specific outcome. In addition, data showed craving to have a significant additional effect on the prediction of treatment outcome, the CP subset having the best performance, although this additional effect was small (3%). Its value was comparable to the univariate predictive value,
illustrating that baseline craving is an independent though modest predictive variable.

Concerning the potential effect of time window of prediction, our hypotheses could only partially confirmed: it was confirmed in the CRAV subset, but not in the CP subset. In the CP subset separate values of the different subsets at each period had a lower predictive value than baseline craving. As such, the CP subset did not perform better in predicting short term treatment outcomes as opposed to more prolonged relapse. A possible explanation can be found in the time frame measured by the OCDS. Craving can be understood either as a “trait” phenomenon (i.e. a persistent general desire referred to as “craving-past”) or as a “state” phenomenon (i.e. an instant desire triggered by cues, referred to as “craving-now”) (Franken and Hendriks, 2002). The OCDS asks patients to rate the items as they were experienced in the last seven days and can be considered a questionnaire measuring craving-past. This may explain why baseline craving did not do worse than craving measured during treatment: these were all measures of craving-past instead of risky increases of craving triggered by cues. However, in the CRAV subset separate values at each period had a higher predictive value than baseline craving ranging from 0.2% at baseline to 8% at 28 weeks. By using cumulative values of the CRAV subset, prediction of abstinence at 6 month follow-up increased from 0.2% to 14.7%, resulting in a reasonable predictive value. We conclude that the pattern of alcohol craving during treatment, as measured with the CRAV subset, is predictive of treatment outcome.

Considering the differences in predictive value of the defined subsets of the OCDS, we must conclude that these are modest. There were no significant differences in predictive value of the baseline craving measures. However, the CP subset performed slightly better in its additional predictive value on other predictors. Taken into account the time window, the CRAV subset performed better in short term prediction of relapse and when used cumulative during treatment. These results indicate that the theoretically constructed five-item subset better represents the concept of subjective craving than the other subsets.

The strength of the present study is that we were able to assess variations in time window in a 28-week treatment trial with a large sample size, and that different outcome measures were studied. Also, different subsets of OCDS items could be applied. However, some limitations of this study must be considered. First, concerning the research question on cumulative OCDS scores, only data could be used of patients who provided OCDS scores on all measurements (n=115, 47.7%). We can assume that these were the more successful patients in terms of treatment completion and, possibly, outcome. As a result of lack of heterogeneity in treatment outcome data and, possibly, craving intensity, we might have found low predictive value. Second, treatment outcome was assessed with self-report measures that were not corroborated with information collected from collateral informants. Finally, acamprosate was prescribed to all patients. This
medication is known to reduce subjective craving (Hammarberg et al., 2009). As a consequence there might have been only limited variance in OCDS scores during treatment, negatively influencing the predictive value of cumulative OCDS.

Although the presumed relationship between craving and relapse to drinking seems to have high face validity, our findings strongly suggest that subjective craving is overestimated as a predictor of treatment outcome. It might be that subjective experience of craving may not directly predict substance abuse, but relapse might be predicted from the correlates and underlying mechanisms of craving (Drummond, Litten, Lowman & Hunt, 2000). Subjective craving can be considered a phenotypic or clinical indicator, i.e. a patient characteristic that is the joint product of both genotypic and environmental influences. Studies using clinical or phenotypic variables in pharmacotherapy studies have produced overall inconsistent and disappointing results (Ooteman et al., 2005). This suggests that these variables might not be closely enough related to the biological process of addiction and relapse to be able to predict treatment outcome. In contrast, genetic indicators and endophenotypic indicators (e.g., neurophysiological cue reactivity) might be more related to the underlying process of addiction and craving or relapse mechanisms and are therefore more promising (Ooteman et al., 2005). Studies indicate that self-reported subjective craving correlates very low with neurophysiologically measured cue reactivity (Ooteman et al., 2006; Tiffany, 1990) and that self-reported craving is less predictive of relapse than physiological cue-reactivity (Kosten et al., 2006). Also findings in the field of pathological gambling and opiate-dependence show that endophenotypic indicators, e.g. attentional bias and neurocognitive functions, predict relapse much better than subjective craving and self-reported personality styles (Goudriaan, Oosterlaan, de Beurs & van den Brink, 2008; Marissen et al., 2006)

The clinical value of using the OCDS as a measure for treatment planning and assessing treatment progress in terms of risk for relapse, as is often suggested, could not be confirmed by our data. We conclude that measuring subjective craving at baseline or during treatment, is of only limited additional value for predicting relapse. Neurobiological indicators, for example attentional bias and cue reactivity, seem to be more promising in predicting treatment outcome. Future research should clarify how these indicators can be used in clinical practice in selecting patients who are at risk. Until then, subjective craving could be assessed most cost-effectively in daily practice by using the theoretically driven five item subset of the OCDS using multiple measures from the start of and during treatment.
CHAPTER 6

GENERAL DISCUSSION
INTRODUCTION

This thesis reported on the effectiveness of treatment of alcohol use disorders and the concept of craving. Results of a randomized clinical trial (RCT) testing the additional value of psychosocial interventions to the prescription of acamprosate in treatment seeking patients with an alcohol use disorder were presented. In addition, the effectiveness of manual based cognitive behavioural therapy for alcoholic patients in routine practice was examined in a large cohort study. Furthermore two studies are reported, using data of the RCT on the Obsessive Compulsive Drinking Scale: a study on the structure of craving and a study on its predictive value for relapse into drinking after initial abstinence. In this chapter the findings are discussed in the context of recent research findings, conclusions are drawn and clinical implications and recommendations for further research are given.

TREATMENT EFFECTIVENESS

Combining pharmacotherapy and psychosocial interventions in the treatment of alcohol use disorders

The large body of research on new medications for treatment of alcohol use disorders has shown very clearly that acamprosate and naltrexone add to the effectiveness of psychosocial treatment in alcohol patients. In contrast, the amount of research on the additional effect of psychosocial treatment on pharmacotherapy was very limited and methodologically rather weak. However, the few available studies indicated that this combination might be beneficial. Therefore, the main RCT in this thesis investigated the additional value of two forms of evidence-based psychosocial treatment on the effect of acamprosate (chapter 2). In contrast to our hypotheses a clear supplemental value of minimal and brief psychosocial intervention to the prescription of acamprosate was not demonstrated. There were no statistically significant differences between treatment groups in treatment duration, drop-out rates, medication compliance, drinking outcomes or psychological distress at the end of treatment nor were there any significant effects at six months follow-up. However, because a significant interaction between centre and treatment group was found, we could not rule out the possibility that, although the general results showed no supplemental value of extra psychosocial intervention, in some centres there was a positive effect of additional psychosocial intervention, while in others there was a negative or no effect of such intervention. We concluded that the widely held belief that pharmacotherapy for alcohol dependence should always be combined with psychosocial intervention is debatable and merits further research.
Since the publication of our study in 2002 several studies on the effectiveness of combined pharmacotherapy and behavioural interventions for alcohol dependence have been published. An overview of these studies and their main results are described in this paragraph. First, studies on acamprosate are presented, followed by studies on naltrexone. Special attention is paid to studies on the efficacy of medication compliance strategies.

