Psychobiological pathways to alcohol craving and their relevance for patient-treatment matching

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Citation for published version (APA):
Psychobiological pathways
to alcohol craving
and their relevance for
patient-treatment matching
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Cover design: R.O. Eschweiler
Lay out: C. van Weerdenburg
Printed by: Febodruk, Enschede

The studies presented in this thesis were conducted as part of the 'Addiction' pro-
gram granted by The Netherlands Organization for Health Research and Devel-
opment (ZonMw/NWO). These studies were supported by ZonMw grant no.
985-10-013 and 985-10-506, and by Merck bv.

Financial support for the printing of this thesis was kindly provided by:
Merck bv and J.E. Jurriaanse Stichting.
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Contents

Chapter 1 General Introduction 7

Chapter 2 Patient-treatment matching with anti-craving medications in alcohol-dependent patients: A review on phenotypic, endophenotypic and genetic indicators 17

Chapter 3 Development and validation of the Amsterdam Motives for Drinking Scale (AMDS): an attempt to distinguish relief and reward drinkers 47

Chapter 4 Measuring craving: an attempt to connect subjective craving with physiological cue reactivity 69

Chapter 5 The effect of naltrexone and acamprosate on cue-induced craving and physiological cue reactivity in alcoholics 97

Chapter 6 Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using phenotypic, endophenotypic and genetic indicators 119

Chapter 7 Summary and General Discussion 141

Samenvatting [Summary in Dutch] 167
List of frequently used abbreviations 180
Dankwoord 183
List of publications 187
About the author 189
ZELFPORTRET IN KRIJT

hij wil graag de waarheid weten
en zoekt die in vergetelheid

maar de gezelligheid kent geen tijd
om de diepte op te meten

dus neemt hij op de lat het glas
waarin hij zich het liefste ziet

de afdronk waar hij van geniet
maakt liefde altijd waterpas

en de dag die hij ondergaat
heeft genoeg aan zijn eigen kwaad

Arie Visser
Uit: Licht en Vuur, gedichten, 1996
CHAPTER 1

General Introduction
This chapter provides a general theoretical background for the study and gives a short description of the research questions and a general outline of this thesis.

**Background of the study**

People drink alcohol for a variety of reasons. The consumption of beer, wine or liquor can be tasty, relaxing or make a party going. However, there are also a lot of reasons to cut down or quit your drinking. Alcohol is an addictive substance; excessive use can lead to tolerance, withdrawal, and various physical illnesses, such as diseases of the liver, the pancreas, the heart, the central and peripheral nervous system, and various malignancies. Data on the prevalence of heavy drinking, alcohol abuse, and alcohol dependence in the Netherlands have been collected in a large prospective study in the general population, the Netherlands Health Survey and Incidence Study (NEMESIS) (Verdurmen et al., 2003). According to the Dutch National Drug Monitor (NDM), about 81% of the Dutch residents over 12 years drink alcohol (Trimbos Institute, 2004). Within this general population sample of regular drinkers, about 10% can be classified as an excessive user of alcohol (> 14 alcohol units (AU)/week for women and > 21 AU/week for men). This rate is fairly similar to the prevalence in other Western populations (e.g., Grant et al., 2004; Kraus et al., 2000). Heavy drinking (defined as > 35 AU/week for women and > 50 AU/week for men) is present in 1.6% of the general population: 2.4% in men and 0.8% in women. Last year prevalence of alcohol abuse and alcohol dependence were 4.6% and 3.7% respectively.

According to DSM-IV criteria (American Psychiatric Association, 1994), alcohol abuse involves a maladaptive pattern of alcohol use with at least one of the following problems: 1) failure to fulfill major role obligations, 2) recurrent use in hazardous situations, 3) recurrent legal problems, and 4) continuing despite social or interpersonal harm. Alcohol dependence (or alcoholism) is characterized by a destructive pattern of alcohol use leading to three or more of the following problems: 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 or recovering, 6) important activities are given up or reduced, and 7) continuing despite physical or psychological harm (American Psychiatric Association, 1994).
CHAPTER 1

Contrary to the ICD-10 and the Craving Withdrawal Model (CWM) classification (De Bruin et al., 2004), in the DSM-IV classification craving (a strong or overwhelming urge to drink) is absent in the criteria of alcohol use disorders. However, the DSM-IV admits that craving is an important symptom and an essential clinical component that is experienced by many subjects with alcohol dependence. Craving can persist for months or years after the subject’s last alcohol intake (Mathew et al., 1979). Further, it is widely believed that the development of craving plays a role in the transition from controlled drinking to alcohol dependence (e.g., Wise, 1988), that craving is part of the mechanism underlying relapse (e.g., Anton et al., 1996; Bottlender and Soyka, 2004; Ludwig et al., 1974), and that reduction of craving is crucial in the treatment of alcoholism (e.g., Volpicelli et al., 1992; O’Brien, 2005).

However, there are many unresolved issues regarding the concept and the role of craving in the development and course of addictive behaviors. For example, inconsistent findings on the relationship between craving and relapse may be the result of inconsistencies in the measurement of craving (Rohsenow and Monti, 1999; Tiffany, 1990). In turn, these inconsistencies are the consequence of a series of interrelated problems such as a lack of consensus about the definition of craving and the lack of concordance between self-reported craving and physiological measures of cue reactivity.

Clinical studies provide consistent evidence for the efficacy of so-called anti-craving compounds (O’Brien, 2005), such as acamprosate (e.g., Sass et al., 1996; Mann et al., 2004) and naltrexone (e.g., Volpicelli et al., 1992; Roozen et al., 2005) in reducing relapse rates, yet the mechanisms underlying their effectiveness are poorly understood (Spanagel and Ziegglänsberger, 1997). In general, however, these anti-craving compounds are found to be only moderately effective (see reviews: Mann, 2004; Srisurapanont and Jarusraisin, 2005a, 2005b) with a mean difference in relapse rates between placebo and the active compound of about 15% and the number of patients that needs to be treated to obtain one additional responder (Number Needed to Treat = NNT) of about seven. These moderate effect sizes may be due to inadequate matching of specific patients to specific treatments. However, the literature lacks clear hypotheses about the characteristics of those who are most likely to respond to either or both compounds and those who are not (Verheul et al., 1999).

Obviously, progression has been limited because craving and effectiveness studies have typically not taken into account individual differences with respect to the mechanisms underlying craving (Niaura et al., 1988). Converging evidence suggests that craving may result from distinct psychobiological pathways, each of which can be identified through individual differences with respect to genetic, neurochemical, psychophysiological and clinical characteristics such as drinking...
motives. Heterogeneity with respect to drinking motives and craving pathways may have important treatment implications.

In 1999, Verheul et al., proposed a comprehensive three-pathway model of craving in alcoholics, which could be helpful in unraveling the mechanisms of anti-craving compounds and therefore holds promise for a better match between certain patients and specific pharmacotherapies (Verheul et al., 1999) (see Figure 1). The model predicts that naltrexone most likely reduces craving in reward cravers (possibly, through blocking of opioid receptors), that acamprosate might decrease craving in relief cravers (most likely, through a reduction of neuronal hyperexcitability that accompanies withdrawal symptoms and/or anxiety states), and that selective serotonin re-uptake inhibitors (SSRIs) might reduce craving in so-called obsessive cravers. The model also predicts that those alcoholics who score high on reward seeking and/or hedonism and who are predominantly characterized by enhancement motives for drinking, inability to abstain, binge drinking, familial and early-onset alcoholism, will respond better to opioid antagonist naltrexone than those who score high on stress reactivity or anxiety reactivity and who are predominantly characterized by coping or relief motives for drinking, withdrawal symptoms, non-familial alcoholism, and late-onset alcoholism. The latter group is assumed to respond better to glutamate antagonist acamprosate. Those who score high on disinhibition and who are predominantly characterized by obsessive thinking about alcohol, compulsive drinking, loss of control and alcohol-related impairments might respond best to SSRIs. Up to now, the proposed types of drinkers only exist in a theoretical unvalidated model and the matching hypotheses are not yet validated.

Since not all patients seem to benefit from the different anti-craving compounds, the use of matching procedures might enhance the effectiveness of these treatments (e.g., Kiefer et al., 2005). In principal, potential matching variables can be conceptualized and measured at three levels: (1) phenotypic or clinical indicators, (2) endophenotypic indicators, and (3) genetic indicators (Gottesman and Gould, 2003). Phenotypic indicators are directly observable characteristics of an organism, which are the joint product of both genotypic and environmental influences. Endophenotypic indicators are measurable components along the pathway between disease and genotype, e.g., neurophysiological, biochemical, endocrinological, neuroanatomical, or neuropsychological parameters. Genetic indicators can be measured at the genome level with techniques of molecular biology such as polymerase chain reaction (PCR) and DNA sequencing.

The proposed matching indicators of the three-pathway model (Verheul et al., 1999) can be categorized according to these three levels of assessment. It must be noted that, for the current study, only relief and reward matching indicators for acamprosate and naltrexone can be studied, since the gamma-aminobutyric acid
(GABA) agonist topiramate and the serotonergic anti-craving compounds are still rather experimental in nature.

The most important phenotypic indicators of Verheul et al.'s model are motives for drinking, directly indicating and preceding the type of craving. In addition, Verheul et al.'s model includes associated symptoms with the different craving pathways (e.g., familial alcoholism, age of onset, and withdrawal severity) (see Figure 1). One of the endophenotypic indicators of the model is based on physiological (hyper)arousability, which can be operationalized as physiological cue reactivity. As genetic indicators of the model, genotypes relevant for dysregulated or (de)sensitized receptors of the GABA, glutamate, dopamine, and opioid system can be studied. For example, in line with Verheul’s matching hypotheses, a recent study by Oslin et al. showed that a specific polymorphism of the µ-opioid receptor gene (OPRM1) was associated with a significant decrease in relapse following naltrexone treatment (Oslin et al., 2003). Until now, this is the only study that directly investigated the predictive value of genotypes on relapse after treatment with anti-craving medication. However, studies on the association between GABA, glutamate, dopamine, and opioid receptor genes and presence of alcohol dependence provide a promising basis for exploring the matching properties of genotypes (e.g., Connor et al., 2002; Wernicke et al., 2003; Bart et al., 2005; Sander et al., 1999; Loh and Ball, 2000).

**Aims and outline of this thesis**

The purpose of the current study is to validate the treatment matching properties of phenotypic, endophenotypic, and genetic indicators of relief and reward drinking as proposed by Verheul et al. (1999) in order to improve patient-treatment matching with acamprosate and naltrexone. The study has considerable relevance with respect to a better understanding of the mechanism of craving, the reduction of craving through pharmacotherapy, and the potential of matching patients to treatments through the recognition of individual differences.

The primary research question is:

Does naltrexone exert its anti-craving effect primarily in reward drinkers, whereas acamprosate exerts its anti-craving effect primarily in relief drinkers? This research question can also be phrased in the following—clinically more relevant—way: can we identify potential matching indicators of reward and relief drinking for naltrexone’s and acamprosate’s efficacy in the reduction of cue-induced craving and physiological cue reactivity?

The secondary research questions are:

1. Can reward and relief drinkers be distinguished based on their drinking motives?
(2) What is the relationship between cue-induced craving and physiological cue reactivity?

(3) Are naltrexone and acamprosate differentially effective with respect to the reduction of cue-induced craving and physiological cue reactivity?

Chapter 2 provides a comprehensive review with regard to the literature on predicting or matching variables of alcoholics for the reduction of craving and/or relapse with acamprosate, naltrexone, and serotonergic medications. The review constitutes an important theoretical background and contains empirical suggestions for the selection of matching variables for the current study.

Chapter 3 describes the development and validation of a questionnaire on drinking motives that is hypothesized to distinguish relief and reward drinkers at the phenotypic level.

Chapter 4 describes the development and validation of a new self-report questionnaire for the assessment of the core aspects of craving, taking into account different time frames and emphasizing the psychophysiological aspects of craving. It is hypothesized that certain subscales of this questionnaire will show higher concordance with measures of cue reactivity than existing self-report craving questionnaires.

Chapter 5 reports on the study of the differential effect of acamprosate and naltrexone on cue-induced craving and physiological cue reactivity in alcoholic patients. It is hypothesized that naltrexone will exert its effect primarily on self-reported cue-induced craving and endocrinological cue reactivity (cortisol), whereas acamprosate will exert its effect primarily on physiological parameters associated with withdrawal and anxiety (heart rate, skin conductance).

Chapter 6 aims to test the matching hypotheses proposed by Verheul et al. (1999) using phenotypic, endophenotypic, and genetic indicators of reward and relief drinking. It is hypothesized that naltrexone primarily exerts its effect through a reduction in self-reported cue-induced craving in reward drinkers, whereas acamprosate exerts its effect primarily through a reduction in physiological cue reactivity in relief drinkers.

In the general discussion (chapter 7), a summary is presented of the major findings presented in this thesis. Limitations and recommendations for future research are pointed out. The relevance of the results for clinical practice is discussed and remaining research questions are discussed in relation to recent topics of interest in alcoholism research.
Figure 1. Three-pathway psychobiological model of alcohol craving.
Abbreviations: DA, dopamine; GABA, gamma-aminobutyric acid; GLU, glutamate; 5HT, serotonin.

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CHAPTER 1


CHAPTER 2

Patient-treatment matching with anti-craving medications in alcohol-dependent patients: A review on phenotypic, endophenotypic and genetic indicators

Abstract

OBJECTIVES: Craving plays an important role in the development and maintenance of alcohol dependence and in relapse after periods of abstinence. Anti-craving compounds, such as acamprosate, naltrexone or serotonergic compounds, are found to be only moderately effective. These moderate effects might be due to inadequate matching of specific patients to specific treatments. In 1999, Verheul et al. proposed a three-pathway model of craving in alcoholics, which hypothesized that reward drinkers would better respond to naltrexone, relief drinkers to acamprosate and obsessive drinkers to serotonergic compounds. However, these matching hypotheses are not yet validated. This article reviews the literature on predictors and matching variables of the effectiveness of pharmacological interventions in alcohol-dependent patients directed at the reduction of craving and the prevention of relapse.

METHODS: Studies were selected through a literature search in September 2004, focusing on matching or predicting variables for anti-craving compounds in the treatment of alcoholics. Matching or predicting variables were categorized as either phenotypic (e.g., level of baseline anxiety), endophenotypic (e.g., physiological cue reactivity) or genetic (e.g., μ-opioid receptor polymorphisms).

RESULTS: Studies using clinical or phenotypic effect modifiers have produced inconsistent and rather disappointing results. In contrast, the predictive value of genetic effect modifiers is quite promising (e.g., μ-opioid receptor polymorphisms). No studies that looked at endophenotypic predicting or matching variables were identified.

CONCLUSION: It is concluded that phenotypic matching variables might be too distal, i.e., far removed from the pathogenic process, and that matching research should shift its attention toward more proximal variables (e.g., genetic and endophenotypic variables).
Patient-treatment matching with anti-craving medications

Introduction

The concept of craving is widely held to be essential for understanding the pathogenesis and maintenance of addiction (Wise, 1988; Robinson and Berridge, 1993; Tiffany, 1997), and the mechanisms underlying relapse or reinstatement of drinking (Ludwig et al., 1974; Niaura et al., 1988; Cooney et al., 1997). In general, craving mainly refers to the strong desire or urge to experience the effect of a previously experienced psychoactive substance (UNDCP/WHO 1992). Despite the simplicity of this definition, a wide variety of craving concepts is used in the research and clinical field. Until now it is not known whether craving is primarily an emotional response (e.g., subjective desire or urge), a physiological response (e.g., heart rate response) or a cognitive response (e.g., attentional bias) to an internal (e.g., mood) or external cue (e.g., alcohol odor). Another possibility is that these are independent (sub)types of craving or interrelated elements of craving.

Clinical studies provide substantial evidence supporting the efficacy of so-called anti-craving agents, such as acamprosate (e.g., Sass et al., 1996; Whitworth et al., 1996; Geerlings et al., 1997; Carmen et al., 2004) and naltrexone (e.g., Volpicelli et al., 1992; O’Malley et al., 1996; Carmen et al., 2004) in reducing craving and relapse rates. A recent meta-analysis including 17 randomized controlled trials and a total of 4,087 patients showed that the effectiveness of acamprosate is consistent over trials and populations, but that the effect size is only modest (overall pooled difference in success rates between acamprosate and placebo 13.3% (95% CI, 7.8-18.7%) and Number Needed to Treat is 7.5) (Mann et al., 2004). Similar results were obtained in a meta-analysis including 19 controlled studies on the effectiveness of naltrexone (Srisurapanont and Jarusuraisin, 2005).

Acamprosate and naltrexone are explicitly known for their anti-craving potential. Anti-craving medications with a more experimental character include, among others, serotonergic compounds. No final conclusions can be drawn about the efficacy of the various serotonergic compounds that have been used in the treatment of alcohol-dependent patients, i.e., serotonin reuptake inhibitors (SSRIs: e.g., fluoxetine, sertraline) or serotonin receptor agonists (e.g., buspirone, ondansetron) (e.g., Mann, 2004). These reviews and meta-analyses indicate that anti-craving drugs are effective in the treatment of alcohol dependence, but that only certain patients seem to benefit from these medications. Moreover, different medications might be effective for different subpopulations of alcohol-dependent patients, and subsequently treatment outcome might be improved if patients could be matched to specific treatments. However, it is unknown which patients are most likely to respond to different anti-craving compounds and those who are not, because the mechanisms underlying their efficacy are still
poorly understood (Spanagel and Ziegglänsberger, 1997). A possible important predictor or matching variable in the treatment of alcoholism with anti-craving compounds is type of craving or craving typology. Although the concept of craving is not completely clear, converging evidence suggests that different types of craving may result from different pathways, each of which is related to dysfunctions in distinct neural circuitries or neurotransmitter systems and individual differences in personality structure (Littleton et al. 1996; Spanagel and Ziegglänsberger, 1997; Merkle, 1999).

Based on a literature review, Verheul et al. (1999) have proposed a novel three-pathway model of craving in alcoholics, suggesting that craving is likely to result from distinct psychobiological mechanisms and that the efficacy of different anti-craving compounds is associated with individual differences in craving. In addition, Verheul et al. (1999) suggested that different types of craving are strongly associated with clinical characteristics such as family history, age of onset, drinking patterns (e.g., binge drinking) and the severity of withdrawal symptoms. According to this psychobiological model of craving, three pathways of craving can be distinguished:

1. The first pathway (the reward pathway) suggests that craving or desire for the rewarding, stimulating and/or enhancing effects of alcohol might result from either dopaminergic/opioidergic dysregulation or a personality style characterized by reward seeking and/or hedonism, or a combination of both. Furthermore, Verheul et al. assumed that reward cravers are characterized by associated symptoms such as inability to abstain, binge drinking, familial alcoholism and early-onset alcoholism.

2. The second pathway (the relief pathway) suggests that craving or desire for the reduction of tension, arousal or withdrawal might result from either GABAergic/glutamatergic dysregulation or a personality style characterized by stress reactivity, anxiety sensitivity, and/or hyperarousability, or a combination of both. In addition, Verheul et al. assumed that relief cravers are characterized by associated symptoms such as withdrawal symptoms, non-familial alcoholism and late-onset alcoholism.

3. The third pathway (the obsessive pathway) can be defined as lack of control over intrusive thoughts about drinking resulting in impaired functioning. This pathway of craving might result from a serotonin deficiency or a personality style characterized by low constraint or disinhibition, or a combination of both. Verheul et al. assumed that obsessive cravers are characterized by compulsive drinking, loss of control and alcohol-related impairment.

The three-pathway model proposed by Verheul c.s. could be helpful in unraveling the mechanisms of anti-craving compounds and therefore holds promise for
a better match between patients and specific pharmacotherapies (Verheul et al. 1999). The model predicts that naltrexone most likely reduces craving in reward cravers (possibly, through blocking of opioid receptors), that acamprosate might decrease craving in relief cravers (most likely, through a reduction of neuronal hyperexcitability that accompanies withdrawal symptoms and/or anxious states) and that selective serotonin re-uptake inhibitors (SSRIs) might reduce craving in obsessive cravers. The model also predicts that those alcoholics who score high on reward seeking and/or hedonism and who are predominantly characterized by enhancement motives for drinking, inability to abstain, binge drinking, familial alcoholism and early-onset alcoholism, will respond better to naltrexone than those who score high on stress reactivity and/or anxiety reactivity and who are predominantly characterized by coping motives for drinking, withdrawal symptoms, non-familial alcoholism, and late-onset alcoholism. The latter group is assumed to respond better to acamprosate. Those who score high on disinhibition and who are predominantly characterized by obsessive thinking about alcohol, compulsive drinking, loss of control and alcohol-related impairment might respond best to SSRIs.

Recently, Heinz et al. (2003) conducted a study, which partially contributes to the validation of the three-pathway model. They tested the three-pathway model in 38 detoxified alcoholics. Heinz et al. found that appetitive reactions to alcohol-associated cues correlate positively with drinking in positive situations and contribute significantly to the craving factor 'interference' of the Obsessive Compulsive Drinking Scale (Anton et al., 1996). The severity of withdrawal-like symptoms preceding alcohol intake contributes to the craving factor 'obsession'. However, contrary to the hypothesis, this measure of conditioned withdrawal correlated with drinking not only in negative but also in positive situations. These findings support the notion of different craving factors with separate underlying mechanisms. However, the three-pathway model was only partially validated by this study.

It should be noted that the three-pathway model by Verheul et al. (1999) and related matching hypotheses might not cover all possible mechanisms of action of anti-craving medications. For example, a recent study showed that naltrexone not only induces an opioid-receptor blockade, but that it (indirectly) also increases hypothalamic-pituitary-adrenocortical (HPA) activity resulting in higher adrenocorticotropic hormone (ACTH) and cortisol levels which in turn may be partially responsible for the effect of naltrexone on drinking and craving (O’Malley et al., 2002). Although the results of this study must be considered preliminary given the small sample, the findings shed new light on the complex neurobiological mechanisms underlying the effectiveness of opioid antagonists in the management of alcoholism.
CHAPTER 2

Since not all patients seem to benefit from the different anti-craving compounds, the use of matching procedures might be important in improving the effectiveness of treatment with anti-craving compounds. In principal, potential matching variables can be conceptualized and measured at three levels. Indicators can be divided into (1) phenotypic or clinical indicators, i.e., patient characteristics that are the joint product of both genotypic and environmental influences (e.g., addiction severity, baseline level of anxiety, drinking history, drinking patterns, drinking motives, alcohol outcome expectancies, and personality styles), (2) genotypic indicators (e.g., μ-opioid receptor polymorphisms) and (3) so called endophenotypic indicators, i.e., measurable patient characteristics between phenotype and genotype (e.g., neurophysiological cue reactivity, neurochemical markers) (Gottesman and Gould, 2003). At the time that the three-pathway model was introduced, the proposed matching hypotheses were not yet tested directly. In an attempt to test these matching hypotheses, this literature review was conducted to unfold and update the predicting and matching variables for anti-craving compounds. The study aims to describe the phenotypic, endophenotypic and genetic variables of adult alcoholics that have been shown to predict or match with the short-term and long-term effects of naltrexone, acamprosate and serotonergic medications on craving and/or drinking behavior (e.g., relapse).

Method

Randomized (placebo) controlled trials (RCTs), controlled clinical trials (CCTs), and reviews or meta-analyses of RCTs and CCTs were included. All studies had to include participants with alcohol abuse or dependence (DSM-III-R or DSM-IV) between 18 and 75 years of age. Both in- and outpatient settings, as well as non-treatment-seeking alcoholics, were included. The studies had to report data on at least one of three types of possible anti-craving medications: (1) opioid receptor antagonists (naltrexone, nalmefene); (2) glutamate antagonists (acamprosate) or (3) serotonergic compounds: SSRIs (sertraline, fluoxetine, citalopram, fluvoxamine) and serotonin receptor agonists and antagonists (ritanserin, ondansetron, buspirone, nefazodone). It should be noted that disulfiram was not included in this review since the objective of disulfiram is to create an aversion to alcohol, rather than to reduce craving for alcohol or to modulate alcohol’s neurochemical effects. Dopaminergic drugs, tricyclic antidepressants (TCAs), mood stabilizers (e.g., lithium) and anxiolytics were not reviewed, since these compounds have not shown to be effective in the reduction of alcohol craving or relapse until now (Mann, 2004). The studies had to report data on at least one of the following outcome measures: (1) craving (in the field or cue-induced in the
Patient-treatment matching with anti-craving medications

labouratory); (2) relapse, with relapse defined as drinking four alcoholic drinks for women, five for men on a single day; (3) (continuous) abstinence, confirmed by urine samples, blood samples or self-reports; (4) frequency of substance abuse (percentage of drinking days); or (5) time to first relapse or time to first drink.

Relevant studies meeting the inclusion criteria were identified by:

1. A computer-aided search using the following databases: Pubmed, EMBASE, PsychINFO, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects. All databases were searched for all publication years. The search was conducted in September 2004, using the search strategy recommended in the Cochrane Handbook. This strategy was followed in conjunction with combinations of the following MESH terms: (drug) therapy, naltrexone, acamprosate, anti-depressants, anti-anxiety agents, fluoxetine, sertraline, citalopram, fluvoxamine, ondansetron, buspirone, ritanserin, alcoholism, substance dependence, alcohol abuse, alcohol(-)related disorder(s), addictive behavior, drinking behavior, treatment outcome, signs and symptoms. In addition, free text words were used: alcohol dependence, alcohol addiction, drug treatment, medication, nefazodone, nalmeffene, craving, urge, relapse, match*, predict*, alcohol*, cue(s), pharmacotherapy, subtype(s), topology(s), genotype(s), genetics, polymorphism(s), endophenotype(s), risk factor(s). Only studies that were published in the English language were included.

2. Reference checking of identified trials, reviews and meta-analyses.

Results

Below, the results of the literature review are presented. It must be noted that most of the studies that were identified show results on prediction of effectiveness for one anti-craving compound rather than on matching of patients to different anti-craving compounds. Although predictors do not prove the existence of matching (patient by treatment interaction), predictors might be a first step in the identification of possible matching variables.

Predicting and matching variables for acamprosate

In 1996, Lesch and colleagues conducted a long term prospective study based on four subtypes of alcohol-dependent patients to assess the efficacy of acamprosate (Lesch and Walter, 1996). Consistent with their hypothesis (and with the matching hypothesis based on the three-pathway model of Verheul et al. in 1999) acamprosate differentially reduced alcohol intake in patients who drink alcohol.
to counteract withdrawal symptoms (Type I) and in patients who use alcohol as a conflict-solving and anxiety-reducing agent (Type II), but not in patients who ingest alcohol to self-medicate affective disorders (Type III) or patients with a history of cerebral impairment that precedes the development of alcohol dependence (Type IV). Similarly, Whitworth et al. (1996) found that Type I and II according to the typology of Lesch responded better to acamprosate. In contrast, Chick et al. were not able to show a predictive effect of the Lesch typology in their negative acamprosate study (Chick et al., 2000).

Also consistent with the matching hypotheses proposed by Verheul et al. (1999), a randomized trial by Gerra et al. suggested that acamprosate was differentially effective among non-familial alcoholics and that the potential of acamprosate to counteract alcohol intake does not apply to familial alcoholic patients, while familial alcoholics responded only to treatment with the SSRI fluoxetine (Gerra et al., 1992).

A recent study including the pooled data of 1,485 alcohol-dependent patients from 7 randomized controlled trials comparing acamprosate and placebo, directly tested the hypothesis of Verheul et al. (1999) that acamprosate would be most effective in patients with high physical dependence at baseline, negative family history of alcoholism, late age of onset, serious anxiety symptomatology at baseline, severe craving at baseline, and female gender (Verheul et al., 2004). In contrast to the expectations, the authors found that none of these theoretically relevant clinical matching variables predicted treatment effectiveness of acamprosate. Similarly, another pooled analysis of 11 European trials by Sass et al. (1995) did not find any demographical, psychopathological or biological predictors for acamprosate efficacy.

Although both pooled analyses did not identify any predictors of effect, Pelc et al. (2002) in a multicenter acamprosate study found that multiple physical and psychiatric comorbidities, and a history of drug addiction, were negatively correlated with outcome, as were, to a lesser extent, multiple previous episodes of detoxification, unemployment, and living alone. Older age and stable employment were positively associated with outcome. Two recent reviews concluded that acamprosate might be useful in a therapeutic approach targeted at achieving abstinence rather than at controlling or reducing consumption (Carmen et al., 2004; Mann, 2004). Although there is no evidence yet, these findings are suggestive for ‘treatment goal’ or ‘readiness to change’ as possible predictors of acamprosate efficacy.

In summary, prediction and treatment matching data of acamprosate are restricted to the phenotypic level and no consistent support for the matching hypotheses posed by Verheul et al. (1999) was found (see Table 1).
An early study suggested that employment at the start of naltrexone therapy is significantly related to better outcome in alcoholic veterans (Greenstein et al., 1983). Consistent with the matching hypotheses of Verheul et al. (1999), a study among hazardous drinkers suggested that naltrexone may be particularly effective in reducing cue-elicited positive reinforcement of alcohol for those with high positive alcohol outcome expectancies. Positive outcome expectancies also moderated the effects of naltrexone on subjective reports of stimulation following drinking (Palfai et al., 1999). Some studies looked at predicting or matching variables for dually diagnosed patients. Salloum et al. (1998) for example, found a decrease in alcohol use and in urges to drink alcohol with naltrexone (50 mg/day) among depressed alcoholics who had failed to abstain from alcohol during treatment with an SSRI. A preliminary study by Oslin et al. suggested that naltrexone (150 mg/day) may be effective in reducing both cocaine and alcohol use in patients dependent on both alcohol and cocaine (Oslin et al., 1999). However, an earlier study by Hersh et al. found that naltrexone at a lower dose (50 mg/day) is not effective in this population (Hersh et al., 1998).

Another possible predictor of response to naltrexone is baseline level of craving. Some studies found that patients with high levels of alcohol craving are most likely to benefit from naltrexone treatment (Volpicelli et al., 1995; Jaffe et al., 1996; Monterosso et al., 2001). However, no distinction was made in those studies between reward, relief and obsessive craving. Volpicelli et al. (1995) also found that naltrexone was more effective in patients with higher levels of somatic symptoms and Jaffe et al. (1996) found that patients experiencing poorer cognitive functioning may have the greatest benefit from naltrexone. In a recent review by Rohsenow (2004), the author suggested that individuals that are most likely to benefit from naltrexone are those who have stronger urges to drink or who are more limited in cognitive abilities.