Acamprosate
In 2002, two other studies addressing combining acamprosate with certain psychosocial interventions were published (Pelc et al., 2002; Soyka et al., 2002). Both are multi-centre, open and non-randomized studies. Patients were allocated to psychosocial treatment according to the physician’s decision about its appropriateness. The study of Pelc et al. (2002), the so-called European NEAT program, was conducted in five European countries. The objective was to study the effect of acamprosate under conditions of standard clinical care of alcohol dependence in Europe. A total of 1,289 alcohol dependent patients were recruited and treated for 24 weeks with acamprosate and various psychosocial interventions within the setting of standard patient care. Psychosocial interventions were categorized as brief intervention; relapse prevention; individual therapy; group therapy and; family therapy. The proportion of cumulative abstinence days was 0.48. When treatment outcome was reviewed in relation to the different psychosocial interventions provided, no difference in outcome was noted. When known prognostic factors were controlled for, a significant effect of type of psychosocial intervention on outcome were observed, favouring family therapy over the other psychosocial interventions. However, the number of patients in family therapy was very small, and these results should be interpreted with caution (Pelc et al., 2002). Soyka et al. (2002) also performed a 24-week non-blind multi-centre study (75 centres, 759 patients) to evaluate the use of acamprosate with various kinds of psychosocial support in routine care. In addition to the prescription of acamprosate, each patient was assigned to one of five types of psychosocial intervention. These were individual therapy, group therapy, brief intervention, behavioural therapy, and family therapy. A standardized definition of each psychotherapeutic intervention was given, but treatment was not manual-based. Allocation to one of the five treatment arms was not randomised but depended on the therapist’s judgement. Since only two patients entered family therapy, this group was not analyzed separately. Abstinence rates were very similar across the different arms of the study. Although baseline differences in patient characteristics between the treatment groups were not controlled for in the study of Soyka et al., it is interesting to note that the least intensive (brief) intervention in combination with pharmacotherapy resulted in at least as favourable treatment outcomes as other more
costly and time-consuming interventions (Soyka et al., 2002). In these two studies patients were not assigned randomly to the different treatment modalities. In particular, because of differences in local practices and preferences, the number of patients allocated was not balanced by site, and treatment conditions were not equivalent in size. Therefore, the results of the studies should be treated with caution and no definite conclusion can be drawn.

In 2004, Hammarberg et al. compared two levels of psychosocial intervention in combination with acamprosate medication for the treatment of alcohol dependence in a randomized trial. A total of 70 patients were prescribed acamprosate and randomized to either Minimal Psychosocial Intervention (MPI) or Extended Psychosocial Intervention (EPI). MPI patients met a psychiatrist for 20-30 min sessions on four occasions during a six month period. EPI patients were offered 10-15 sessions with a psychiatric nurse in addition to the visits to the psychiatrist. The EPI consisted of behavioural and cognitive coping skills training to deal with high risk situations. All patients were assessed four times during the 24-week study by self-report and laboratory tests. Although it was hypothesized that EPI would be more effective than MPI in reducing the number of days with heavy drinking and the cumulative number of drinking days, in addition to increasing the time to first drink, the results showed no significant differences for any of the drinking outcomes between patients in MPI and EPI.

Reid et al. (2005) investigated the additional value of a compliance enhancement intervention to the prescription of acamprosate in alcohol dependent patients. Forty patients in acamprosate treatment were randomly allocated to receive usual medical care or usual medical care plus compliance therapy. Acamprosate was prescribed for four months. Usual medical care consisted of seven medical reviews of 15 minutes. Compliance therapy consisted of four to six individual sessions of sixty minutes in which beliefs about medication, side effects, ambivalence, the benefits of treatment, treatment maintenance, and relapse prevention were addressed and explored using techniques of Motivational Interviewing and cognitive behavioural therapy. Intention-to-treat analyses showed no significant difference between the two groups in the outcome drinking measures. However, the ‘per protocol’ analysis revealed that participation in three or more sessions of compliance therapy significantly increased adherence to acamprosate and improved overall treatment outcomes. Of course, it should be noted that a ‘per protocol’ analysis is liable to selection bias.

Pelc et al. (2005) evaluated the effect of follow-up visits by a community nurse on abstinence and retention rates in the out-patient treatment of alcohol-dependent patients treated with acamprosate. One hundred patients were prescribed acamprosate for 26 weeks and randomised to either ‘physician only’ follow-up or physician plus regular visits from a community nurse. Drinking behaviour was assessed monthly. Twenty-eight
patients completed the study: 20 in the nurse follow-up group (40%) and eight in the physician only group (16%). The nurse follow-up group showed significantly better treatment retention and drinking outcomes. The principal effect of the intervention is likely to be a reduction of drop-out due to the frequent contact by the nurse. The effect on abstinence rates may be an artefact of the improved retention, since drop-outs were considered to be non-abstinent. Moreover, all follow-up visits were conducted by one community nurse, raising the question whether the effect should be attributed to the type of intervention or to the specific nurse.

So far, the most ambitious study on combined pharmacotherapy and behavioural interventions for alcohol dependence is the so-called COMBINE study (Anton et al., 2006). In this multi-centre RCT, 1,383 recently alcohol-abstinent patients were randomized to one of nine treatment conditions. All patients received medical management (MM) in which a medication adherence plan was developed in collaboration with the patient. Eight groups of patients received 16 weeks of naltrexone and/or acamprosate and/or both placebos, with or without a combined behavioural intervention (CBI). CBI integrated aspects of cognitive behavioural therapy, 12-step facilitation, motivational interviewing and support system involvement external to the study. Flexibility was permitted in the number of sessions and selection of modules to address each patient’s needs. A ninth group received CBI only. Patients were evaluated up to one year after treatment. Surprisingly, acamprosate showed no significant effect on drinking as compared to placebo, either by itself or with any combination of naltrexone, CBI, or both. The results on naltrexone are discussed in the next paragraph.

Naltrexone
In addition, several studies on combining naltrexone and psychosocial treatment have been conducted since 2002. Balldin et al. (2003) investigated the combination of naltrexon or placebo with a nine session manual-based cognitive behavioural therapy (CBT) or supportive therapy in 118 alcoholic patients. Similar to the original study of O’Malley et al. (1992), an extended treatment period of 24 weeks was chosen. There was a significantly more favourable outcome for those patients receiving naltrexone and CBT than for patients receiving naltrexone and supportive therapy, which is in line with the results of the studies of O’Malley et al. (1992) and Heinälä et al. (2001).

Anton et al. (2005) were the first to investigate the efficacy of naltrexone when combined with Motivational Enhancement Therapy (MET) as compared to CBT in 160 alcoholic patients. MET may be better applicable across a variety of treatment settings and is potentially less costly to deliver. For both treatments the manuals of Project Match were used. The combination of naltrexone with CBT showed to be superior to naltrexone alone. Fewer CBT-naltrexone patients relapsed and those that did had both fewer
relapses and more time between subsequent relapses. However, the combination of naltrexone with MET did not give better outcomes than naltrexone alone.

Next to studies on the added value of (structured) cognitive behavioural interventions on naltrexone, a growing interest has recently been noted on time-limited interventions that might be applicable in a variety of medical treatment settings. Most of these interventions mainly pay attention to the medication compliance, which is considered one of the most important weaknesses of current pharmacotherapy. This is well demonstrated with the prescription of naltrexone (Volpicelli et al., 1997): compliance with naltrexone played an important role in the increased efficacy in naltrexone over placebo.

BRENDA is a manual-based compliance enhancing program designed specifically for use in combination with pharmacotherapy in addictive patients. BRENDA consists of six components (Starosta et al, 2006).

1) Biopsychosocial evaluation
2) Report to the patient on assessment
3) Empathetic understanding of the patient’s situation
4) Needs collaboratively identified by the patient and treatment provider
5) Direct advice to the patient on how to meet those needs
6) Assess reaction of the patient to advice and adjust as necessary for best care

BRENDA is assumed to be effective because it includes elements of empirically proven interventions, such as brief interventions and motivational enhancement therapy (Miller & Wilbourn, 2002). It was first applied in a study on the efficacy of long-acting injectable naltrexone (Garbutt et al., 2005), but because BRENDA was included in all three conditions no conclusions could be drawn on its efficacy. In a recent study (Osling et al., 2008), the impact of three different types of psychosocial treatment combined with either naltrexone or placebo was investigated in 240 alcoholic patients: cognitive behavioural therapy (CBT) plus medication clinic; BRENDA plus medication clinic; and a medication clinic model with limited therapeutic content. CBT was found to be slightly more effective than BRENDA and medication clinic alone. In should be noted, however, that there was no evidence in this study that adding naltrexone to a psychosocial intervention improved drinking outcomes and no medication by psychosocial treatment interaction was found.

O’Malley et al. (2003) performed a nested sequence of three randomized trials to investigate the effectiveness of a primary care approach to the management of alcohol dependence with naltrexone therapy. This is an important issue given the fact that studies revealed that the benefits of treatment declined after discontinuation of naltrexone therapy, suggesting the need for longer treatment (O’Malley et al. 1996; Anton, Moak & Latham, 2001). Primary care physicians tend to have an ongoing relationship with their patients and are thus in the position to provide long-term
treatment. Study 1 compared 10 weeks CBT and Primary Care Management (PCM) as combined interventions with naltrexone in 1197 patients with alcohol dependence. Both interventions were manual-guided. PCM consisted of an initial 45-minute visit, followed by seven 15 to 20 minute sessions. Sessions were delivered weekly or biweekly, depending of the treatment phase. The PCM sessions included a review of alcohol use since the last visit, treatment compliance and advice for subsequent weeks. The CBT consisted of an initial 1.25 hour session, followed by ten sessions of 50 minutes, and was similar to that used in Project MATCH (Project MATCH, 1997). Study 2, the PCM naltrexone maintenance trial, compared an additional 24-weeks of PCM plus naltrexone maintenance therapy with PCM plus placebo in 53 responders to the PCM arm of study 1. Study 3, the CBT naltrexone maintenance trial, compared an additional 24-weeks of naltrexone maintenance therapy plus CBT with placebo plus CBT in 60 responders to the CBT arm of study 1. The results from this sequence of studies showed that PCM and CBT yielded comparable outcomes during the first 10 weeks of active treatment with naltrexone, suggesting that naltrexone therapy is promising as a therapy that could be used effectively with a low intensity PCM model of counselling. After an initial 10 weeks of combined PCM and naltrexone, maintenance naltrexone plus PCM during the subsequent six months was significantly more likely to result in sustained improvement among initial treatment responders than placebo plus PCM. However, maintenance naltrexone plus CBT therapy conferred no significant advantage over placebo plus maintenance CBT after an initial 10 weeks of combined CBT and naltrexone. The maintenance studies suggest that the value of continued naltrexone use after a positive response on an initial course of naltrexone and counselling may depend on the type of behavioural counselling provided.

In the previously mentioned COMBINE study (Anton et al., 2006) the effect of naltrexone with or without CBI was investigated. The results showed that across several drinking measures, patients receiving medical management showed better outcomes when also receiving either CBI or naltrexone: in the absence of CBI, naltrexone was effective; without naltrexone, CBI was effective. However, the combination of CBI plus naltrexone did not further improve outcomes. These data suggest that naltrexone can be effective within the context of medical management without specialist behavioural treatment.

**Final conclusions on combined pharmacotherapy and psychosocial treatment in alcohol use disorders**

Our RCT was the first to investigate the added value of psychosocial treatment on the medical prescription of acamprosate. The findings of our RCT on acamprosate are in line
with the studies of Hammarberg et al. (2004), and the ITT analysis of Reid et al (2005), indicating that there seems to be no additional value of behavioural interventions to the prescription of acamprosate. In addition, some naturalistic studies did not find a differential effect for different types of combined psychosocial treatment. In contrast, in naltrexone a clear beneficial effect of additional coping skills training is established (O’Malley, et al, 1992; Heinälä et al, 2001; Baldin, 2003: Anton et al., 2005). Moreover, this combination seems to be superior to combinations with supportive therapy or MET. In addition, we can conclude that the prescription of naltrexone in the context of medical management or primary care management is an effective treatment strategy (O’Malley et al., 2002; Anton et al., 2006). Adding specialist behavioural treatment might not be always necessary. These findings are in contrast with the common held belief in clinical practice that adding psychotherapy leads to better treatment outcomes.

**Treatment of alcohol dependence in routine clinical practice**

The RCT on the added value of psychotherapy on the prescription of acamprosate in the treatment of alcohol dependent patients, starting in 1997 (chapter 2), was the first large scale multicentre trial in substance use disorder patients in the Netherlands using manual-based treatments. As such, this trial appeared to be important in the introduction of cognitive-behavioural interventions and motivational interviewing. Conducting research in a clinical setting appeared to be an effective way of disseminating evidence-based treatment into clinical practice. Naturalistic outcome studies are important to provide information on the effectiveness of treatments in the real world of addiction treatment services as an addition to evidence regarding the efficacy from the laboratory like conditions in RCTs. Therefore, another research question in this thesis concerned the effectiveness of evidence-based psychotherapeutic interventions in routine clinical practice. Treatment outcomes of two manual-based cognitive behavioural interventions were evaluated. In addition, it was assessed whether clinical patient characteristics were predictive of treatment outcome. It was concluded that treatment outcomes in routine clinical practice were similar to those of alcohol RCTs. In addition, the results showed that several variables were predictive for treatment outcome, but the overall variance accounted for by the predictors was small.

Our results are in line with studies in the field of anxiety disorders and depression, where there is substantial evidence that treatment outcomes of CBT in routine practice are comparable to the results from RCTs (Franklin et al., 2000; Lincoln et al., 2003; Persons, Bostram & Bertagnolli, 1999; Persons, Roberts, Zalecki & Brechwald, 2006; Stuart, Treat & Wade, 2000). However, some important limitations have to be noted
when comparing the current naturalistic study in routine practice to existing data from RCTs. In our study, the follow-up rate was only 52% as opposed to the 80% regularly recommended as a lower limit in experimental studies. Since non-responders were overrepresented on variables that were negatively related to treatment outcome, our treatment outcomes are likely to be an overestimation of the real treatment success. This pattern was confirmed in another study by our group (Oudejans et al., 2009). Also, in comparing the results of our effectiveness study with those in RCTs on motivational enhancement and CBT, it must be taken into account that in our naturalistic study a different follow-up window and lower response rate possibly resulted in an overestimation of the abstinence rate. Fortunately, due to the use of standardized procedures we were able to assess these methodological differences between the experimental Project MATCH study and our naturalistic study, resulting in fair and careful conclusions (Oudejans, 2009). In addition, results from the COMBINE study show that ‘good clinical outcome’ was reported at 1-year follow-up for a maximum of 50% of the cases; 46.8% for behavioral treatment without medication and 50.4% for behavioral treatment with naltrexone (Anton et al., 2006). These figures are not fully comparable with our figures, due to different assessment instruments and follow-up times, but show that even in carefully designed trials, at 1-year follow-up about half of the patients are in need of more, extended or repeated treatments.

An important question, elaborating on the meaning of the results of CBT in routine practice, is whether these results are good enough and whether they represent good value for money. In considering alcohol dependence as a chronic condition, we can compare the results from our alcohol study with studies on other chronic diseases such as asthma, hypertension and diabetes. McLellan et al., mention similar ‘relapse’ rates for patients with hypertension and diabetes. ‘approximately 30% to 50% of patients with Type I diabetes and 50% to 70% of adult patients with hypertension or asthma experience recurrence of symptoms each year to the point where they require additional medical care to re establish symptom remission’ (McLellan, Lewis, O’Brien & Kleber, 2000; Graber et al., 1992; Clark, 1991).

One of the major strengths of our study is the use of treatment manuals. A major challenge for effectiveness research is to standardize interventions while preserving usual care conditions (Wells, 1999). Our study is, as far as we know, the first naturalistic effectiveness study in the field of alcohol use disorders that used manual based treatments. Other naturalistic studies on treatment outcomes of psychotherapeutic interventions for alcohol use disorders (e.g. Bottlender & Soyka, 2005; Gual, Lligona & Colom, 1999; Ojehagen et al., 1994) focus on intensive, long-term interventions consisting of a mixture of psychotherapeutic methods. It is unclear whether these treatments were evidence-based. Also, because treatment manuals were not used, there
is a high risk of therapists not conducting the therapies as intended. The current study is a contribution to the field, because it focuses on the effectiveness of broadly implemented proven effective interventions that were manualized in great detail. The use of treatment manuals in our study provided greater assurance that the core elements of CBT were systematically included in the structure of therapy. However, we must note that it is unclear whether therapists in the current study indeed adhered to the manuals. While in our RCT on the additional value of psychosocial treatment on the prescription of acamprosate the adherence to the guidelines was monitored by reviewing audiotapes and rated on a coding system, this was not the case in the naturalistic effectiveness study. Research indicates that the dissemination of CBT manuals in the Netherlands did overall not guarantee that therapists adhered to the manuals (van Dijk, Visser & Schippers, 2006). Also in the field of treatment of other psychiatric disorders therapist drift is a common phenomenon and usually involves a shift from “doing therapies” to “talking therapies” (Waller, 2009). Although CBT has a strong empirical base for the majority of psychological and psychiatric disorders, including alcohol use disorders, many clinicians feel that this treatment method is not appropriate for their patients and that it is not effective in real life settings (Waller, 2009). We, therefore, can not rule out the possibility that therapists adherence to the manuals in our effectiveness study was in some cases low, because the therapist believed that treatment needed to be individualized to obtain positive results. However, there is some evidence that therapist adherence to treatment protocols is related to positive outcome in psychiatric patients. For example, poor adherence to the treatment protocol is predictive of poor outcome in panic disorder patients whose motivation is low (Huppert et al., 2006). Also, research indicates that standardized manual based CBT results in better treatment outcomes than individualized CBTs (Schulte & Eifert, 1992; Emmelkamp, Bouman & Blaauw, 1994). These findings are contrary to most therapists’ beliefs. Treatment outcomes in routine practice might therefore be further improved by supervising therapists on how to adhere to the treatment manuals in order to reduce therapist drift.