Rohsenow (2004) also suggested that naltrexone does not increase the chance of staying completely abstinent but rather reduces the intensity or frequency of any drinking that does occur. In 2001, Sinclair reviewed eight double-blind placebo-controlled clinical trials on naltrexone efficacy (Sinclair, 2001). He suggested that naltrexone is useful when naltrexone is paired with drinking rather than when given during absolute abstinence. Based on these findings, he proposed that naltrexone should be administered to patients who were actively drinking (e.g., as in controlled drinking programs). Similarly, other studies suggested that naltrexone can lead to reductions in relapse, alcohol consumption,
drinking days or craving among alcoholics who drank during treatment and did not have abstinence as a goal (Volpicelli et al., 1992; Oslin et al., 1997; Maxwell and Shinderman, 2000; McCaul et al., 2000; Heinala et al., 2001; Rubio et al., 2002; Drobès et al., 2003). Consistent with these clinical data, a recent clinical laboratory paradigm suggested that the effectiveness of naltrexone on alcohol consumption may be somewhat dependent on pattern of consumption (Anton et al., 2004a). When the subjects had delayed access to alcoholic drinks, naltrexone-treated subjects consumed fewer drinks and had a slower progression of drinking. Anton et al. (2004a) hypothesized that, since naltrexone seems to disrupt the connection between alcohol-induced stimulation and further alcohol consumption, there may be a time-critical period between drinks necessary for alcoholics to benefit from its effects. In line with these findings, Rohsenow et al. found that naltrexone was able to reduce urge to drink and self-reported attention to alcohol cues, not at the initial exposure, but after repeated exposures to alcohol cues (Rohsenow et al., 2000). These findings are suggestive for pre-treatment patient characteristics such as ‘treatment goal’ or ‘readiness to change’ as possible predictors of naltrexone efficacy. However, other investigators have suggested that naltrexone also exerts its effects during controlled abstinence and independent of alcohol consumption (Kranzler and Van Kirk, 2001; Streten and Whelan, 2001; Kiefer et al., 2003).

Another possible predictor of response to naltrexone is the patient’s family history of alcohol problems. In a double-blind, placebo-controlled naltrexone trial, predictors of naltrexone response were explored (Monterosso et al., 2001). In line with the matching hypothesis by Verheul et al. (1999), significant interactions were observed between treatment condition and family history of alcohol problems ($p<0.05$). Whereas this study showed that responders to naltrexone were related to familial alcoholism, another study showed that non-responders to naltrexone were not related to a family history of alcoholism (Davidson et al., 1999). In a recent review, Rohsenow (2004) concluded that individuals who are most likely to benefit from naltrexone are those with close relatives who also had alcohol problems. In line with these findings, King et al. found that social drinkers with a high loading of familial alcohol problems (FH+) showed marked reductions in the subjective effects of alcohol after pretreatment with naltrexone (King et al., 1997). Other studies have investigated individual differences with respect to sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis to naltrexone administration. An important individual difference factor in sensitivity of the HPA axis to naltrexone administration may be the presence of a positive family history of alcoholism (FH+) (King et al., 2002). King examined neuroendocrine and mood responses to oral naltrexone as a function of biological family history of alcoholism. The results demonstrated the potential biological bases of
altered opioidergic sensitivity in those persons with an assumed greater inherited vulnerability for future alcoholism. Other studies, examining sensitivity to intravenous naltrexone infusion, have also shown differential HPA response based on the presence of biological family history of alcoholism compared with no family history of alcoholism (FH-) (Wand et al., 1998, 1999, 2001). However, intermediate- and long-term studies are needed in order to determine whether these effects may be predictive of clinical response to oral naltrexone.

The role of family history as a predictor of treatment response has led some to speculate that naltrexone may function differently in genetically predisposed individuals. Naltrexone has high affinity for the $\mu$-opioid receptor, which is hypothesized to be the principal site of action of the medication. It has been hypothesized that sequence variation in the gene encoding the $\mu$-receptor (genetic locus OPRM1), may result in a receptor with altered expression, structure or function, and as a consequence increase or decrease an individual’s susceptibility to substance dependence and his response to naltrexone (Lichtermann et al., 2000). In a re-analysis of existing data, and consistent with the original hypothesis of Verheul et al. (1999), Oslin et al. (2003) demonstrated that the opioid system is involved in the reinforcing properties of alcohol and that allelic variation at OPRM1 is associated with a differential response to naltrexone. The authors concluded that if these findings are replicated, OPRM1 genotyping may prove to be an efficient mechanism for identifying patients who are most likely to respond to treatment with naltrexone.

In summary it seems that in addition to clinical variables also a genetic variable was tested and that some support for the matching hypotheses proposed by Verheul et al. (1999) was found (see Table 1). As hypothesized by Verheul et al. (1999), some supportive evidence was found for a predicting role of positive outcome expectancies, familial alcoholism, inability to abstain and $\mu$-opioid receptor polymorphisms.

**Nalmefene**

Nalmefene is another opioid receptor antagonist with similar pharmacological properties to naltrexone. Several studies showed that nalmefene is effective in preventing relapse to heavy drinking in alcoholics (Mason et al., 1994, 1999; Drobes et al. 2003, 2004). Comparable to the findings for naltrexone, Drobes et al. (2003, 2004) demonstrated that nalmefene is effective in alcoholics who do not attempt to reduce drinking. In contrast, a recent study in outpatient alcoholics showed no superior efficacy outcomes with nalmefene treatment compared to placebo (Anton et al., 2004b). In summary, the results on the efficacy of nalmefene are not consistent and no predictors are yet identified.
Table 1. Overview of predictors or matching variables for anti-craving compounds: positive findings.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Compound</th>
<th>Reference</th>
<th>Predictor</th>
<th>Category</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>Acamprosate</td>
<td>Lesch &amp; Walter 1996</td>
<td>Lesch Type I and II</td>
<td>Phenotype</td>
<td>Alcohol intake</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Acamprosate</td>
<td>Whitworth et al. 1996</td>
<td>Lesch Type I and II</td>
<td>Phenotype</td>
<td>Time to first relapse</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Acamprosate</td>
<td>Gerra et al. 1992</td>
<td>Non-familial alcoholism</td>
<td>Phenotype</td>
<td>Alcohol intake</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Pelc et al. 2002</td>
<td>Older age, stable employment</td>
<td>Phenotype</td>
<td>Proportion of cumulative abstinenve days</td>
<td></td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Greenstein et al. 1983</td>
<td>Employment</td>
<td>Phenotype</td>
<td>Treatment outcome at 1-month follow up</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Palfai et al. 1999</td>
<td>Positive outcome expectancies</td>
<td>Phenotype</td>
<td>Cue-induced reinforcement, subjective stimulation</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Salloum et al. 1998</td>
<td>Depressed SSRI nonresponders</td>
<td>Phenotype</td>
<td>Alcohol use, craving</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Oslin et al. 1999</td>
<td>Dually addicted</td>
<td>Phenotype</td>
<td>Alcohol use</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Volpicelli et al. 1995</td>
<td>High somatic symptoms</td>
<td>Phenotype</td>
<td>Number of drinking days</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Jaffe et al. 1996; Rohsenow 2004</td>
<td>Poor cognitive functioning</td>
<td>Phenotype</td>
<td>Drinking outcomes</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Volpicelli et al. 1995; Jaffe et al. 1996; Monterosso et al. 2001; Rohsenow 2004</td>
<td>Baseline craving</td>
<td>Phenotype</td>
<td>Drinking outcomes</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Volpicelli et al. 1992; Oslin et al. 1997; Maxwell &amp; Shinderman 2000; McCaul 2000; Sinclair 2001; Heinla et al. 2001; Rubio et al. 2002; Drobes et al. 2003</td>
<td>Active drinking</td>
<td>Phenotype</td>
<td>Relapse, alcohol consumption, drinking days, craving</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Anton et al. 2004</td>
<td>Pattern of consumption</td>
<td>Phenotype</td>
<td>Alcohol consumption</td>
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<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Monterosso et al. 2001; Rohsenow 2004</td>
<td>Family history</td>
<td>Phenotype</td>
<td>Amount of drinking</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Oslin et al. 2003</td>
<td>μ-Opioid polymorphism</td>
<td>Genotype</td>
<td>Relapse and abstinence rates</td>
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### Patient-treatment matching with anti-craving medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Compound</th>
<th>Reference</th>
<th>Predictor</th>
<th>Category</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalmefene</td>
<td>Drobes et al. 2003, 2004</td>
<td>Active drinking</td>
<td>Phenotype</td>
<td>Alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>5-HT compounds</td>
<td>Fluoxetine</td>
<td>Gerra et al. 1992</td>
<td>Familial alcoholism</td>
<td>Phenotype</td>
<td>Alcohol intake</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Pettinati et al. 2000, 2004</td>
<td>Low risk/severity men (Type A)</td>
<td>Phenotype</td>
<td>Drinking</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Brady et al. 2003</td>
<td>Low dependence severity, polydrug abuse, early-onset PTSD</td>
<td>Phenotype</td>
<td>Drinking</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Moak et al. 2003</td>
<td>Depressed alcoholics</td>
<td>Phenotype</td>
<td>Drinking</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Naranjo et al. 2000</td>
<td>Male alcoholics</td>
<td>Phenotype</td>
<td>Alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Johnson et al. 2000; 2002, 2003; Kranzler et al. 2003</td>
<td>Early-onset alcoholics (EOAs)</td>
<td>Phenotype</td>
<td>Drinking and craving</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Sellers et al. 1994</td>
<td>Lower baseline drinking, high education</td>
<td>Phenotype</td>
<td>Drinking</td>
<td></td>
</tr>
<tr>
<td>Ondansetron + Naltrexone</td>
<td>Johnson et al. 2000; Ait-Daoud et al. 2001; Johnson et al. 2002</td>
<td>Early-onset alcoholics (EOAs)</td>
<td>Phenotype</td>
<td>Drinking, craving</td>
<td></td>
</tr>
<tr>
<td>Buspirone</td>
<td>Tollefson et al. 1991, 1992; Kranzler 1994, 1996</td>
<td>Anxious alcoholics</td>
<td>Phenotype</td>
<td>Alcohol consumption, heavy drinking</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Brown et al. 2003; Hernandez-Avila et al. 2004</td>
<td>Depressed alcoholics</td>
<td>Phenotype</td>
<td>Alcohol consumption</td>
<td></td>
</tr>
</tbody>
</table>

### Predicting and matching variables of serotonergic medications

**SSRIs**

One of the SSRIs used in alcoholism treatment is fluoxetine. Although the efficacy of SSRIs is debated (Mann, 2004), it cannot be excluded that certain subtypes of patients do benefit. Cornelius et al. conducted several clinical trials, all suggesting persistent efficacy for fluoxetine in the treatment of both depressive symptoms and drinking in depressed alcoholics (Cornelius et al., 1993; Cornelius et al., 1995; Cornelius et al., 1997; Cornelius et al., 2000). However, other studies
have shown no effect of fluoxetine on alcohol use after controlling for the effect on depression. They found that the absence of a comorbid mood or anxiety disorder was a predictor of poor outcome, both in mild to moderate severe alcoholics (Kranzler et al. 1995) as well as in high risk/severity (Type B) alcoholics (Kranzler et al., 1996; Kabel and Petty, 1996). Kranzler (1996) concluded that alcoholic subtypes identified by cluster analysis seem to be differentially responsive to the effects of fluoxetine treatment on drinking-related outcomes. Serotonergic abnormalities previously identified among a subgroup of alcoholics who are also characterized by impulsivity and severity of alcohol dependence may help to explain the differential medication effect. One study found conflicting results. Janiri et al. (1996) found that additional psychiatric diagnoses, medical problems, and familial alcoholism were negatively correlated with abstinence in fluoxetine-treated detoxified alcoholics. Although no clear evidence on the predictive value of comorbid anxiety/depression is available yet, the reviewed studies are suggestive for a predictive role of these comorbid symptoms.

The findings of one trial by Cornelius et al. (1998) suggested that comorbid cocaine abuse acts as a robust predictor of poor outcome for the drinking and the depressive symptoms of depressed alcoholics. In a study by Gerra et al. (1992), it was found that the familial alcoholics showed a significant decrease in ethanol intake after fluoxetine therapy.

The most recent studies of SSRIs in alcohol dependence concern sertraline. A few studies looked at subtypes of alcoholics. Pettinati et al. showed that lower risk/severity (Type A) alcoholic men, but not Type A alcoholic women, had consistently better drinking outcomes with sertraline compared to placebo. There were no differences in drinking with sertraline compared to placebo in Type B alcoholic men or women (Pettinati et al. 2000; Pettinati et al. 2004). Other studies looked at alcoholics with comorbidity. One study found that sertraline-treated subjects with less severe alcohol dependence, more polydrug abuse and early-onset Post Traumatic Stress Disorder (PTSD) had significantly greater decreases in drinking (Brady et al., 2003). One study suggested that sertraline may provide some modest benefit in terms of drinking outcome and improved depression in depressed alcoholics (Moak et al., 2003). However, two other studies showed that sertraline also results in an advantage in reduced drinking in alcoholics without (lifetime) depression (Pettinati et al., 2001; Coskunol et al., 2002).

Another SSRI that has been used in the treatment of alcohol dependence is citalopram. One study found that male alcoholics may benefit more than female alcoholics from citalopram (Naranjo et al., 2000). Earlier, the same author used a qualitative computational approach to predict response to citalopram (Naranjo et al., 1997) and found that response could be predicted by age, anxiety, depression, alcohol dependence and baseline alcohol intake. Although conducted in
heavy drinkers and not in alcoholics, a possibly relevant endophenotypic finding has been reported by Berggren et al. (2001). They found that alcohol-dependent patients who had low or no prolactin response to fenfluramine (a measure of central serotonergic function), tended to have a worse drinking outcome after citalopram treatment than patients with a more normal prolactin response. Also in a study with heavy drinkers, a possible genetic predictor was found by Eriksson et al. (2001). They found that when subjects were grouped according to the presence or absence of the DRD2 A1 allele, those with the genotype DRD2 A2/A2 were found to transiently reduce their alcohol consumption during citalopram treatment.

The last SSRI that will be presented here is fluvoxamine. A recent study by Chick et al. (2004) found a trend for the fluvoxamine group to do worse than the placebo group on abstinence and relapse. However, when typology of alcoholism was assigned by scores on the Tridimensional Personality Questionnaire (Cloninger, 1987), Type II patients in the fluvoxamine group relapsed more frequently than Type I patients. When typology was assigned on the basis of age of onset of alcohol problems, early-onset patients in the fluvoxamine group relapsed more frequently than late-onset patients in that group. As a possible explanation for this they hypothesized that impulsivity in early-onset or Type II patients may be accentuated by serotonin enhancement. In contrast, one study showed that fluvoxamine-treated subjects have statistically higher rates of continuous abstinence compared to non-treated subjects (Angelone et al., 1998). However, Chick et al. noted that the fluvoxamine group had a relatively high proportion of women and tended to be 'late-onset patients' in this study. These findings are in line with two studies on fluoxetine and sertraline that were mentioned earlier (Kranzler et al., 1996; Pettinati et al., 2000). Chick et al. therefore concluded that, unless there is an over-riding clinical reason such as specific psychiatric comorbidity, caution should be exercised in the use of SSRIs in early-onset or Type II patients (Chick et al., 2004). This new hypothesis is inconsistent with the matching hypothesis based on the three-pathway model by Verheul (1999), since that hypothesis predicts that SSRIs are effective in obsessive/impulsive patients with serotonergic disturbances.

**Serotonin receptor agonists and antagonists**

Some studies have found that the 5-HT3 receptor antagonist ondansetron leads to a significantly greater reduction of various drinking related outcome measures and craving in Early Onset Alcoholics (EOAs) than in Late Onset Alcoholics (LOAs) (Johnson et al., 2000a; Johnson et al., 2002a; Johnson et al., 2003; Kranzler et al., 2003). Another study found that lower baseline drinking and higher level of education were significant and strong predictors of drinking reduction dur-
CHAPTER 2

ing treatment with ondansetron (Sellers et al., 1994). Sloan et al. demonstrated that a decrease in anxiety during ondansetron treatment was associated with fewer drinks per day (Sloan et al., 2003). Finally, some studies showed that combining ondansetron and naltrexone acts synergistically at improving various drinking outcomes or craving scores in Early Onset Alcoholics (Johnson et al., 2000b; Ait-Daoud et al., 2001a, 2001b; Johnson et al., 2002b).

The 5-HT1A receptor agonist buspirone is an anxiolytic which has been shown to diminish the desire to consume alcohol, heavy drinking and anxiety symptoms in anxious alcoholic patients (Tollefson 1991, 1992; Kranzler et al., 1994; Kranzler, 1996). In a review of five controlled studies on the effects of buspirone, Malec et al. (1996) concluded that the main effect of buspirone in the treatment of alcoholism is not on ethanol consumption per se, but on associated psychopathological symptoms. Although no evidence on the predictive or matching value of comorbid anxiety is available yet, the reviewed studies are suggestive for a matching effect between comorbid anxiety and buspirone treatment of alcoholism.

Few studies looked at predicting variables for the antidepressant nefazodone, a norepinephrine and 5-HT reuptake blocker and 5-HT2 receptor antagonist. In two recent studies, nefazodone significantly reduced some measures of alcohol consumption in depressed alcoholics (Brown et al., 2003; Hernandez-Avila et al., 2004). However, in another study nefazodone treatment was superior to placebo in alleviating depression in depressed alcoholics but did not add in terms of drinking outcomes (Roy-Byrne et al., 2000). No evidence of clinical efficacy in alcohol dependence has been obtained with ritanserin (Mann, 2004).

In summary, it seems that prediction and treatment matching data of serotonergic medications are restricted to the phenotypic level and that no support for the matching hypotheses as proposed by Verheul et al. (1999) was found (see Table 1).

Discussion

Most of the studies in this review only explored phenotypic variables in outpatient settings, used relapse or subjective craving as an outcome measure rather than cognitive or physiological cue reactivity, and did not use different competitive medications at the same time. In addition, some studies were limited by too small patient numbers in order to perform valid subgroup-analyses with adequate statistical power. Although many studies investigated potential genotypes or endophenotypes in the development of alcoholism, genetic or endophenotypic studies that focused on prediction or matching with anti-craving compounds in alcoholics are scarce.
Only modest indications of treatment matching variables were found. Most studies did not find phenotypic predictors of acamprosate effectiveness. In contrast, some studies have found a limited number of phenotypic predictors for the effect of naltrexone and serotonergic medications in alcohol-dependent patients. Phenotypic predictors for naltrexone might be the level of baseline craving and/or familial alcoholism. Although further research is needed, a suggestive differential predictor for naltrexone efficacy is the patient’s goal of treatment (reduced/controlled drinking). The phenotypic predictors for serotonergic agents (e.g., fluoxetine, buspirone) might be comorbidity of a mood or anxiety disorder, although treatment of the underlying psychiatric problems may thus have an important beneficial secondary effect in reducing alcohol consumption (Swift, 1999; Mann, 2004). A possible predictor of poor outcome after SSRI treatment is early-onset or Cloninger Type II alcoholism. Interestingly, Johnson (2000) proposed a model that attempts to explain this by focusing on the influence of a common genetic variant in the serotonin transporter regulatory region (5-HTTLPR) on serotonin (5-HT) and dopamine (DA) function, which has recently been extended into a computer simulation by Stoltenberg (2003). Further studies should be conducted to test this hypothesis. Genetic indicators for treatment effectiveness were rarely studied or discovered: only one study found a genetic indicator for naltrexone effectiveness. If the findings of Oslin et al. (2003) are replicated, OPRM1 genotyping may prove to be an efficient mechanism for identifying patients who are most likely to respond to naltrexone and those for whom other available treatments, such as acamprosate, may be more efficacious. Such a pharmacogenomic approach to treatment could reduce the likelihood of exposing patients unnecessarily to a medication that will be ineffective for them.

In this review, no study was found that investigated endophenotypic indicators as matching variables for alcoholics. In contrast, many studies investigated the role of endophenotypes in the development of alcohol dependence, in relapse or in craving. Iacono et al. (2000), for example, suggest a multivariate endophenotype to identify individuals at high risk for substance dependence using psychophysiological measures (P300 event-related potential amplitude, electrodermal response modulation, anti-saccade eye-tracking task). Others investigated the role of leptin and atrial natriuretic peptide (ANP) in withdrawal-induced craving (Kiefer et al., 2001, 2002) or the role of electrophysiological endophenotypes (electroencephalography (EEG)) in alcoholism (e.g., Hesselbrock et al., 2001, Winterer et al., 2003). Recent neuroimaging studies found decreased dopamine receptors (Volkow et al., 1996) or serotonin transporters (Heinz et al., 1998) in the alcoholic brain or found strong functional relationship between craving and activation of the ventral striatum (Braus et al., 2001) or between craving and µ-opioid receptor binding (Bencherif et al., 2004) in the alcoholic brain.
In summary, the results of pharmacological prediction or matching studies using clinical effect modifiers (e.g., anxiety, subjective craving) have been inconsistent and rather disappointing. Matching studies for psychosocial interventions (e.g., Project MATCH, 1993) show similar inconsistent and disappointing findings. In contrast, the first results with genetic modifiers are quite promising.

A possible explanation might be that phenotypes are the result of a very heterogeneous interaction between genes and environment and as such they are not closely enough related to the biological process of addiction and relapse to be able to predict positive treatment responses for different pharmacological interventions. At the same time, these hybrid phenotypes are not uniquely related to the psychosocial processes underlying addiction and relapse, and therefore clinical modifiers are also not very likely to predict positive treatment responses for psychosocial interventions in alcohol-dependent patients. As far as gene polymorphisms predict differential drug responses, genotyping might be a more powerful tool in assessment and patient-treatment matching.

A rather unexplored area in the field of prediction or matching are the neurobiological correlates of the disorder, the so-called endophenotypes. Endophenotypes are measurable aspects unseen by the unaided eye along the pathway between the genotype and the phenotype. An endophenotype may be neurophysiological (e.g., physiological cue reactivity), biochemical (e.g., alcohol-metabolizing enzymes or neurotransmitter-metabolizing agents), endocrinological (e.g., cortisol responsivity), neuroanatomical (e.g., brain morphology), cognitive (e.g., attentional bias), or neuropsychological (e.g., memory function, planning) in nature (Gottesman and Gould, 2003). Like genetic indicators, endophenotypic indicators might be more related to the biological process of addiction and craving or relapse mechanisms. Due to the expected phenotypic heterogeneity, endophenotyping might be a necessary intermediate step to find better links with genetic subtypes. However, to be most useful, endophenotypes for psychiatric disorders must meet certain criteria, including association with a candidate gene or gene region, heritability that is inferred from relative risk for the disorder in relatives, and disease association parameters. Other terms with patently synonymous meaning, such as 'biomarker', may not reflect genetic underpinnings but may rather reflect associated findings (Gottesman and Gould, 2003). Since an endophenotype lies somewhere along the line between genotype and phenotype, some patient characteristics are difficult to categorize (see Figure 1). Variables that are generally regarded as phenotypic (e.g., familial alcoholism, age of onset) or genetic (chromosome variability) might be endophenotypic in nature.
In this review predicting and matching variables of patients were studied. However, there are also important effect modifiers that are not related to patient characteristics such as dosage, length of treatment, and treatment compliance, which might play an important role in predicting effectiveness of medication. Volpicelli et al. (1997) for example showed that only good compliers with naltrexone had better outcomes. In order to study possible predicting or matching variables, it is therefore important to enhance treatment compliance and take other possible effect modifiers into account.

**Conclusion**

Only limited support was found for the matching hypotheses based on the three-pathway model by Verheul et al. (1999). One explanation could be that most of the studies are prediction studies that are conducted in small samples of outpatients, with relapse or subjective craving as the only outcome measures. We therefore recommend that future (matching) studies shift their attention to larger, more heterogeneous samples (inpatients, outpatients and/or non-treatment-seeking alcoholics), in which subgroup-analyses for two or more competitive medications are conducted, with cognitive and/or physiological cue reactivity (e.g., attentional bias, heart rate responses) as additive outcome measures. Another possibility could be that the matching hypotheses by Verheul et al. (1999) do not cover all possible mechanisms of action of the anti-craving compounds reviewed in this article.
At the same time there are promising findings suggesting that genotypes have potential in terms of patient-treatment matching (Oslin et al., 2003) and unexplored endophenotypic indicators might have unknown predicting value. We therefore recommend that pharmacological matching studies should shift from a clinical point of view to a more neurobiological focus. In addition to clinical predictors (phenotypes), individual differences of patients with regard to the genotype (e.g., pharmacogenomics) and endophenotype (e.g., electrophysiological and psychophysiological cue reactivity, neurochemical and neuroendocrinological measures, and neuroimaging parameters (e.g., PET, SPECT, fMRI)), should be taken into account. This may ultimately result in more precise targeting of the biological deficits underlying those subtypes through distinct pharmacotherapies and possibly gene-therapies.

Another promising strategy in relapse prevention of alcoholism might be the combination of different anti-craving compounds. Besson et al. (1998) found that concomitant administration of disulfiram improved the effectiveness of acamprosate. In 2003, Kiefer et al. conducted the first double-blind, placebo-controlled study comparing and combining naltrexone with acamprosate in 160 patients. Naltrexone, acamprosate and the combined medication were significantly more effective than placebo. 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. The combined medication was most effective with significant lower relapse rates than placebo and acamprosate but not naltrexone. Kiefer noted that statistically and clinically relevant improvements can be obtained by combining naltrexone and acamprosate. Most patients described both ‘reward’ and ‘relief’ as important motivational factors for their alcohol intake. The enhanced efficacy may result from tackling both alterations. Kiefer concluded that further studies are warranted on the basis of more specific identification of these distinct subtypes. An alternative explanation would be that there is a pharmacokinetic drug interaction between acamprosate and naltrexone, or that there is an additive effect in every single patient (Kiefer, 2003). It could be concluded from these studies that polypharmacy is a promising strategy for patients with an inadequate response to monopharmacy. Since polypharmacy has some disadvantages over monopharmacy with respect to the risk of more side effects, matching patients to one anti-craving compounds is still preferred as the ideal option. However, it must be noted that clinical matching variables (e.g., self-report questionnaires) have little scientific evidence so far, whereas future matching variables such as endophenotypes or genotypes are promising, but may be time consuming and expensive in daily clinical practice.

Some patients might improve when they are matched with a treatment that
Patient-treatment matching with anti-craving medications

consists of a combination of an anti-craving compound with psychotherapy. We therefore recommend further investigation of matching patients with the combination of anti-craving medication with psychotherapy. A promising, uncompleted study in this respect is Study COMBINE (COMBINE Study Research Group, 2003) that seeks to evaluate the efficacy of naltrexone and acamprosate, both single and together, when combined with different intensities of behavioral therapies. In a study by O’Malley et al. for example, medication interacted with the type of psychotherapy received (O’Malley et al., 1992). Naltrexone was found to be superior to placebo in measures of drinking and alcohol-related problems, and the cumulative rate of abstinence was highest for patients treated with naltrexone and supportive therapy. For those patients who initiated drinking, however, patients who received naltrexone and coping skills/relapse prevention therapy were the least likely to relapse. However, most completed studies regarding this strategy have failed to find additive value of psychotherapeutic interventions to the prescription of anti-craving compounds (e.g., De Wildt et al., 2002) and showed that many patients do not benefit from these (combined) treatments. In addition, no differential effects were obtained with different types or intensities of additional psychotherapy (Pelc et al., 2002; Soyka et al., 2002). This suggests that other or additional interventions are needed for these resistant patients.

It could be concluded that more research is needed in order to test the matching hypotheses by Verheul et al. (1999) and to identify potential evidence-based matching variables for the various anti-craving compounds reviewed in this article. We recommend that future matching research should shift its focus from clinical variables to genetic and endophenotypic matching variables. Currently, we are aware of two European projects, of which one by our own research group, investigating potential genetic, endophenotypic and phenotypic indicators (Ooteman, Verheul and Van den Brink et al., PROJECT CRAVING PATHWAYS, in progress; Mann et al., PROJECT PREDICT, in progress). Furthermore, we recommend that matching studies in the scientific field and matching procedures in the daily clinical practice should take other options than monopharmacy (e.g., polypharmacy, additive psychotherapy), as well as practical considerations, into account. Hopefully, more insight in individual differences and different treatment options will lead to a better treatment of craving and relapse in alcoholic patients.

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Patient-treatment matching with anti-craving medications

CHAPTER 2

Patient-treatment matching with anti-craving medications


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Patient-treatment matching with anti-craving medications

CHAPTER 3

Development and validation of the Amsterdam Motives for Drinking Scale (AMDS): an attempt to distinguish relief and reward drinkers

Abstract

Aims: Determination of alcoholic subtypes is a promising strategy for patient-treatment matching with anti-craving interventions. The aim of this study is to develop and validate a questionnaire on drinking motives that can distinguish relief and reward drinkers.

Methods: A 103-item self-report questionnaire was developed: the Amsterdam Motives for Drinking Scale (AMDS). The AMDS was tested in two samples of alcoholics (sample A: n=251; sample B: n=197). The psychometric properties were examined in sample A and cross-validated in B.

Results: The AMDS consists of a relief scale and a reward scale, both containing distinct subscales. All (sub)scales had good internal consistency. However, the relief and reward scales were highly correlated (sample A: r=0.84, p<0.01; sample B: r=0.76, p<0.01), and convergent and divergent validity was only partly confirmed. Lowest correlations were found between relief subscale ‘stress and vulnerability’ and reward subscale ‘stimulation seeking’ (sample A: r=0.33, p<0.01; sample B: r=0.13, p<0.01).

Conclusions: The AMDS reliably measures two types of motives. However, the relief and reward scales are highly correlated. Lower correlations were found only at the subscale level. It is concluded that most treatment-seeking alcoholics have both relief and reward motives. More research is needed on the relation between motives for drinking and other phenotypic, endophenotypic and genetic indicators of relief and reward drinking, and appropriate cut off points. Only than we can draw firm conclusions regarding the potential of drinking motives for patient-treatment matching.
Introduction

Alcohol use is widespread and carries a significant risk of adverse psychological, social and physical health consequences. Effective treatment of alcoholism is important to limit these negative consequences. However, not all patients benefit from the different treatment options available. A promising strategy to improve the effectiveness of existing treatments is more efficient patient-treatment matching.