**Implications for future research**

At present several effective psychosocial treatments and pharmacological treatments are available in the treatment of alcohol use disorders. Future research should direct attention to second-phase treatment of patients non-responding to one of the evidence-based treatment modalities. The question is whether non-responding patients have a reasonable chance to benefit from an additional or alternative evidence-based treatment. The importance of this line of research is that it will provide clinical guidelines for routine
practice with regard to the planning of evidence based treatment in a specific patient using a stepped care model.

Secondly, research aimed at identification of patient variables that can reliably predict treatment outcome in CBT and pharmacotherapy or specific combinations is needed to provide routine practice with guidelines on matching alcoholic patients to the appropriate treatment modality. While findings of matching and prediction research using clinical or phenotypic variables are overall disappointing, the predictive value of endophenotypic and genetic variables seems to be quite promising (Ooteman et al, 2005). Research should move forward to investigate endophenotypic and genetic variables in order to make progress in selecting responsive subgroups for different types of treatment.

Third, more effectiveness studies are needed to investigate the merits of empirically proven interventions in routine practice. It is recommended to consider naturalistic effectiveness studies as a necessary phase in the development of new treatment interventions, parallel to the development of new pharmacological treatments. Critical issues that need to be addressed in future research are generalizability (will this treatment work with different practitioners, patients and settings) and implementation (what kind of training is necessary for what kind of professional). Given the fact that in MATCH, COMBINE and our RCT site effects were observed, research on setting variables during treatment (e.g. site characteristics and therapist behaviour) is important to elucidate the impact of these factors on the process of change. An important spin-off of this kind of research is that it attributes to the dissemination of evidence-based interventions and helps to bridge the gap between research and practice.

Finally, cost-effectiveness studies are needed to provide insight in the economic aspects of empirically proven treatments and the financial impact of certain combinations of interventions. Especially in combining empirically proven interventions one need to know whether the direct extra medical costs leads to net savings. This kind of research is of interest for clinicians as well as policy makers. For example, the cost-effectiveness of adjuvant acamprosate therapy was retrospectively studied by Poldrugo et al (2005) and Schädlich & Brecht (1998). Only two prospective cost effectiveness studies have been conducted until now (Zarkin et al., 2008; UKATT Research Team, 2005), with only one focusing on the cost-effectiveness of combining pharmacotherapy and psychosocial treatment (Zarkin et al., 2008). More research is needed. Because health care resources are limited, understanding the costs and cost-effectiveness is important to enable efficient allocations of these resources.
Implications for clinical practice

With respect to clinical practice, research suggests that pharmacotherapy in the treatment of alcohol dependence could be effectively used with a low intensity primary care model of counselling. Treatment by a general practitioner might be especially valuable in new alcoholic patients as a first step in a stepped care approach. In the Dutch Multidisciplinary Guidelines for alcohol use disorders it is stated that general practitioners should either use a brief intervention or a proven effective medication dependent on their familiarity and perceived competence, but always in the context of motivational enhancement (Nederlandse Vereniging voor Psychiatrie, 2009).

Also, in specialized addiction treatment centers, prescription of pharmacotherapy without structured CBT seems to be a cost-effective treatment option for specific patients. For example, patients with low motivation for a structured CBT and as a result a high chance of drop out, might benefit from pharmacotherapy combined with compliance enhancement interventions. In general, however, in routine practice patients are always offered a CBT aimed at reduction of substance use. The patient is allocated to the appropriate Level of Care according to the stepped care principle and, as such, intensity of the CBT can differ depending on problem severity and treatment history (Merkx et al., 2007). Acamprosate, naltrexone or disulfiram is prescribed as an ‘add-on’ if CBT alone is not effective enough or the patient is suffering from high levels of craving. In routine practice it is rarely the case that patients are prescribed medication without CBT. Research suggests that medication plus medical management also has to be considered a treatment option in specialized addiction treatment centers. A least costly and time consuming compliance enhancement intervention might be a sufficient option. Comparable to guidelines for the treatment of other psychiatric disorders, for example generalized anxiety disorder, social phobia or depression (Nederlandse Vereniging voor Psychiatrie, 2004a, 2004b), one might consider two treatment options in allocating an alcohol dependent patient: pharmacotherapy plus medical management or monotherapy with CBT depending on the preference of the patient. Combining pharmacotherapy and structured psychosocial treatment should only be considered when monotherapy turns out not to be effective. To implement these recommendations the stepped care algorithms for treatment allocation that are used in Dutch substance abuse treatment centres need to be adapted.

Timely evaluation of treatment progress is necessary to identify non-responders on monotherapy as early as possible. Routine Outcome Monitoring, designed to support decision-making in the treatment process, is recommended (De Beurs & Zitman, 2007; Oudejans et al., 2009). Several studies in mental health care showed that outcome of poorly responding patients in an early stage of treatment can improve with feedback on
outcome (Lambert et al., 2005). In addition, given the chronic nature of alcohol addiction and the proportion of relapsing patients, implementing post-treatment telephone-based evaluations, identifying patients who are in need of more intensive treatment, is essential as an essential strategy in a stepped care approach (chapter 3). Implementation of Routine Outcome Management, e.g. assessment of treatment outcomes which are used for an aggregated feedback strategy, is recommended to be able to conduct effectiveness studies, which are needed to bridge the gap between research and practice (chapter 1).

The outcomes of our naturalistic study (chapter 5) and the treatment x centre interaction found in our RCT (chapter 2) suggest that the quality and effectiveness of psychosocial treatment of alcohol dependence could be improved. Clinical practice could probably benefit from supervising therapists on how to adhere to the CBT treatment manuals in order to reduce therapist drift. Motivational Interviewing (MI) is considered to be an essential competence for professionals in addiction treatment centres. Not only is it useful in conducting CBT manuals, it is also an important component of medical management strategies. It is known that the transfer of MI skills is limited when there is there is no support or coaching following training (Miller & Moyers, 2006). Supervision on how to perform MI adequately is therefore recommended. Medical doctors and psychologists appear to obtain a higher effect from MI than other health care providers (Rubak, 2005). Given the fact that a large proportion of the professionals in routine practice belongs to the group of nurses or social workers, special attention should be paid to education and supervision of these professionals.

**THE CONCEPT OF CRAVING AND ITS PREDICTIVE VALIDITY**

In our study on the structure of alcohol craving, previously found factor structures of the OCDS were evaluated using structural equation modeling and compared with alternative causal models, based on modern theories about craving. Data showed that the previously reported factor structures had to be rejected. It was shown that the OCDS contains many items that do not represent the core concept of craving, but instead measures the consequences of craving. We concluded that subjective craving, in a narrow sense, can be reliably assessed with a theory-driven subset of only five items.

Since the publication of our study two other studies were conducted in which the five item subset was investigated. A study of Nakovics et al. (2008) confirmed the stability and reliability of this short 5-item version of the OCDS: it obtained a similar retest-reliability score (0.76) and was as valid as the two-factor solution of the 12 item version. It was concluded that, when considering the objective of stability and economy in the assessment of craving, the theoretically constructed short version of the OCDS
seems to be sufficient. In addition, it was suggested that when different effects on a
cognitive and a behavioural level are expected, the 12 item version without alcohol
consumption items should be applied. Also, data of a recent Mexican study on the factor
structure and concurrent validity of the Spanish-translated version of the OCDS,
supported our findings on the advantages of the 5-item version (Cordero et al., 2009).