Successful patient-treatment matching must be based on adequate understanding of individual differences between alcoholics and the relationship between these individual differences and the effectiveness of different treatment approaches. Our own research group recently reviewed the literature on phenotypic, endophenotypic and genetic matching indicators for the effectiveness of anti-craving medications in alcoholics (Ooteman et al., 2005). We concluded that most studies have been conducted on phenotypic indicators (e.g., self-report questionnaires), producing inconsistent and rather disappointing results. Studies on genetic and endophenotypic indicators were scarce, but promising. Recently, Verheul et al. (1999) proposed a novel typology of drinkers, based on two distinct reinforcing properties of alcohol: anxiety/stress dampening properties (relief drinkers) and rewarding/stimulating properties (reward drinkers). Although Verheul et al. did not present tools for the identification of relief and reward drinkers, he did propose two hypotheses for more efficient patient-treatment matching. Relief drinkers would benefit from the anti-craving compound acamprosate (a glutamate antagonist), most likely through a reduction of neuronal hyperexcitability, whereas reward drinkers would benefit from the anti-craving compound naltrexone (an opiate antagonist), most likely through blocking of opioid receptors.

Until now, attempts to distinguish relief and reward drinkers empirically have been scarce. Farber et al. (1980), who tried to distinguish relief and reward drinking by looking at drinkers’ drinking motives, found that 93% of alcoholics would be classified as relief drinkers using the Reasons for Drinking Questionnaire (RDQ). In addition, Kiefer et al. (2003) showed that most patients mention both ‘relief’ and ‘reward’ motives for their alcohol intake. These findings seem to indicate that no questionnaire is yet able to clearly distinguish between relief and reward drinkers. Equally, relief and reward drinking have never been defined precisely, and therefore these findings may also represent insufficient conceptual distinction and/or insufficient measurement. The current study attempts adequately to distinguish the concepts of relief and reward drinking and subsequently to develop and test a new questionnaire.
In general, the term 'relief drinking' is associated with negative reinforcement, which is the termination of an aversive stimulus immediately following a performance. The term 'reward drinking' is generally associated with positive reinforcement, which can be defined as the presentation of a reinforcing stimulus immediately following a performance. Following this definition, the stimulus can be a negative emotion (e.g., stress or anxiety) that is terminated by drinking alcohol (relief drinking) or a positive emotion (e.g., a kick or euphoria) following drinking alcohol (reward drinking) (Ferster et al., 1975). A more practical definition has been proposed by Cox and Klinger (1988), who suggested that individuals may drink in order to obtain positive outcome (positive reinforcement) or to avoid a negative one (negative reinforcement). Both theory and empirical research suggest that the desire to regulate one's affective experience (emotion) is an important motive for drinking alcohol (e.g., Lang et al., 1999; Wills and Shiffman, 1985). According to Wills and Shiffman (1985), individuals use alcohol to reduce negative affects when they are anxious and overaroused, or to enhance positive effects when they are fatigued and underaroused.

Based on these findings, Cooper et al. (1994, 1995) developed a motivational model of alcohol use that tried to distinguish coping and enhancement motives. However, coping and enhancement motives correlated quite highly in both the adolescent and adult non-alcoholic sample (respectively $r=0.44, p<0.001$; $r=0.59, p<0.001$). In addition, in the adult sample, only 11% could be classified as pure coping drinkers and only 13% as pure enhancement drinkers (Cooper et al., 1995). A similar correlation between positive and negative reinforcement motives was found by Carey and Correia (1997) in a sample of non-alcoholic university undergraduates using the Reasons for Drinking Questionnaire ($r=0.44, p<0.001$). Again, it seems that relief and reward drinking are overlapping concepts and no practical classification of relief versus reward drinkers can be made. Cooper’s model integrated the valence (positive versus negative) and the intensity of arousal (low versus high) that drinkers seek. The idea that motives can vary in the valence as well as in the intensity of arousal sought, shows similarities with the circumplex model of emotion (Russell, 1980; Larsen and Diener, 1992) representing emotions in a circular order around an arousal axis and a valence axis (see Figure 1a). However, Cooper’s model does not clearly define the nature of pre-existing emotional states for enhancement motives or post-existing emotional states for coping motives (Cooper et al., 1995). When looking at Cooper’s questionnaire, all enhancement motives are positively formulated and therefore refer solely to the post-existing state (e.g., ‘I drink to get high,’ ‘I drink because it is fun’) and most coping motives are negative formulated (e.g., ‘I drink to forget my worries,’ ‘I drink to forget about problems’) and therefore are primarily referring to the pre-existing state.
In addition, Cooper’s coping and enhancement scales are validated in a sample from the general population. Therefore certain motives that are specifically reported by alcoholics (often suffering from comorbidity such as depression) are not present in Cooper’s questionnaire and are difficult to fit into her model, e.g., ‘I drink to feel less passive’, ‘I drink to feel less empty’, ‘I drink to feel calmer’, ‘I drink to feel more at ease’, ‘I drink in order to be able to relax’, ‘I drink to fall asleep more easily’.

In order to further improve the measurement of relief and reward drinking, we developed a new two-dimensional model of relief and reward motives for alcoholics. This new model is based on Cooper’s motivational model (Cooper et al., 1995), extended with motives integrating a wide array of (potentially pre-existing and post-existing) affective states as proposed by the circumplex model of emotion (Russell, 1980; Larsen and Diener, 1992; see Figure 1b). A diagonal reward axis is distinguished from a diagonal relief axis representing two distinct orthogonal dimensions. According to this model, reward motives aim at approaching or obtaining a positive reinforcing emotion with higher arousal than the current emotion of the patient (e.g., drinking for the kick), whereas relief motives aim at dampening or terminating a negative reinforcing emotion, resulting in an emotion with lower arousal than the current emotion of the patient (e.g., drinking to reduce stress).

The first aim of the current study is to develop a new questionnaire for drinking motives, the Amsterdam Motives for Drinking Scale (AMDS), which is based on the circumplex model of emotion (Russell, 1980; Larsen and Diener, 1992) and on Cooper’s motivational model of alcohol use (Cooper et al., 1995). The second aim is to evaluate its psychometric properties. It is expected that this study will shed empirical light on the concepts of relief and reward motives in alcoholics, resulting in a measure that is able adequately to distinguish relief and reward drinkers and that could be used in patient-treatment matching strategies.

Materials and Methods

Development and validation of the Amsterdam Motives for Drinking Scale

First, we conducted a review of the published literature and instruments on drinking motives, expectancies, drinking situations and anticipations of drinking outcome. The reason we also reviewed instruments on theoretical constructs other than motives (Wiers et al., 1997) is because it has been questioned whether some of these constructs can be meaningfully distinguished (Goldman et al., 1999). A pool of 626 items was created (a complete list can be obtained from W.O.). If the original item represented a construct other than a drinking motive, the item was rewritten as a motive, using the format: ‘I drank alcohol in order to...’


**Figure 1a.** The circumplex model of emotion (Russell, 1980; Larsen and Diener, 1992).

**Figure 1b.** 2D model of motives for drinking alcohol in alcoholics.
Experience less/more [emotional state]. For example, ‘After many drinks people become romantic’ is rewritten as ‘I drink to feel more romantic’. The reason we chose the motives format is that motives are generally seen as the most proximal determinant of consumption (Cooper et al., 1995). Both external (interpersonal) and internal (intrapersonal) motives were included.

Second, all items were then allotted to one of the two dimensions of the model. The two-dimensional model of drinking motives consists of (1) relief motives, which are to eliminate or dampen a negative emotion with higher arousal than the post-existing emotional state, and (2) reward motives, which are to achieve or enhance a positive emotion with higher arousal than the pre-existing emotional state (see Figure 1b). All items that did not fit the model or that contained no emotion in the motive were excluded. Furthermore, we excluded overlapping items, items exclusively aiming at youths or adolescents (e.g., conformity to peer pressure) and items with an unclear intensity of arousal or an unclear valence (e.g., ‘I drink because I like the feeling’, ‘I drink because I like the taste of alcohol’, ‘I drink to become a better driver’). By excluding these items we tried to focus on motives with a strong emotional component and a clearly defined valence and arousal intensity.

Third, the remaining 193 items were then allotted to the distinct aspects of the relief and reward dimensions. The five aspects of relief motives were reduction of anxiety (anx), reduction of vulnerability and stress (vul), reduction of angry hostility (hos), reduction of autonomic hyperarousal (aut) and reduction of social anxiety/shyness (shy). The four aspects of reward motives were achievement of stimulation (sti), achievement of hedonic positive affect (paf), achievement of energy (eny) and achievement of dominance (dom). Items that did not fit with the relief and reward aspects were excluded.

Finally, these 193 items were judged by the research group in terms of their clarity, lack of ambiguity, simplicity, formulation, generalization, and overlap. Based on consensus, 11-13 items were selected for each motivational aspect, leaving 103 items for the study. Each motivational aspect included some negatively formulated items (e.g., ‘I drink to feel less bored’) and some positively formulated items (e.g., ‘I drink for the kick’). The rationale for subscale breakdown into positive and negative wording is based partly on the theory of positive and negative reinforcement. Positive reinforcement is generally defined as achieving something pleasant (e.g., feeling more elated), whereas negative reinforcement is the mechanism of reducing something unpleasant (e.g., feeling less anxious). This definition uses a positive formulation for positive reinforcement and a negative formulation for negative reinforcement only. However, when looking at our circular model (Figure 1b), positive reinforcement motives can be positively and negatively formulated (e.g., ‘I drink to feel more elated’ and ‘I drink to feel less

Development and validation of the Amsterdam Motives for Drinking Scale
empty’), as can negative reinforcement motives (‘I drink to feel less anxious’ and ‘I drink to feel more relaxed’). We therefore wanted to formulate both positive and negative items for the relief and reward scale. For example, the motivational aspect stimulation seeking (‘sti’) consists of ‘sti-pos’ (positively formulated items) and ‘sti-neg’ (negatively formulated items). The order of the statements was determined randomly. Ten items were duplicated in order to test consistency, resulting in a total of 113 items in the original AMDS. Of the 113 items, 54 were selected, resulting in a short version for efficient cross-validation in a second sample (AMDS-short). The AMDS answer format is a 6-point scale measuring the frequency of each drinking motive in the past 12 months ranging from ‘never’ (0) to ‘very often’ (5).

SUBJECTS

Two groups of alcohol-dependent patients were used for the validation of the AMDS. A large sample (sample A) of treatment-seeking subjects from four different alcohol treatment centers in The Netherlands (Jellinek, Boumanhuis, Parnassia, Kuno van Dijk Stichting), was used for the investigation of the psychometric properties of the AMDS. Another sample (sample B) was used for cross-validation of the AMDS. This latter sample contained treatment-seeking and non-treatment-seeking alcoholics who were recruited at the Jellinek addiction treatment clinic in Amsterdam and through advertisement in newspapers and radio interviews.

All subjects had a primary DSM-IV diagnosis of alcohol dependence. They were required not to have had heavy drinking days (≥ 5 units) for 1 week to 6 months in order to secure adequate recollection. Exclusion criteria were comorbid cocaine or heroin dependence, cocaine or heroin use in the last 30 days before intake, current psychosis, current use of anti-psychotic medication; current use of anti-craving compounds (naltrexone, acamprosate) and disulfiram, severe cognitive deficits, and insufficient command of the Dutch language.

A total of 1019 subjects were screened: 495 subjects in sample A and 524 subjects in sample B. A total of 80 (sample A) and 188 (sample B) subjects refused to participate. Finally, 107 (sample A) and 139 subjects (sample B) had to be excluded; the most important reasons for exclusion were no primary diagnosis of alcohol dependence and ≥ 6 months of abstinence (sample A), medical conditions and current use of anti-craving compounds (sample B). This left 308 subjects in sample A and 197 in sample B. A total of 251 of 308 subjects (81.5%) in sample A and 185 of 197 subjects (92.9%) in sample B completed the study. A subgroup of 34 subjects in sample A was asked to administer the AMDS twice with a 3 week interval in order to establish test-retest reliability.
Sample A was used for scale construction and estimation of convergent and divergent validity of the AMDS. Sample B was used for cross-validation. All clients in samples A and B self-administered a set of self-report questionnaires. The administration took ~1.5 h. All subjects received vouchers for 12.50 Euro after completion.

All participants in samples A and B completed the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 1992). AUDIT scores can range from 0 to 40, and the generally accepted cut off point for identifying a potential alcohol problem is 8. All participants in sample B completed the short version (54 items) of the AMDS. All participants in samples A and B also completed the following additional questionnaires in order to estimate the convergent and divergent validity of the AMDS: the Motives for Drinking Questionnaire (MDQ) (Cooper et al., 1994, translated in Dutch by W.O. and R.V.), the BIS/BAS-Scale (Carver and White, 1994), the Alcohol Effects Questionnaire (AEFQ) (Rohsenow, 1985), the NEO-PI-R Personality Inventory (Costa and McCrae, 1992), the Anxiety Sensitivity Index (ASI) (Reiss et al., 1986), the High Sensitive Person (HSP) Scale (Aron and Aron, 1997), the Boredom Proneness Scale (Farmer and Sundberg, 1986), the Jellinek Alcohol Craving Questionnaire (JACQ) ‘now’ and ‘past’ version (Ooteman et al., 2006), the Mood Adjective Checklist (MACL) (Mackay et al., 1978), the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and a series of self-constructed items to assess the family history of alcoholism (FH), withdrawal symptoms and binge drinking. A positive family history was defined as at least one first-degree relative (parents or siblings) having (had) an alcohol problem.

A principal component analysis (PCA) with varimax rotation was performed to explore whether the underlying structure of the individual AMDS items resembles the theoretical two-dimensional motivational structure. Next, the internal consistency of the theoretical scales was determined by computing Cronbach’s alphas, and these values were compared with the internal consistency of the scales that resulted from the PCA. Interscale correlations, test-retest reliability, convergent validity and divergent validity were assessed using Pearson correlation coefficients. For family history and binge drinking effect sizes were presented as Cohen’s d values. Divergent validity in our definition means that an AMDS scale correlates low (r ≤ 0.30) with variables reflecting a theoretically unrelated construct and convergent validity means that an AMDS scale
correlates high ($r \geq 0.60$) with variables reflecting a theoretically related construct.

In order to distinguish between extreme groups of relief and reward drinkers, difference scores were calculated by subtracting the z transformed score on the reward scale from the z transformed score on the relief scale (z transformation adjusts for differences in mean and variance between the scales). The 10% of subjects with a difference-score $> 0.77$ were defined as relief drinkers, whereas the 10% with a difference-score $< -0.70$ were defined as reward drinkers. A similar procedure was used for with the two relief and reward scales with the lowest interscale correlation: the positively formulated ‘stimulation seeking’ subscale (stipos) and the negatively formulated ‘vulnerability’ subscale (vul-neg). The 10% of subjects with a score $> 1.50$ were defined as relief drinkers, whereas the 10% with a score $< -1.57$ were defined as reward drinkers. Differences between relief and reward drinkers with respect to demographics and alcohol-related variables were tested using $t$-tests. Differences between reward and relief drinkers were tested with an $\alpha$ of 0.01. This $\alpha$ value takes into account both a Bonferroni correction for multiple testing and the relatively small sample sizes, which affect the power of the tests.

**Results**

**Sample Characteristics**

Table 1 shows that most study participants were Dutch, male, of low educational level, unemployed and unmarried. In sample A, most subjects were inpatient alcoholics (77.7%), whereas in sample B 29.9% were inpatient, 41.1% were outpatient and 28.9% were currently not seeking treatment. Most subjects had moderate to severe levels of alcohol dependence. Sample A was less well educated and more severely addicted according to the AUDIT scores than sample B. These differences seem to be related to the presence of non-treatment-seeking alcoholics in sample B who were more highly educated ($p<0.01$) and less severely addicted according to the AUDIT ($p<0.01$) then the treatment-seeking alcoholics in sample B.

**Factor Structure and Internal Consistency of the AMDS (Sub)Scales (Content Validity)**

As a first step, the internal consistencies of the theoretical AMDS scales were calculated in sample A. Internal consistencies of the relief and reward scales were high ($\alpha=0.97$ for both scales). Internal consistencies of the nine subscales were also good (ranging from $\alpha=0.90$ to $\alpha=0.95$ for the relief subscales and ranging from $\alpha=0.87$ to $\alpha=0.94$ for the reward subscales).
We expected to find low correlations between relief and reward scales. However, the relief and reward scales correlated $r=0.84$ ($p<0.01$), whereas the correlations between the relief and reward subscales ranged from $r=0.46$ to $r=0.83$ ($p<0.01$) (Table 2). The lowest correlations were found between the negatively formulated relief and the positively formulated reward subscales, ranging from $r=0.33$ ($p<0.01$) for the correlation between the negatively formulated ‘vulnerability’ subscale (vul-neg) and the positively formulated ‘stimulation seeking’ subscale (sti-pos) to $r=0.78$ ($p<0.01$) for the correlation between the positively formulated ‘dominance’ subscale (dom-pos) and the negatively formulated ‘shyness’ subscale (shy-neg) (Table 3). Given the generally high interscale correlations between reward and relief motives, it was questioned whether the AMDS really measures two dimensions of drinking motives. In order to explore this question, a PCA was performed. Most of the variance (37.0%) was explained by a factor closely resembling the relief scale and a much smaller portion of the variance (6.9%) was explained by a factor resembling the reward scale. The internal consistency of the explorative scales was high and very similar to those of the theoretical scales ($\alpha=0.97$ for both relief and reward). Since the content and the internal consistency of the explorative AMDS scales were very similar to those of the

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**Table 1. Patient characteristics and alcohol-related variables.**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Sample A (n=251)</th>
<th>Sample B (n=197)</th>
</tr>
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<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>45 (9)</td>
<td>48 (10)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>67.3</td>
<td>73.1</td>
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<td>Dutch ethnicity (%)</td>
<td>83.3</td>
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<td>Inpatients (%)</td>
<td>77.7</td>
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<tr>
<td>In treatment at a clinic (%)</td>
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<tr>
<td>Higher education (%)</td>
<td>19.2</td>
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<tr>
<td>Mean years of education (SD)</td>
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<td>13.4 (4.3)</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>44.1</td>
<td>48.7</td>
</tr>
<tr>
<td>Married (%)</td>
<td>22.6</td>
<td>21.3</td>
</tr>
<tr>
<td>Alcohol-related variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AUDIT score (SD)</td>
<td>24.7 (5.1)</td>
<td>21.5 (5.4)</td>
</tr>
<tr>
<td>Mean age of onset (SD)</td>
<td>32.6 (10.5)</td>
<td>36.2 (10.4)</td>
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theoretical scales, it was decided to use the theoretical scales for further analysis.

As a final step, a short version of the AMDS was constructed that was used in sample B. In sample A, this 54-item version of the AMDS correlated .99 ($p<.01$) with the 113-item version. When the theoretical scales of the AMDS-short were cross-validated in sample B, interscale correlations and internal consistencies were in the same range as for the original long version of the AMDS in sample A. Again, relief and reward correlated highly ($r=0.76, p<0.01$), with the lowest correlations between the positively formulated ‘simulation seeking’ subscale (sti-pos) and the negatively formulated subscale ‘anxiety’ (anx-neg), ‘vulnerability’ (vul-neg) and ‘angry hostility’ (hos-neg) ($r=0.18, p>0.01; r=0.13, p>0.01$; and $r=0.12, p>0.01$ respectively).

Table 2. Interscale correlations for the AMDS.

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<tbody>
<tr>
<td></td>
<td>Relief</td>
<td>Reward</td>
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<td></td>
<td>(n=251)$^{a}$</td>
<td>anx</td>
<td>vul</td>
<td>hos</td>
<td>aut</td>
<td>shy</td>
<td>sti</td>
<td>paf</td>
<td>eny</td>
<td>dom</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>shy</td>
<td>0.72</td>
<td>0.69</td>
<td>0.70</td>
<td>0.56</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reward</td>
<td>sti</td>
<td>0.51</td>
<td>0.50</td>
<td>0.59</td>
<td>0.46</td>
<td>0.56</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>paf</td>
<td>0.69</td>
<td>0.72</td>
<td>0.71</td>
<td>0.56</td>
<td>0.69</td>
<td>0.74</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>eny</td>
<td>0.58</td>
<td>0.67</td>
<td>0.69</td>
<td>0.59</td>
<td>0.65</td>
<td>0.62</td>
<td>0.76</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>dom</td>
<td>0.66</td>
<td>0.70</td>
<td>0.76</td>
<td>0.56</td>
<td>0.83</td>
<td>0.63</td>
<td>0.69</td>
<td>0.71</td>
<td>1</td>
</tr>
<tr>
<td>Relief</td>
<td>0.91</td>
<td>0.91</td>
<td>0.87</td>
<td>0.80</td>
<td>0.86</td>
<td>0.86</td>
<td>0.59</td>
<td>0.79</td>
<td>0.73</td>
<td>0.81</td>
</tr>
<tr>
<td>Reward</td>
<td>0.69</td>
<td>0.74</td>
<td>0.80</td>
<td>0.62</td>
<td>0.79</td>
<td>0.84</td>
<td>0.91</td>
<td>0.89</td>
<td>0.87</td>
<td>0.84</td>
</tr>
</tbody>
</table>

All subscales are the sum of both positively formulated items and reversed negatively formulated items. Abbreviations: anx=anxiety, vul=vulnerability, hos=angry hostility, aut=automatic hyper-arousal, shy=social anxiety/shyness, sti=stimulation/novelty seeking, paf=hedonic positive affect, eny=energy, dom=dominance/power. $^{a}$All correlations are significant at the 0.01 level.
Based on scores on the relief and reward scales, subjects in sample A were divided in relief and reward drinkers. When the difference scores on the relief and reward scale were used, 20 patients (8%) were defined as relief drinkers and 20 patients (8%) were defined as reward drinkers. The remaining 211 subjects (84%) were defined as combination drinkers and were left out of further analyses. We used these criteria because currently we do not have an external criterion such as clinically relevant cut off scores. Relief and reward drinkers were not significantly different with respect to most of the patient characteristics. However, a significant effect was found for education ($p<0.01$), with lower education in the relief group.

When the definition of relief and reward was based on difference scores of the negatively formulated subscale 'vulnerability' (vul-neg) and positively formulated subscale 'stimulation seeking' (sti-pos), 24 subjects (10%) were defined as re-
relief drinkers and 24 subjects (10%) were defined as reward drinkers. A significant effect was found for gender and AUDIT scores ($p<0.01$), with more females and higher AUDIT scores in the relief group.

Also in sample B, 17 relief drinkers (9%) and 17 reward drinkers (9%) were not significantly different with respect to any variables, except that a significant effect was found for education and the subject’s setting ($p<0.01$), with lower education and more inpatients in the relief group. When the definition of relief and reward was based on the negatively formulated ‘vulnerability’ and positively formulated ‘stimulation seeking’ subscales, a significant difference was found between the 18 relief drinkers (9%) and the 17 reward drinkers (9%) in setting: relief drinkers were more likely than reward drinkers to be inpatients ($p<0.01$). A trend was found for treatment-seeking ($p<0.05$). Relief drinkers were more likely to be in treatment.

**TEST-RETEST RELIABILITY ($n=34$)**

For sample A, the test-retest reliability of AMDS was assessed in 34 subjects. For most subscales pre-test scores were not significantly different from the scores on the retest 3 weeks later. Relief and reward scores at pre-test were highly correlated with relief and reward scores 3 weeks later ($r=0.93$ and $r=0.94$, respectively; $p<0.01$). The test-retest results for the subscales were very similar: ranging from $r=0.86$ to $r=0.90$ ($p<0.01$) for the relief subscales and ranging from $r=0.84$ to $r=0.95$ ($p<0.01$) for the reward subscales.

**CONVERGENT AND DIVERGENT VALIDITY OF THE AMDS**

As Table 4 shows there is not much evidence for convergent validity of the relief and reward scales. Most correlations with instruments and variables measuring constructs theoretically related to the constructs of the relief and reward scale were below threshold, with the exception of the correlations for the relief scale with the coping scale of the MDQ ($r=0.67; p<0.01$) and withdrawal symptoms ($r=0.60; p<0.01$) and correlations for the reward scale with the enhancement scale of the MDQ ($r=0.63; p<0.01$) and the global positive scale of the AEFQ ($r=0.64; p<0.01$). There is evidence for moderate to good divergent validity of the relief scale. Correlations < 0.30 were found with the BAS scale ($r=0.10; p>0.01$), the extraversion scale of the NEO-PI-R ($r=-0.15; p>0.01$), the arousal scale of the MAACL ($r=-0.23; p<0.01$) and the social pleasure scale of the AEFQ ($r=-0.28; p<0.01$). However, the divergent validity of the reward scale was low, except for a below-threshold correlation with the relaxation scale of the AEFQ ($r=0.25; p<0.01$).

As expected, the correlation pattern with all variables was very similar for the AMDS relief and reward scales probably reflecting the high correlation between
Development and validation of the Amsterdam Motives for Drinking Scale

Table 4. Divergent and convergent validity: correlations with the AMDS scales.

<table>
<thead>
<tr>
<th>Sample A (n=251)</th>
<th>Relief</th>
<th>Reward</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDQ cop</td>
<td>0.67</td>
<td>0.49</td>
</tr>
<tr>
<td>MDQ con</td>
<td>0.51</td>
<td>0.54</td>
</tr>
<tr>
<td>BIS</td>
<td>0.51</td>
<td>0.42</td>
</tr>
<tr>
<td>AEFQrel</td>
<td>0.41</td>
<td>0.25</td>
</tr>
<tr>
<td>NEO-N</td>
<td>0.56</td>
<td>0.45</td>
</tr>
<tr>
<td>Anx sens</td>
<td>0.55</td>
<td>0.42</td>
</tr>
<tr>
<td>HSP</td>
<td>0.55</td>
<td>0.43</td>
</tr>
<tr>
<td>MACLstr</td>
<td>0.40</td>
<td>0.30</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>0.60</td>
<td>0.49</td>
</tr>
<tr>
<td>MDQ soc</td>
<td>0.44</td>
<td>0.59</td>
</tr>
<tr>
<td>MDQ enh</td>
<td>0.42</td>
<td>0.63</td>
</tr>
<tr>
<td>BAS</td>
<td>0.10</td>
<td>0.27</td>
</tr>
<tr>
<td>AEFQpos</td>
<td>0.56</td>
<td>0.64</td>
</tr>
<tr>
<td>AEFQagg</td>
<td>0.46</td>
<td>0.55</td>
</tr>
<tr>
<td>NEO-E</td>
<td>-0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>Boredom</td>
<td>0.41</td>
<td>0.31</td>
</tr>
<tr>
<td>JACQnow</td>
<td>0.32</td>
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</tr>
<tr>
<td>JACQpast</td>
<td>0.58</td>
<td>0.48</td>
</tr>
<tr>
<td>MACLaro</td>
<td>-0.23</td>
<td>-0.16</td>
</tr>
<tr>
<td>FH*</td>
<td>-0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Binging*</td>
<td>0.22</td>
<td>-0.25</td>
</tr>
</tbody>
</table>

The upper half of the table shows variables expected to show high correlations with relief and low correlations with reward. The lower half shows variables expected to show high correlations with reward and low correlations with relief.

Abbreviations: agg=power/aggression, anx sens=anxiety sensitivity, aro=arousal, con=conformity, cop=coping, cu=careless unconcern, E=extraversion, enh=enhancement, FH=family history of alcoholism, HSP=highly sensitive person, N=neuroticism, pos=global positive, rel=relaxation/tension reduction, sex=sexual enhancement, soc=social expressiveness, spp=social/physical pleasure, str=stress.

Correlations indicating divergent validity (r≤0.30) and convergent validity (r≥0.60) are printed in bold.

* For the family history and binge drinking effects, sizes are presented as Cohen’s d values.
the AMDS relief and reward scales ($r=0.84$) - a situation that was also observed for the AMDS subscales, although to a slightly lesser extent. Very similar patterns of correlations were found in sample B.

**Discussion**

The aim of the current study was to develop and validate a self-report questionnaire measuring two theoretically independent motives for drinking: relief and reward.

First, the explorative factor analysis showed a factor solution that was similar to our theoretical model. We therefore decided to continue our analyses with the scales that were based on our theoretical model.

Second, the AMDS showed good test-retest reliability, high internal consistencies of all (sub)scales and high interscale correlations between relief and reward motives ($r=0.84$). The high correlation does not support that reward and relief motives are independent factors. Only at a narrowly defined subscale level were lower correlations found.

In sample A the negatively formulated relief aspect ‘vulnerability’ correlated low with the positively formulated reward aspect ‘stimulation seeking’ ($r=0.33$). Apparently, these subscales showed the best discrimination. After inspection of the model (Figure 1b), it can be concluded that the negatively formulated ‘vulnerability’ and the positively formulated ‘stimulation seeking’ subscales, as well as Cooper’s scales, represent only the upper half of our model. This result is in line with the definition of positive and negative reinforcement, using a positive formulation for reward and a negative one for relief. However, when all negative formulated items were correlated with all positive formulated items of the AMDS, we did not find high discrimination, which may indicate that the content rather than the wording of the subscales is of importance. In sample B, the correlation between the subscales ‘vulnerability’ and ‘stimulation seeking’ was even lower ($r=0.13$, $p>0.01$), which may be explained by the fact that in sample B a more heterogeneous sample with less severely dependent non-treatment-seeking alcoholics was studied. It is suggested that in alcoholics at the start of their pathological drinking career (first admissions, non-treatment-seeking alcoholics) it is easier to distinguish reward and relief motives, whereas chronically addicted inpatients with a long history of treatment may have developed secondary relief drinking owing to the adverse effects of their addiction (e.g., withdrawal symptoms) or may have developed a behavioral drinking pattern that is driven by automatic processes rather than by rational motives. This post hoc explanation is supported by the observed trend that treatment-seeking alcoholics showed a tendency to endorse more relief motives than non-treatment-seeking alcoholics.
Third, relief and reward drinkers were not significantly different with respect to most of the demographic or alcohol-related variables. There may be a relationship with education and setting. In our study, relief drinkers were more likely to be less well educated and inpatients. When the definition of relief and reward motives was based on the subscales ‘vulnerability’ and ‘stimulation seeking’ only, relief drinkers were also more likely to be treatment-seeking females with more severe alcohol problems. These findings are partially in line with the definition of a relief drinker by Verheul c.s. (Verheul et al., 1999).