Our next study on alcohol craving aimed to establish the effect of instrument
variation, variations in time window and the type of outcome in the relationship between
subjective craving and treatment outcome in abstinent alcoholics in order to better
understand and improve the predictive value of subjective craving. Our results showed
that the predictive power of baseline craving differed for different types of drinking
outcome. No significant differences were found between different subsets of the OCDS.
Although baseline measures of subjective craving significantly predicted treatment
outcome, craving was a very modest predictor explaining a maximum of 4.2% in the
variance of treatment outcome. Other predictors were able to explain 29% of the
variance in the total number of abstinence days. Baseline craving was able to
independently add a maximum of 3%. The theoretically constructed five-item subset of
the OCDS performed best in short term prediction of relapse and when used cumulatively
during treatment. It was concluded that measuring craving at baseline or during
treatment is of only limited additional value for the prediction of relapse. It can be
assessed most cost-effectively in routine practice by using the five item subset of the
OCDS at baseline and during treatment.

The fact that the predictive value of craving on relapse showed to be limited might
be attributed to inadequate measurements (Drummond, 2000). However, this explanation
seems to be unlikely. Not only did we use different subsets, we also used a theoretically
constructed five-item subset (chapter 4). The results of our prediction study indicate that
this subset better represents the concept of subjective craving than any other subset and,
as such, support the conclusion of our study on the structure of alcohol (chapter 4). Another
critical issue elaborating on our findings on the predictive validity concerns the temporal
dynamics of craving. Craving may vary considerably over time, and, hence, the temporal
dynamics of craving may influence its predictive value depending on how and when it is
measured. It is stated that the timing of craving measurement may prove to be a critical
determinant of its predictive validity (Drummond, 2000). However, in our study the timing
of craving measurement had no effect on the prediction of relapse. The OCDS asks patients
to rate the items as they were experienced in the last seven days and can be considered a
questionnaire measuring "craving-past". Alternatively, it is possible that craving is only
predictive under certain conditions. For example, Niaura (2000) suggested that both craving
and low self-efficacy need to be present for relapse to occur. In our study this was not
investigated.

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Finally, it might be that autonomic and/or behavioural correlates of craving or the determinants or mediators of craving might be predictive for relapse in stead of the subjective experience of craving itself. We believe that this is the most valid explanation for our findings and findings of other studies in which no (substantial) relationship was found between craving and relapse (Tiffany & Conklin, 2000). Although the presumed relationship between craving and relapse to drinking seems to have high face validity, our findings suggest that subjective craving is somewhat overestimated as a predictor of treatment outcome. It might be that subjective experience of craving may not directly predict substance abuse, but relapse might be predicted from the correlates and underlying mechanisms of craving, e.g. attentional bias and cue-reactivity (Drummond, Litten, Lowman & Hunt, 2000). Subjective craving can be considered a phenotypic or clinical indicator, i.e. a patient characteristic that is the joint product of both genetic and environmental influences. Overall, studies using clinical or phenotypic variables in pharmacotherapy studies in alcohol dependence treatment have produced inconsistent and generally disappointing results (Ooteman et al., 2005). Also, in our naturalistic study on CBT several variables were predictive for treatment consumption and treatment effectiveness, but the overall explained variance was relatively small. This suggests that clinical variables, like subjective craving, might not be closely enough related to the biological process of addiction and relapse to be able to predict treatment outcome. In contrast, genetic indicators and endophenotypic indicators may be stronger related to the underlying process of addiction and craving or relapse mechanisms and are therefore more promising (Ooteman et al., 2005). Moreover, studies indicate that self-reported subjective craving correlates very low with neurophysiological cue reactivity (Robbins et al., 1997; Tiffany, 1990; Ooteman, 2006) and that self-reported craving is less predictive of relapse than physiological cue-reactivity (Kosten et al., 2006). Also findings in the field of pathological gambling and opiate-dependence show that endophenotypic indicators, e.g. attentional bias and inhibition deficits, predict relapse much better than subjective craving and self-reported personality styles (Goudriaan et al, 2008; Marissen, 2006).

Several integrative models of craving have been developed in which attentional bias and subjective craving have reciprocal and excitatory effects on each other (e.g. Franken, 2003a; Field & Cox, 2008). These models are based on the evidence which suggests that substance-related attentional bias, subjective craving, and expectations of the opportunity to use a substance are interrelated reactions to substance-related stimuli that seem to develop through classical conditioning. They suggest that subjective craving and attentional bias have reciprocal, excitatory effects on one another, such that an increase in subjective craving leads to an increase in the attention-grabbing properties of substance-related cues. In turn, the attentional focus on substance-related cues increases the strength of the craving. Although attentional bias and craving are different
phenomenon, research shows they are clearly related (Field, Munafo & Franken, 2009). This suggests that craving, by measuring attentional bias, can be measured partly on a cognitive level. Different tasks are available to measure attentional bias. The most well known are the emotional Stroop test (see Cox et al., 2006 for an overview) and the visual probe test. Research shows that attentional bias is a more powerful predictor of relapse than self-reported craving (Cox et al., 2002; Marissen, 2006).

**Implications for future research**

Future craving research should focus on development of new measurements of craving. Self-reported subjective craving showed to have low predictive value on relapse and it is also know that it only modestly correlated with physiological measures (Tiffany, 1990). In addition, self-reported craving, at least when measured in treated patients in a clinical setting, is influenced by the tendency to answer in a social desirable manner (Marissen et al., 2005). The weakness of physiological measures of cue reactivity is that they may reflect more than craving alone, e.g. reflect general emotional states. Therefore, craving research should focus on development of new measurements that are more capable to objectively catch the core of craving than physiological measures and self-reports. Neuroimaging techniques to measure brain activity (EEG, FMRI) are promising and need further research to further elucidate the concept of craving (Franken et al., 2008).

Further research on the predictive value of endophenotypic variables and more implicit measures, like attentional bias, is recommended. Treatment of alcohol dependent patients could benefit from a moving away from a pure assessment of clinical variables, as is the case in routine practice now, towards assessing deficits in neuropsychological functions and genetic variations. As in effectiveness studies on new treatments, research is needed on the application, implementation, cost-effectiveness and usefulness of these new kind of predictors in routine practice.

Another topic for future research is the development and testing of new techniques to directly influence attentional bias. Interventions aiming at training of attentional processes might be a valuable addition to the current treatment options of pharmacotherapy and behavioural skills training. First results on this kind of research are promising and more research is needed (Wiers et al., 2006).
Implications for clinical practice

With respect to clinical practice, subjective craving can be measured with the theory-driven five item subset of the OCDS. It is recommended to measure not only at baseline but periodically during treatment to enhance predictive value and select patient groups who are at risk for relapse. In such a design, it would be useful to integrate the OCDS subset in Routine Outcome Monitoring.

In routine practice, it is common that patients are educated on the phenomenon of subjective craving and cue reactivity. However, emphasis is put on the classical conditioning theory and the predictive value of craving on relapse. Patients are trained to early recognize signals of craving in order to avoid relapse. Considering the results of this thesis, clinicians should also pay attention to educate patients on more implicit processes and the relation of subjective craving with attentional bias. This is especially important for patients who do not report craving and who might therefore believe they are not at risk of relapse. In educating patients it might be helpful to distinguish subjective craving from cue-reactivity and implicit attentional bias.

Neuropsychologists and neuropsychological assistants are needed to perform neurocognitive tests in order to better inform the therapists on the severity of attentional bias, cue reactivity and other neuropsychological outcome predictors. This clinical relevant information might help to reduce the probability of relapse during treatment and to improve their overall quality.
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Alcohol dependence or addiction is generally conceptualized as a multifactorial disease with biological, psychological and social determinants. Scientific advances over the last decades have emphasized the position that addiction is a chronic brain disease, which is characterized by an intermittent course of recovery and relapses. The current theories on the development and persistence of addictive behaviours are dominated by findings from neurobiological research, clarifying the biological basis of the behavioural and psychological factors that contribute to dependence.