Fourth, with respect to the convergent and divergent validity of the AMDS, it can be concluded that convergent and divergent validity for the relief and reward scales are only partly confirmed. The AMDS was strongly correlated with the MDQ, which is probably due to a large overlap in content and formulation. However, it should be noted that the MDQ does not include all emotions of the circumplex model of emotion (Figure 1a). Therefore we expected slightly lower correlations between the relief and reward scales of the AMDS and the MDQ.

The correlation pattern of the relief and reward scales of the AMDS with the other variables was quite similar. These findings probably reflect the high correlation between the relief and reward scales of the AMDS (r=0.84). Both relief and reward motives correlated only moderately with craving now (JACQ-now; r=0.32 and r=0.33, respectively) and rather highly with craving in the past (JACQ-past; r=0.58 and r=0.48, respectively), suggesting that the concepts of craving in the past and drinking motives are related phenomena. Therefore, the reported types of motives may be an indication for the patient’s pathways underlying a patient’s craving. However, craving may not necessarily be accompanied by a motive or vice versa. More research is needed to unravel the relation between motives and craving.

Fifth, and most important, we found that most patients proved to be so-called drinkers with combined motives, whereas the extreme groups of relief and reward drinkers were very small (16-20%). Apparently, most treatment-seeking alcoholics report both relief and reward motives. This is in line with earlier studies (Farber et al., 1980; Kiefer et al., 2003). The most likely explanation may be that the subjects had distinct relief or reward motives in the past but have developed both motives for drinking as a result of their dependence. However, the existing questionnaires, including the AMDS, may not be able to differentiate between persons with a (predominantly) positive reinforcement history and persons with a (predominantly) negative reinforcement history. We therefore suggest investigating the effect of the course of an alcohol problem on the development of reward and relief motives, say by developing a ‘past’ version of the AMDS. Another option would be to investigate the influence of drinking career on relief and reward drinking by looking at genotypic and endophenotypic indicators of relief.
and reward drinking in addition to phenotypic indicators, as genotypic and endophenotypic indicators are less influenced by environmental factors.

An alternative explanation may be that positive and negative reinforcement mechanisms are two distinct mechanisms that have always co-existed in similar extend in most drinkers (activated simultaneously or depending on the situation). If future research would indicate this, the distinct subtypes ‘relief drinker’ and ‘reward drinker’ do not exist, according to our model.

An import factor with respect to the validity of the AMDS and other drinking motives questionnaires is that there may be individual differences in the extent to which patients are consciously aware of their implicit underlying mechanisms resulting in (excessive) drinking. The degree of awareness or detection of motivational mechanisms can therefore influence the way the AMDS is filled out. Results from a previous study by our research group may illustrate this important point. It was shown that the explicit (aware) phenotype ‘craving’ and the related but implicit (not necessarily aware) endophenotype ‘physiological cue reactivity’ correlated poorly because of individual differences in detection levels of physiological cue reactions (Ooteman et al., 2006). Motives are by definition subjective experiences and the end product of various factors. Knowing your motives implies a sufficient level of awareness and explicit information processing. In fact, sufficient awareness of these mechanisms is a prerequisite for valid administration of the AMDS, and therefore a prerequisite for valid distinction of relief and reward drinkers (e.g., for patient-treatment matching). In addition, we do not know whether patients always report what they experience. However, the mechanisms of positive and negative reinforcement do not assume sufficient awareness or honest reporting. Therefore, more research is warranted on the relation between the AMDS and indicators of relief and reward drinking that require lower levels of awareness and that are less affected by report bias such as (1) other (more objective) phenotypic indicators (age of onset); (2) endophenotypic indicators (physiological cue reactivity); and (3) genetic indicators (µ-opioid receptor polymorphism) of relief and reward drinking. This may shed light on the external validity of the AMDS. However, we do not think that lack of awareness is a very likely explanation for the high correlation between the relief and reward motives of the AMDS. If our patients had had low level of awareness, we would have expected low to moderate correlations between the (sub)scales owing to a lack of variance.

A final limitation of this study is that our definition of relief and reward drinking was based on difference scores on the relief and reward scales, and not on clinically relevant cut off scores. Therefore our percentages may not be accurate. More research is needed on appropriate cut off scores.

In conclusion, it seems that the AMDS is a reliable questionnaire for measur-
Development and validation of the Amsterdam Motives for Drinking Scale

ing different types of drinking motives, but that it is not able to distinguish between relief and reward drinkers in a population of mainly treatment-seeking alcoholics. Apparently, the broad concepts of relief and reward motives are closely related in moderate to severe alcoholics. This is disappointing because it seems that currently the AMDS cannot be used in the process of patient-treatment matching. More research is needed regarding the external validity of the AMDS, i.e., correlations with phenotypic, endophenotypic and genetic indicators of relief and reward drinking. Research is also warranted regarding the use of appropriate clinical cut off points and the discriminative properties of AMDS (sub)scales. Only then will we be able to draw firm conclusions regarding the potential of using drinking motives for patient-treatment matching. However, even if we will be able to distinguish relief and reward motives in the future, this does not automatically imply predictive value in patient-treatment matching. And the opposite applies as well: even if we still find overlap in relief and reward motives and the AMDS cannot be used for matching strategies based on our model, this would not per se speak against a use for matching strategies based on other models. Until now, these issues have remained empirical questions. Future research will have to show whether categorization of extreme groups of relief and reward drinkers will contribute to better patient-treatment matching and whether a combination of interventions (e.g., polypharmacy) is the future strategy for drinkers with both relief and reward motives.

Appendix

AMDS-short (54 item-version, translated from Dutch)

This questionnaire aims at getting an impression of your reasons to drink alcohol during the past 12 months, or in other words what your motives were to drink. The questionnaire contains a few statements (motives) that ask about reasons to drink alcohol. Please indicate how often your experience matched each of the following statements by placing a circle around one of the numbers. There are no wrong or right answers. For example: the number ‘5’ indicates that your experience matched the statement often; the number ‘0’ indicates never. We are interested in your own reasons to drink alcohol in the ‘PAST 12 MONTHS’. If you have quit drinking, please fill out the questionnaire for the time when you were still drinking. Please read carefully, but do not think too long about your answer. Usually your first impression is the best one. Please complete every item.
In the past 12 months I drank alcohol...
1. to feel at ease
2. to feel less empty
3. to let little annoyances frustrate me less
4. because it was exciting to get drunk
5. to feel less anxious
6. to get enthusiastic and elated
7. to relax after a busy day or annoying event
8. to feel less down
9. to get rid of my withdrawal symptoms
10. to get a lot of energy
11. to become more peppy
12. to feel less tired
13. to be able to produce greater effort
14. to feel less angry how things went
15. to forget a fight with my partner, family-member or a friend
16. to feel less restless
17. to talk to people more easily
18. to get rid of my boredom
19. because I wanted to experience something exciting
20. to conquer my shame
21. to let my heart beat more slowly
22. to enjoy a party optimally
23. to have less fear of failure
24. to feel more fit
25. to feel less lethargic or passive
26. to loose myself less quickly in a crisis situation
27. to become more active
28. for the kick
29. to feel less helpless when everything seemed to go wrong
30. to keep talking longer in a conversation
31. because I wanted to have a sensational feeling
32. to calm down my stomach
33. to escape from the daily routine
34. to relax my muscles
35. to reduce the pressure at my chest
36. in order to feel less trembling
37. to enhance my sexual pleasure
38. to conquer my fear of speaking in public
39. to feel more self confident in a group
Development and validation of the Amsterdam Motives for Drinking Scale

40. to calm down when I was nervous
41. to sweat a bit less
42. to get rid of my nausea
43. to make my life seem less boring and monotonous
44. to be less scared to fail in company with others
45. to feel less pessimistic
46. to experience nice things more intense
47. to feel less sleepy
48. to relax myself
49. to stand up for myself
50. to feel less tense or nervous
51. to keep my emotions under control
52. to feel less submissive
53. to get ‘high’
54. to reduce my stress in problematic situations.

Acknowledgements

We thank Simone Höhner, Premal Koning, Ron Baas, Sigrid Wittenberg, Dorine Eeken, Kai Hulstijn, Weena Chen, Gjalt de Vries and Hans Kronemeijer for their assistance.

References

CHAPTER 3


CHAPTER 4

Measuring craving:
an attempt to connect subjective craving
with physiological cue reactivity.

CHAPTER 4

Abstract

BACKGROUND: Better insight in craving may contribute to the development of more efficient relapse prevention strategies. Inconsistent findings on the relation between craving and relapse may be owing to difficulties in the measurement of craving. These difficulties are accounted for by 3 interrelated problems: lack of consensus regarding the definition of craving, the use of different time frames (craving now vs. craving in the past), and lack of concordance between self-reported craving and psychophysiological measures of cue reactivity. The aim of this study is to develop and validate a new self-report questionnaire for the assessment of the core aspects of craving, taking into account different time frames and emphasizing the psychophysiological aspects of craving. It is hypothesized that this questionnaire will show higher concordance with measures of physiological cue reactivity than existing self-report craving questionnaires.

METHODS: Based on a semantic mapping sentence, a 24-item self-report questionnaire was developed: the Jellinek Alcohol Craving Questionnaire (JACQ). The questionnaire was tested in 2 samples of treatment-seeking alcohol-dependent patients (sample A: n=251; sample B: n=48). Psychometric properties were examined in sample A and cross-validated in sample B. The association with psychophysiological and neuroendocrine measures of cue reactivity were studied in sample B.

RESULTS: The JACQ consists of 1 dimension with the following 4 aspects: (1) emotional urge, (2) physical sensations, (3) temptation to drink, and (4) uncontrolled thoughts. All (sub)scales had a good internal consistency (α=0.77-0.95), and were highly intercorrelated (r=0.57-0.86). Craving in the past correlated low with craving now (r=0.32). Craving-now (sub)scales were moderately associated with heart rate (0.46-0.49), but not with respiration rate, skin conductance or cortisol production in saliva following cue exposure. In contrast, craving-past (sub)scales were moderately associated with cortisol production in saliva (0.15-0.42) following cue exposure. Remarkably, the physical symptoms scale was not stronger associated with psychophysiological and neuroendocrine measures than the other subscales.

CONCLUSIONS: The JACQ reliably measures 1 dimension including 4 aspects of craving for distinct time frames. Despite the presence of a special subscale for physical sensations, only moderate relationships were found between self-reported craving and biological indicators of cue reactivity. These findings suggest individual differences between alcoholics in the detection and/or reporting of cue-related psychophysiological signs as indicators of cue reactivity. Further re-
search should focus on the nature of these individual differences. In addition, more research is needed on the relative predictive validity of subjective phenotypic indicators of craving (such as self-reported craving) versus objective endophenotypic indicators of craving (such as physiological measures of cue reactivity) for example in the prediction of relapse.

**Introduction**

Craving is a core feature of alcoholism that can persist for months after the last alcohol intake (Mathew et al., 1979). In addition, craving is believed to play a crucial role in the development of alcohol dependence (Ludwig et al., 1974; Robinson and Berridge, 1993; Wise, 1988). There is also evidence that better insight in the mechanism of craving will contribute to the treatment of alcoholism (Drummond et al., 1995; Littleton, 1995; Volpicelli et al., 1992), e.g., the development of more efficient relapse prevention strategies such as the development of anti-craving medications (O’Brien, 2005).

Craving mainly refers to the desire or urge to reexperience the effect of a previously experienced psychoactive substance (UNDCP/WHO, 1992). Despite the simplicity of this definition, several theoretical models of craving have been developed (e.g., Kozlowski and Wilkinson, 1987; Pickens and Johanson, 1992; Rankin et al., 1979). In addition, there is no consensus on the role of self-reported craving in the processes underlying reinstatement of alcohol use after a period of abstinence (relapse). In fact, published correlations between self-reported craving and relapse are inconsistent (Rohsenow and Monti, 1999). Some studies found a positive correlation (e.g., Anton et al., 1999; Bottlender and Soyka, 2004; Cooney et al., 1997; Roberts et al., 1999), whereas others did not find a relation (Rohsenow et al., 1994) or have questioned the ability of subjective craving to predict relapse (e.g., Tiffany, 1990; Kranzler et al., 1999; Van den Brink, 1997). These findings have raised questions regarding the validity of currently existing self-report measures of craving, and underscore the need for a novel measure of subjective craving. Three interrelated reasons have been mentioned for the existing difficulties in measuring craving as follows: (1) lack of consensus regarding the definition, (2) use of various time frames, and (3) lack of data on the biological aspects of craving.

First, various definitions of craving have been suggested. For example, craving has been hypothesized to arise either from the positive-reinforcing properties of the drug (Marlatt, 1985; Niaura et al., 1988; Wise, 1988), from negative-reinforcing properties (Ludwig and Wikler, 1974; Poulos et al., 1981; West and Schneider, 1987), or from both positive and negative reinforcement (Baker et al., 1986; Heinz et al., 2003; Verheul et al., 1999). Alternatively, some authors have argued that
craving is independent of reinforcement mechanisms (e.g., Robinson and Berridge, 1993), but is instead related to neural sensitization. Finally, there is some evidence that a cognitive account may be more appropriate (Tiffany, 1990; Anton et al., 1995). Instruments for the assessment of craving typically focus on specific aspects of subjective craving. For example, the Obsessive Compulsive Drinking Scale (OCDS) primarily focuses on the cognitive correlates of craving, while other craving questionnaires, such as the Alcohol Urge Questionnaire (AUQ) (Bohn et al., 1995) and the Alcohol Craving Questionnaire (ACQ) (E.G. Singleton et al., unpublished work, 1994; Singleton et al., 1994) primarily focus on the emotional aspects of craving. Most authors agree that craving possesses both cognitive and emotional aspects. Most authors also agree that physiological reactions (e.g., heart rate (HR), skin conductance) are part of the craving concept and that these reactions do occur in response to alcohol-related cues (Niaura et al., 1988). However, psychophysiological aspects of craving are absent in all currently available questionnaires on craving.

The second problem is the time frame of craving measures. 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 et al., 2002). For example, the AUQ (Bohn et al., 1995) and the ACQ (E.G. Singleton et al., unpublished work, 1994; Singleton et al., 1994) measure craving-now, whereas the OCDS (Anton et al., 1995, 1996) measures craving-past during the last week. The comparison between craving-past and craving-now is hampered by the fact that these questionnaires show only partial conceptual overlap. To date, no questionnaire measures craving over various time frames.

The third problem is the lack of concordance between psychophysiological reactions to alcohol-related stimuli (physiological cue reactivity) and the various self-report measures of craving. Several studies have demonstrated physiological reactions in response to alcohol-related cues in alcoholic persons (e.g., Cooney et al., 1997; Niaura et al., 1988). However, the correlations between physiological cue reactivity and subjective craving have always been rather low (the average of all correlations, regardless of sign, is 0.38; Tiffany, 1990). This lack of concordance weakens theories on craving that claim conditioned physiological responses to be the most important substrate for craving (e.g., Ludwig et al., 1974). An explanation may be that concordance of physiological cue reactivity and subjective craving is only present in a subgroup of alcoholic persons (Verheul et al., 1999). Alternative explanations are the wide array of time frames used in the studies or the lack of physical aspects of craving in the available self-report questionnaires.