The first part of this thesis addresses the treatment of alcohol use disorders. Effective psychosocial treatment of alcohol use disorders aims at enhancing the motivation to change drinking behaviour and consists of several cognitive behavioural interventions, paying attention to the patient’s social support network. Supervised disulfiram, naltrexone and acamprosate are empirically proven pharmacological treatment options. The question is whether and how to combine these agents with psychosocial treatments. There is ample evidence that naltrexone and acamprosate adds to the effectiveness of psychosocial treatment of patients with alcohol use disorders. In contrast, the amount of research on the additional effect of psychosocial treatment on pharmacotherapy is very limited, but the few available studies indicate that this combination might be beneficial. Questions concerning the necessity, nature and intensity of such psychosocial interventions and the efficacy of particular treatment combinations need to be addressed.

Therefore, the main RCT in this thesis investigated the additional value of two forms of evidence-based psychosocial treatment on the effect of acamprosate. In chapter 2, the results are presented. 248 patients meeting DSM-IV criteria for alcohol dependence or abuse were recruited in 14 substance use treatment centres and randomized into one of three treatment conditions: 1) prescription of acamprosate; 2) prescription of acamprosate plus minimal intervention aimed at motivational enhancement (3 weekly sessions of 20 minutes); and 3) prescription of acamprosate plus brief cognitive behavioural therapy (7 weekly sessions of 60 minutes). In contrast to our hypotheses there were no statistically significant differences in treatment duration across the three treatment conditions, and no differences in drop-out rates or reasons for termination. Also, no statistically significant differences were found between treatment groups for any of the drinking outcomes either at the end of the 28 weeks of treatment.
or at six months follow-up. There were no statistically significant differences in medication compliance or psychological distress. However, a significant interaction effect was observed between treatment centre and treatment group, indicating that psychosocial interventions were differentially effective in different treatment centres. A clear supplemental value of minimal and brief psychosocial intervention to the prescription of acamprosate was not demonstrated in this study.

Effectiveness studies evaluate effects of treatments under conditions approximating usual care. Effectiveness studies are a necessary addition to RCTs in order to test the ecological validity and to provide information how well a treatment works in routine clinical practice. In pharmacotherapy research these so-called phase IV studies are part of the testing process, but this is less common in psychotherapy research. Effectiveness research can be used as a strategy for bridging the gap between research and practice. There are no large-scale studies available on the effectiveness of empirically proven psychosocial treatments in alcohol use disorders in routine practice. Therefore, chapter 3 of this thesis, addressed the treatment outcomes of manual-based cognitive behavioural therapy for patients with an alcohol use disorder in routine practice. In addition, it was assessed whether clinical patient characteristics were predictive of treatment outcome. A total of 599 alcoholic patients admitted for outpatient treatment in two addiction centers were allocated, based on a stepped care protocol, to a brief cognitive behavioural therapy of four sessions (BCBT) or to standard cognitive behavioural therapy (SCBT) of ten sessions. Treatments were manual-based. Results showed that half of the patients (49%) was treated according to the prescribed sessions. In BCBT 59% completed treatment, in SCBT 41%. Treatment was successful in 43.2% of the patients. Several variables were predictive for treatment outcome, but the overall variance accounted for by the predictors was small. The studies showed that treatment outcomes of alcohol RCTs were preserved in a naturalistic setting. Outcomes might be further improved by additional relapse prevention strategies, for example contingency management and pharmacotherapy. Given the chronic nature of the disorder and the proportion of relapsing patients, implementing post-treatment telephone-based evaluations, identifying patients who are in need of more intensive treatment, will an essential strategy in a stepped care approach.

The second part of this thesis addresses the concept of craving. Although clinicians generally consider craving (e.g. the strong and overwhelming desire to drink) an important aspect of dependence, the phenomenon of craving is still a puzzle. Opinions on the definition, relevance and measurement of craving remain divided. Also, its relation to drinking behaviour and relapse is not well established. Although it is often assumed that craving is predictive of relapse, neither studies of craving and alcohol consumption
in the laboratory nor studies of craving and relapse in the real world have provided strong evidence that craving is directly responsible for alcohol use in alcoholics.

Chapter 4 reported on the findings of a multinational study on the structure of craving. Data from four studies on the Obsessive Compulsive Drinking Scale (OCDS) were used. The factor structures of the OCDS previously found were evaluated and compared with those of alternative causal models based on modern theories: an obsessive-compulsive disorder model, an inhibition model and a cognitive-behavioural model. The data showed that the previously reported factor structures had to be rejected and that the cognitive-behavioural model proved to be superior to other models of craving. The data further showed that the OCDS contains many items that do not represent the core concept of craving, but instead are indicators of the consequences of craving. We concluded that craving, in a narrow sense, can be reliably assessed with only five items of the OCDS.

In Chapter 5 we investigated the predictive value of subjective craving. The study aimed to establish the effect of instrument variation, variations in time window and the type of outcome in the relationship between subjective craving and treatment. Also, the additional predictive value of craving on other well known predictors was assessed. The results showed that, although baseline measures of subjective craving were predictive of treatment outcome, craving was a very modest predictor. No significant differences were observed between predictions using different instruments and/or using different outcome parameters. Surprisingly, later measures of craving had a lower predictive value than baseline craving. The exception was the five-item subset of the OCDS, which performed better in short term prediction of relapse and when used cumulatively during treatment. Other known predictors were able to explain 29% of the variance in the total number of abstinence days. Baseline craving measures were able to independently add a maximum of 3% to the total explained variance. It is, therefore, concluded that measuring subjective craving at baseline or during treatment is of only limited value for the prediction of relapse. Subjective craving could be assessed most cost-effectively in daily practice by using the five item subset of the OCDS at baseline and during treatment.

Chapter 6 is the general discussion. The major findings presented in this thesis are discussed in the context of recent research. Implications for future research and clinical practice are discussed. Regarding the added value of psychosocial treatment on the prescription of acamprosate relevant studies published after 2002 are presented. The results on recent acamprosate studies are in line with the results of our RCT: there seems to be no additional value of psychosocial interventions to the prescription of acamprosate. In contrast, in naltrexone a clear beneficial effect of additional coping skills training is established. In addition, the prescription of naltrexone in the context of
medical management or primary care management showed to be an effective treatment strategy. Adding specialist behavioural treatment might not be always necessary. Regarding the effectiveness of CBT in routine practice we conclude that our results are in line with studies in the field of anxiety disorders and depression, where there is substantial evidence that treatment outcomes of CBT in routine practice are comparable to the results from RCTs. In addition, some limitations of our study are discussed, in particular the follow-up rate, which was lower than the regularly recommended 80%. In elaborating on one of the strengths of our study, the use of treatment manuals, it is suggested that treatment outcomes might be further improved by supervising therapists on how to adhere to the treatment manuals in order to reduce therapist drift.

Future research on treatment of alcohol use disorders should direct attention to second-phase treatment of patients non-responding to one of the evidence-based treatment modalities. Research aimed at identification of endophenotypic and genetic variables that can reliably predict treatment outcome in CBT and pharmacotherapy or specific combinations is needed to provide routine practice with guidelines on matching alcoholic patients to the appropriate treatment modality. Third, more effectiveness and cost-effectiveness studies are needed to investigate the merits and economic aspects of empirically proven treatments in routine practice.

With respect to clinical practice, it is concluded that pharmacotherapy in the treatment of alcohol dependence can be effectively used with a low intensity medical management model of counselling, in primary care as well as in specialized addition treatment centres. Routine Outcome Monitoring during treatment process is necessary to identify non-responders on monotherapy as early as possible. In addition, implementing post-treatment telephone-based evaluations, identifying patients who are in need of more intensive treatment, is an essential strategy in a stepped care approach. Implementation of Routine Outcome Management, e.g. assessment of treatment outcomes which are used for an aggregated feedback strategy, is recommended to be able to conduct effectiveness studies, which are needed to bridge the gap between research and practice.

Regarding our craving studies, the most valid explanation for lack of a (substantial) relationship between craving and relapse is that autonomic and/or behavioural correlates of craving or the determinants or mediators of craving are predictive for relapse in stead of the subjective experience of craving itself. We suggest that craving, by measuring attentional bias, can be measured partly on a cognitive level. Future craving research should focus on development of new measurements of craving, for example neuroimaging techniques to measure brain activity (EEG, FMRI). Also, further research on the predictive value of endophenotypic variables and more implicit measures, like attentional bias, is recommended. As in effectiveness studies on new treatments, research is needed on the
application, implementation, cost-effectiveness and usefulness of these new kind of predictors in routine practice. Another topic for future research is the development and testing of new techniques to directly influence attentional bias.

With respect to clinical practice, subjective craving can be measured with the theory-driven five item subset of the OCDS. It is recommended to measure not only at baseline but periodically during treatment and to integrate the OCDS subset in Routine Outcome Monitoring. Clinicians should pay more attention to educate patients on implicit processes and the relation of subjective craving with attentional bias. It might be helpful to distinguish subjective craving from cue-reactivity and implicit attentional bias. Neuropsychologists and neuropsychological assistants are needed to perform neurocognitive tests in order to better inform the therapists on the severity of attentional bias, cue reactivity and other neuropsychological outcome predictors. This clinical relevant information might help during treatment to reduce the probability of relapse and to improve their overall quality.
SUMMARY IN DUTCH

Alcohol afhankelijkheid of -verslaving wordt beschouwd als een multifactoriële ziekte met biologische, psychologische en sociale determinanten. Wetenschappelijke inzichten van de laatste decennia geven aan dat verslaving een chronische hersenziekte is, gekarakteriseerd door een intermitterend beloop van herstel en terugval. De huidige theorieën over de ontwikkeling en het voortbestaan van verslaving worden gedomineerd door bevindingen uit neurobiologisch onderzoek, welke de biologische basis verhelderen van de gedragstmatige en psychologische factoren die bijdragen aan afhankelijkheid.

Het eerste deel van dit proefschrift betreft de behandeling van stoornissen in het gebruik van alcohol. Effectieve psychosociale behandeling van stoornissen in het gebruik van alcohol richt zich op het vergroten van de motivatie voor verandering van het drinkgedrag en bestaat daarnaast uit verschillende cognitief-gedragstherapeutische interventies. Daarbij wordt ook aandacht besteed aan het ondersteunende sociaal netwerk van de patiënt. Naltrexon, acamprosaat en gesuprerviseerde inname van disulfiram zijn bewezen effectieve farmacotherapeutische behandelopties. De vraag is of en zo ja, hoe deze medicatie gecombineerd dient te worden met psychosociale behandeling. Er is ruime evidentie dat naltrexon en acamprosaat de effectiviteit van psychosociale behandeling van patiënten met een stoornis in het gebruik van alcohol verbetert. De hoeveelheid onderzoek naar het additionele effect van psychosociale behandeling bij farmacotherapie is echter beperkt. De enkele beschikbare studies geven aan dat deze combinatie meerwaarde zou kunnen hebben. Vragen betreffende de noodzaak, de aard en de intensiteit van zulke psychosociale interventies en de effectiviteit van specifieke behandelcombinaties dienen te worden onderzocht.

De hoofdstudie in dit proefschrift onderzoekt daarom de additionele waarde van twee vormen van evidence-based psychosociale behandeling op het effect van acamprosaat. In hoofdstuk 2 worden de resultaten gepresenteerd. 248 patiënten die voldeden aan de DSM-IV criteria voor alcohol afhankelijkheid of -misbruik werden gerekurtueerd in 14 verslavingszorginstellingen en gerandomiseerd in een van de drie behandelcondities: 1) het voorschrijven van acamprosaat; 2) het voorschrijven van acamprosaat plus een minimale interventie gericht op motivatiebevordering (3 wekelijkse
sessies van 20 minuten); en 3) het voorschrijven van acamprosaat plus een kortdurende cognitief-gedragstherapeutische interventie (7 wekelijkse sessies van 60 minuten). In tegenstelling tot onze hypothesen werden er tussen de behandelcondities geen statistisch significante verschillen gevonden in behandelduur, drop-out percentages of reden van beëindiging. Ook ten aanzien van het alcoholgebruik werden geen statistisch significante verschillen gevonden tussen de behandelgroepen; niet aan het eind van de behandeling, noch bij follow-up. Er waren geen statistisch significante verschillen in medicatietrouw of psychisch disfunctioneren. Echter, een significant interactie effect werd gevonden tussen behandelcentrum en behandelgroep. Dit wijst erop dat de psychosociale interventies verschillend effectief waren in de diverse behandelcentra. Een duidelijk toegevoegde waarde van de minimale en kortdurende psychosociale interventie werd in deze studie niet gevonden.

Effectiviteitstudies evalueren effecten van behandeling onder omstandigheden die de zorg in de dagelijkse praktijk benaderen. Ze zijn een noodzakelijke aanvulling op RCTs om de ecologische validiteit te onderzoeken en informatie te generen hoe goed een behandeling werkt in de dagelijkse praktijk. In onderzoek op het gebied van farmacotherapie zijn deze zogenaamde fase IV studie onderdeel van het test proces, maar dit is veel minder gebruikelijk in psychotherapie onderzoek. Effectiviteitonderzoek kan gebruikt worden als strategie om de brug te slaan tussen onderzoek en praktijk. Er zijn geen grootschalige studies beschikbaar naar de effectiviteit van bewezen effectieve psychosociale behandelingen voor stoornissen in het gebruik van alcohol in de dagelijkse praktijk. In hoofdstuk 3 van dit proefschrift worden derhalve de behandelresultaten van geprotocolleerde cognitieve gedragstherapie voor patiënten met een stoornis in het gebruik van alcohol in de dagelijkse praktijk onderzocht. Tevens werd onderzocht in hoeverre klinische patiënt karakteristieken predictief waren voor behandeluitkomsten. 599 alcoholpatiënten geïndiceerd voor ambulante behandeling in twee verslavingszorginstellingen werden, op basis van een stepped care protocol, verwezen naar een kortdurende cognitieve gedragstherapie van vier sessies (KCGT) of naar een standaard cognitieve gedragstherapie (SCGT) van tien sessies. Behandeling was geprotocolleerd. De resultaten lieten zien dat de helft van de patiënten (49%) behandeld werd volgens het aantal voorgeschreven sessies. In KCGT maakte 59% de behandeling af, in SCGT 41%. Behandeling was succesvol bij 43.2% van de patiënten. Verschillende variabelen waren predictief voor het behandelresultaat, maar de verklaarde variantie was gering. De studie laat zien dat behandelresultaten zoals gevonden in RCTs behouden blijven in een naturalistische setting. De resultaten zouden verder bevorderd kunnen worden middels aanvullende terugvalpreventiestrategieën, bijvoorbeeld contingentie management en farmacotherapie. Gegeven het chronische karakter van de stoornis en het percentage terugvallende patiënten is het implementeren van telefonische evaluaties
na de behandeling, met als doel het identificeren van patiënten die een meer intensieve behandeling nodig hebben, een essentiële strategie binnen de stepped care benadering.

Het tweede deel van dit proefschrift behandelt het concept craving. Hoewel clinici craving (e.g. het sterke en overweldigende verlangen om te drinken) beschouwen als een belangrijke aspect van afhankelijkheid, is dit fenomeen nog steeds niet volledig opgehelderd. Er bestaan verschillende meningen over de definitie, de relevantie en het meten van craving. Ook de relatie tot drinkgedrag en terugval is niet geheel duidelijk. Hoewel vaak wordt verondersteld dat craving een voorspeller is voor terugval, leveren laboratorium studies noch studies in de praktijk sterke evidentie voor het feit dat craving direct verantwoordelijk zou zijn voor alcoholgebruik bij patiënten.

**Hoofdstuk 4** rapporteert de bevindingen van een multinationale studie naar de structuur van craving. Er werd gebruik gemaakt van data van vier studies naar de Obsessive Compulsive Drinking Scale (OCDS). De factor structuren van de OCDS zoals gevonden in eerdere studies werden geëvalueerd en vergeleken met die van alternatieve causale modellen gebaseerd op moderne theorieën: een obsessief-compulsieve stoornis model, een inhibitie model en een cognitief-gedragsmatig model. De data lieten zien dat de eerder gerapporteerde factor structuren verworpen dienen te worden en dat het cognitief-gedragsmatige model superieur is ten opzichte van de andere cravingmodellen. De data laten verder zien dat de OCDS veel items bevat die niet de kern van craving representeren, maar eerder indicatoren zijn van de consequenties van craving. We concluderen dat craving, in engere zin, betrouwbaar gemeten kan worden met slechts vijf items van de OCDS.

In **Hoofdstuk 5** onderzochten we de predictieve waarde van subjectieve craving. De studie had tot doel om het effect van variatie in instrument, tijdspanne en type uitkomst vast te stellen in de relatie tussen subjectieve craving en behandeluitkomst. Ook onderzochten we de additionele predictieve waarde van craving bovenop andere bekende predictoren. De resultaten lieten zien dat, hoewel baseline metingen van subjectieve craving predictief waren voor behandeluitkomst, craving slechts een bescheiden predictor was. Geen significante verschillen in predictie werden gevonden tussen de diverse instrumenten en/of het gebruik van verschillende uitkomstmaten. Verrassend genoeg bleken latere metingen van craving een lagere predictieve waarde te hebben dan baseline craving. Uitzondering was de vijf-item subset van de OCDS, die juist beter presteerde in korte termijn predictie van terugval en bij gebruik van de cumulatieve scores tijdens de behandeling. Andere bekende predictoren verklaarden 29% van de variantie in het totaal aantal abstinente dagen. Baseline cravingmaten waren in staat om onafhankelijk hieraan een maximum van 3% toe te voegen. Geconcludeerd werd derhalve dat het meten van subjectieve craving aan het begin of gedurende de behandeling slechts beperkte waarde heeft voor de predictie van terugval. Subjectieve
craving kan in de dagelijkse praktijk het beste op een kosteneffectieve manier gemeten worden aan de hand van de vijf-item subset van de OCDS.

**Hoofdstuk 6** is de algemene discussie. De belangrijkste bevindingen van dit proefschrift worden bediscussieerd in the context van recente onderzoeksbefindingen. Implicaties voor toekomstig onderzoek en de klinische praktijk worden besproken. Ten aanzien van de additionele waarde van psychosociale behandeling bij het voorschrijven van acamprosaat worden de relevante studies die gepubliceerd zijn na 2002 gepresenteerd. De resultaten van latere acamprosaat studies zijn in lijn met de resultaten van onze RCT: psychosociale interventies lijken geen toegevoegde waarde te hebben bij het voorschrijven van acamprosaat. Voor naltrexon is echter wel een duidelijk positief effect van additionele training in coping vaardigheden vastgesteld. Daarnaast is het voorschrijven van naltrexon in een medische context (*medical management* of *primary care management*) een effectieve behandelmethode. Het toevoegen van gespecialiseerde gedragstherapie is dus wellicht niet altijd nodig. Ten aanzien van de effectiviteit van CGT in de klinische praktijk concluderen we dat onze resultaten overeenstemmen met studies naar angststoornissen en depressie, waar er duidelijke evidentie is dat behandelmethode van CGT in de dagelijkse praktijk vergelijkbaar zijn met de resultaten van RCTs. Tevens worden enkele beperkingen van onze studie besproken, met name het follow-up percentage, welke lager was dan de algemeen aanbevolen 80%. Een van de sterke kanten van ons onderzoek was het gebruik van behandleprotocollen. We suggereren dat de behandelresultaten verder verbeterd zouden kunnen worden door therapeuten te superviseren in het uitvoeren van geprotocolleerde behandelingen om te voorkomen dat onnodig van het behandelprotocol wordt afgeweken.

Toekomstig onderzoek naar de behandeling van stoornissen in het gebruik van alcohol zou zich moeten richten op de tweede-fase behandeling van patiënten die niet verbeteren in een van de bewezen effectieve behandelingen. Onderzoek gericht op het identificeren van endophenotypische en genetische variabelen die predictief zijn voor de behandelresultaten van CGT, farmacotherapie en specifieke combinaties is noodzakelijk om de klinische praktijk te voorzien van richtlijnen ten aanzien van het matchen van alcohol patiënten aan de juiste behandelmodaliteit. Ten derde, meer effectiviteit- en kosteneffectiviteit studies zijn nodig om de doelmatigheid en economische aspecten van bewezen effectieve behandelingen in de klinische praktijk vast te stellen.

Ten aanzien van de klinische praktijk concluderen we dat farmacotherapie in de behandeling van alcoholafhankelijkheid effectief kan worden toegepast binnen een laag intensieve medische context, zowel in de eerste lijn als in gespecialiseerde verslavingszorginstellingen. Routine Outcome Monitoring tijdens het behandelproces is noodzakelijk om non-responders van monotherapie zo vroeg mogelijk te identificeren.
Tevens zijn binnen een stepped care benadering telefonische evaluaties na de behandeling essentieel om patiënten te identificeren die een meer intensieve behandeling nodig hebben. Implementatie van Routine Outcome Management, e.g. het verzamelen van behandeluitkomsten voor een geaggregeerde feedback strategie, is aanbevolen om effectiviteitstudies uit te voeren die nodig zijn om de kloof tussen onderzoek en praktijk te overbruggen.

Voor wat betreft de craving studies is de meest valide verklaring voor het gebrek aan een substantiële relatie tussen craving en terugval dat autonome en/of gedragsmatige correlaten van craving of de determinanten of mediators van craving predictief zijn in plaats van de subjectieve ervaring van craving zelf. We suggereren dat craving, middels het meten van attentional bias, deels gemeten kan worden op een cognitief niveau. Toekomstig craving onderzoek zou zich moeten richten op de ontwikkeling van nieuwe metingen voor craving, bijvoorbeeld neuro-imaging technieken om hersenactiviteit te meten (EEG, FMRI). Ook onderzoek naar de predictieve waarde van endophenotypische variabelen en meer impliciete maten, zoals attentional bias, is aanbevolen. Overeenkomstig effectiviteitstudies naar nieuwe behandelingen, is onderzoek nodig naar de toepassing, implementatie en kosteneffectiviteit van deze nieuwe soort predictoren in de klinische praktijk. Een ander onderwerp voor toekomstig onderzoek is de ontwikkeling en het testen van nieuwe technieken om attentional bias te beïnvloeden.

Ten aanzien van de klinische praktijk, stellen we dat subjectieve craving gemeten kan worden met de theoriegestuurde vijf item subset van de OCDS. We bevelen aan niet alleen te meten aan het begin van de behandeling maar periodiek gedurende de behandeling en de vijf OCDS vragen te integreren in Routine Outcome Monitoring. Clinici dienen meer aandacht te besteden aan het voorlichten van patiënten over impliciete processen en de relatie tussen subjectieve craving en attentional bias. Het kan daarbij helpend zijn om subjectieve craving te onderscheiden van cue-reactiviteit en impliciete attentional bias. Neuropsychologen en neuropsychologisch assistenten zijn nodig om neurocognitieve testen uit te voeren ten einde de therapeut beter te informeren over de ernst van attentional bias, cue reactiviteit en andere neuropsychologische predictoren van behandelresultaat. Deze informatie kan gedurende de behandeling helpend zijn om de kans op terugval te verminderen en de kwaliteit van de behandeling te bevorderen.
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Het is af! Na vele jaren is dan eindelijk dit proefschrift voltooid.


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CURRICULUM
VITAE


Naast deze functies heeft zij in de afgelopen jaren regelmatig opgetreden als docent aan de postdoctorale GZ-opleiding en diverse trainingen en cursussen gegeven op het gebied van cognitieve gedragstherapie bij verslaving. Zij is internationaal opgeleid tot trainer in Motivational Interviewing en heeft diverse trainingen en workshops gegeven in deze methodiek.

Momenteel is zij werkzaam als clustermanager behandelzaken van de Business Unit Curatieve Zorg van Arkin, Amsterdam, en verantwoordelijk voor de zorgprogramma’s verslaving, angst, trauma, depressie en soma & psyche.
LIST OF PUBLICATIONS

International scientific


National practically-oriented