The first aim of the study is to develop and evaluate the psychometric properties of the Jellinek Alcohol Craving Questionnaire (JACQ), taking into account
Measuring craving

the following: (1) the core aspects of craving, (2) the general and instant aspects of craving and (3) the physiological aspects of craving. It is hypothesized that the JACQ will outperform other craving measures in terms of the association with psychophysiological and neuroendocrine measures of cue reactivity, as the JACQ is the only measure that includes a special scale for the subjective assessment of psychophysiological symptoms.

Materials and Methods

QUESTIONNAIRE DEVELOPMENT

Following a review of the published literature on instant and general craving, a pool of 129 items was created (a list with the complete pool of 129 items can be obtained from the corresponding author). A set of 79 craving items was compiled by removing overlapping items and items measuring constructs other than craving (e.g., items about actual consumption of alcohol; see also Schippers et al., 1997).

These craving items were then allotted to the various craving subscales. In this process of item allocation, a semantic mapping sentence with 3 facets was used (Roskam, 1989). The semantic sentence is shown in Figure 1. It is based on the following 3 facets: (1) frequency or intensity of the craving experience; (2) core aspects of craving; and (3) time frame.

Primarily based on the second facet, a matrix was constructed, with a core aspect of craving in each of the 4 cells as follows: feelings of urge, physical sensations, temptation to actual drinking, and uncontrolled reoccurring thoughts. All 79 items were placed in one of these quadrants. All nonrepresentative items and items that did not map with the semantic sentence were excluded. The remaining items were then judged on clarity and ambiguity. Finally, based on consensus be-
between 2 of the authors (W.O. and R.V.), 9 items were selected per cell. Each cell of 9 items included 3 negatively formulated and 6 positively formulated items. The order of statements was determined randomly. In the last step, a ‘past’ version (JACQ-past) and a ‘now’ version (JACQ-now) were constructed. For sample B, the JACQ-now version instructed the subjects to rate their craving when an alcohol cue was actually presented, whereas in sample A (no cue-exposure paradigm) the subjects were instructed to imagine that there was alcohol in front of them. The time frame of JACQ-past was defined as the past period in which the subject drank alcohol on a regular basis before admission to treatment. It must be noted that the response categories for the JACQ-past relate to the frequency of a craving experience and that the response categories for the JACQ-now relate to the intensity of a craving experience. The rationale for this is that, in this study, craving-past is conceptualized as a behavioral tendency with a certain frequency over a certain period of time, whereas craving-now is seen as a momentary experience of certain strength. In a first pilot, the negatively formulated items appeared to be too difficult for subjects to answer properly (cf. Raabe et al., 2005). As several subjects asked for help of the investigator, and as conversion into positive items would have been redundant, we decided to ignore the negative items, leaving 24 items for further analysis (see Appendix).

SUBJECTS
Two samples of alcohol-dependent patients were used for the development and validation of the JACQ. A large, heterogeneous sample (A) with inpatients and outpatients from 4 different alcohol treatment centers in the Netherlands (Jellinek, Boumanhuis, Kuno van Dijk Stichting, Parnassia) was used for the development and investigation of the psychometric properties of the JACQ. A smaller sample (B), which was recruited from the Jellinek addiction treatment center in Amsterdam, was used for cross-validation of the JACQ and for the study of the relation between subjective craving and objective cue reactivity.

All subjects had a primary diagnosis of alcohol dependence and were undergoing treatment. They were required to have abstained from heavy drinking (≥ 5 units) for a week (minimum) to 6 months (maximum), in order to attain adequate recollection of their subjective experiences. Exclusion criteria were comorbid cocaine or heroin dependence, cocaine or heroin use in the last 30 days before admission, current psychosis, current use of antipsychotics, current use of the anti-craving compounds naltrexone and acamprosate, current use of disulfiram, severe cognitive deficits, and insufficient command of the Dutch language.

A total of 495 subjects (sample A) and 123 subjects (sample B) were screened. Eighty (sample A) and 40 (sample B) subjects refused participation, and 107 (sample A) and 30 subjects (sample B) fulfilled the exclusion criteria, leaving 308
participants in sample A and 53 in sample B. A total of 251 of 308 (81.5 %) (sample A) and 48 of 53 (90.6 %) (sample B) completed all questionnaires at baseline. A subgroup of 34 subjects in sample A was asked to self-administer the craving questionnaires twice within a 3 week interval in order to assess test-retest reliability. In a subgroup of 41 sample B subjects, psychophysiological and endocrine cue reactivity was assessed during a cue-exposure challenge. Of these, 39 subjects had a full data set (including 6 women).

**Measuring craving**

All subjects in sample A and B self-administered a set of self-report questionnaires directly after their inclusion in the study, and received vouchers of 12.50 Euro (ca. 15$) after completion. Whereas sample A was not assigned to any further research, sample B was prepared for a cue-exposure challenge. Based on a Drinking Triggers Interview (Monti et al., 1993a) and the Inventory of Drinking Situations (IDS) (Annis et al., 1987), individualized audiotaped mood induction scripts were prepared for all subjects in sample B, using procedures developed by Cooney et al. (1991). The aim of the script was to induce the mood in which physiological the subject was most likely to experience craving. Within 1 week after the interview, every subject in sample B was exposed to a cue-exposure challenge, in which physiological cue reactivity and craving scores were measured. The assessment was based on procedures developed by other investigators (e.g., Cooney et al., 1997; Monti et al., 1993b). At the onset of the session, subjects were seated in a comfortable chair, connected to electrodes and acclimatized for 30 minutes. After assessment of subjective pretest anxiety, each subject was then asked to relax for 3 minutes. During these 3 minutes of rest, psychophysiological measures were continuously recorded. The subject’s favorite beverage was then brought into the room and poured in the glass in front of the subject. While the pre-recorded mood-induction script was played over the headphone for 4 minutes, the subject was instructed to sniff the beverage 4 times during the script (at the first, second, third, and fourth minute). During these 4 minutes of cue exposure, subjective craving was assessed by three 11-point visual analogue scales (VAS) (1 in the first minute and 2 in the fourth minute), and psychophysiological measures were continuously recorded. At the end of exposure, the JACQ-now was filled out before bringing the participant back to a relaxed state.

**Measures**

**Self-report measures**

All participants completed the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 1992). Alcohol Use Disorders Identification Test scores can
range from 0 to 40, and the generally accepted cut off point for identifying a potential alcohol problem is 8. In order to estimate convergent validity of the JACQ, the ACQ-now (E.G. Singleton et al., unpublished work, 1994; Singleton et al., 1994), and the OCDS (Anton et al., 1996; Dutch revised version by Schippers et al., 1997) were completed in sample A. In sample B, 3 VAS (containing the question: “How strong is your urge or need to drink right now?”) were filled out.

All participants in sample B completed 2 scales of the JACQ-now, i.e., the urge and the physical scale. All participants also completed some assessments in order to estimate the divergent validity of the JACQ: the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970), and the Mood Adjective Checklist (MACL) (Mackay et al., 1978). In addition they completed an adapted version of the Betts Mental Imagery Questionnaire (BMIQ) (Sheehan, 1967). On a 7-point scale, ranging from ‘No image present at all, just thinking of it’ (1) to ‘Perfectly clear and as vivid as the actual experience’ (7), they could indicate the vividness of their imagery.

Physiological and endocrine reactivity measures
In sample B, the following physiological measures were continuously recorded during the cue-exposure challenge: (1) heart rate (HR); (2) respiration rate (RR); (3a) skin conductance level (SCL); (3b) skin conductance response (SCR); and (4) cortisol production in saliva.

Heart rate and skin conductance were recorded because they had previously been demonstrated to be responsive to alcohol-related cues (e.g., Cooney et al., 1997; Kaplan et al., 1985). We therefore predicted to find a positive correlation between subjective craving and increase in HR and SCL. In addition to mean values of heart rate and skin conductance, Δ peak values were calculated, since subjects may peak at different moments in time and mean values may then mask the effect. Since craving has been associated with negative mood and stress (e.g., Cooney et al., 1997) and since a cortisol response of the hypothalamic-pituitary-adrenal (HPA) axis can be induced by psychological distress (Kirschbaum et al., 1995), we expected to find a positive correlation between Δ peak cortisol and subjective craving.

For heart rate assessment, ECG (electrocardiogram) electrodes were placed on either side of the participant’s chest. A Contact Precision Instruments analogue-digital converter (ADC) sampled the ECG signal at a rate of 300 Hz and calculated the number of interbeat intervals during 10s sampling periods (range 2mV, high pass 10Hz, low pass 200Hz).

Respiration rate was measured by counting breathing waves, with a Contact Precision Respiration coupler and RSG transducer (UFI Pneumotrace), connected to a SAM 16-bit resolution ADC data acquisition unit. Range was set to
Measuring craving

320 mV, with a high-pass filter 0.1 Hz, and a low-pass filter 30 Hz. A breath wave was defined as a positive fluctuation with amplitude above 64 mV (20% of full range). Rate was calculated by counting the number of detected waves in given time epochs throughout the record and expressed as breaths per minute.

For skin conductance assessment, electrodes were taped to the middle phalanx of the forefinger and the middle finger of the participant’s nondominant hand. The skin conductance signal was amplified by a Contact Precision Instruments skin conductance coupler, sampled at a fixed value of 40 Hz. Skin conductance level and response counts were averaged across a 10 s sampling period. The response criterion for SCR was an increase of 0.0015625 µS.

Cortisol was measured in saliva and sampled 7 times during the cue-exposure session. One sample was taken 5 minutes before the start of the cue exposure and 6 samples were taken 15, 20, 25, 30, 35 and 40 minutes after start of the cue exposure, respectively. Saliva was collected using Sarstedt salivettes with a dental cotton roll, frozen at –20 °C and cortisol analyses were performed at the Department of Psychology, TU Dresden, Germany, (Laboratory of Clemens Kirschbaum) using a commercial immunoassay with chemiluminescence detection. The lower sensitivity of the assays is 0.44 nmol/l, intraassay and interassay coefficients of variation are less than 10%.

Statistical analysis
Simultaneous components analysis (SCA) was used to assess whether JACQ scores of the now and past version in sample A have a common factor structure. In addition, we defined (theoretical) factors as the unweighted sum scores of the items comprising our theoretical scales. By definition the SCA factors will account for a larger proportion of variance than the theoretical factors (since SCA uses a statistical optimization criterion). However, this does not mean that our theoretical factors might not account for almost the same amount of variance. In the latter case, we will prefer the theoretical scales. Interscale correlations were calculated using Pearson correlations. Test-retest reliability was estimated by the intraclass correlation coefficient (ICC).

Cortisol responses (Δ peaks) were calculated by subtracting the mean baseline value (sample 1a and 1b were regarded as baseline values since it takes approximately 15 to 25 minutes after the cue before the cortisol reaction becomes apparent) from the highest cortisol value after cue exposure. For HR, RR and skin conductance, Δ peaks were calculated by subtracting the average of the last minute of the baseline period from the maximal value during the 4-minute cue exposure. Significance was tested at the 0.05 level for sample A, and at 0.10 for sample B since the test of the latter sample had limited power due to the relatively small sample size. High-craving and low-craving subjects were defined by a median
split on the JACQ-now and JACQ-past total scores. Differences in \( \Delta \) peak of all parameters between the high-craving and low-craving group were assessed with ANCOVAs with the \( \Delta \) peak value as a dependent variable and mean basal value as the covariate.

**Results**

**SAMPLE CHARACTERISTICS**

Table 1 shows that most study participants were Dutch, male, low educated, unemployed, and unmarried. In sample A most patients were inpatients (77.7\%), whereas in sample B 45.8\% were inpatients and 54.2\% were outpatients. As the high AUDIT scores show, almost all subjects had a severe alcohol problem. In addition, all subjects had a DSMIV diagnosis of alcohol dependence. The mean number of days without heavy drinking was 34 days (SD 40).

**Table 1.** Patient characteristics at baseline for samples A and B.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Sample A (n=251)</th>
<th>Sample B (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>45 (9)</td>
<td>43 (9)</td>
</tr>
<tr>
<td>% Men</td>
<td>67.3</td>
<td>83.3</td>
</tr>
<tr>
<td>% Dutch ethnicity</td>
<td>83.3</td>
<td>77.1</td>
</tr>
<tr>
<td>% Inpatients</td>
<td>77.7</td>
<td>45.8</td>
</tr>
<tr>
<td>% Higher education</td>
<td>19.2</td>
<td>28.9</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>12.1 (3.6)</td>
<td>12.3 (3.7)</td>
</tr>
<tr>
<td>% Employed</td>
<td>44.1</td>
<td>31.1</td>
</tr>
<tr>
<td>% Married</td>
<td>22.6</td>
<td>8.5</td>
</tr>
</tbody>
</table>

**Alcohol-related variables**

| Mean AUDIT score (SD)         | 30.3 (6.3)       | 30.6 (5.0)      |
| Mean age of onset (SD)        | 32.6 (10.5)      | 32.3 (10.4)     |

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test.
As a first step, all positive JACQ items of the now and past version in sample A were subjected to SCA. Simultaneous components analysis was conducted in order to find a common factor structure in the ‘now’ and ‘past’ version of the JACQ, resulting in 2 versions of the JACQ with the same items and the same scales. Simultaneous components analysis resulted in four distinct components that were very similar to the aspects of our theoretical model and accounted for 66.3% of the variance. In another SCA analysis, our theoretical model accounted for a similar percentage of the total variance (65.0%). Internal consistency of both the total score of the JACQ-now and the JACQ-past was high (α=0.96 and α=0.95 respectively). For the exploratory SCA factor solution as well as for our theoretical SCA factor solution, internal consistency of the subscales was good and varied between 0.77 and 0.93. Since the accounted variance and internal consistency of the SCA (sub)scales were very similar to those of the theoretical scales, it was decided to use the (confirmed) theoretical model (subscales) for further analysis.

Table 2 shows that the interscale correlations were rather high for both JACQ-now (r=0.77-0.86) and JACQ-past (r=0.57-0.83) with the lowest correlations between the physical subscale and the emotional subscale (r=0.65) and between the physical subscale and the temptation subscale (r=0.57) of the JACQ-past. Given the high interscale correlations, it was questioned whether the JACQ actually measures 4 dimensions. In order to explore this, principal component analysis was performed (data not shown). The scree-plot suggested the presence of only

<table>
<thead>
<tr>
<th></th>
<th>urge</th>
<th>phy</th>
<th>temp</th>
<th>cogn</th>
<th>JACQ-past</th>
</tr>
</thead>
<tbody>
<tr>
<td>urge</td>
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<tr>
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<tr>
<td>cogn</td>
<td>0.86</td>
<td>0.77</td>
<td>0.77</td>
<td></td>
<td>0.92</td>
</tr>
</tbody>
</table>

Above diagonal: interscale-correlations JACQ-past; below diagonal: JACQ-now.
Abbreviations: urge, urge; phy, physical reactions; temp, temptation to drink; cogn, uncontrolled thoughts; JACQ, Jellinek Alcohol Craving Questionnaire.
All Pearson correlations are significant at the 0.01 level (two-tailed).
one underlying factor that explained 55.6% of the variance for the JACQ-now and 48.8% for the JACQ-past.

**Relation Between the JACQ-Now and JACQ-Past**

In order to investigate the relation between craving in the past (general craving) and craving in the present (instant craving), Pearson correlations were calculated between the scales of JACQ-past and JACQ-now. For sample A, the total score of the JACQ-past correlated only $r=0.32$ with the total score of the JACQ-now ($p<0.01$). Table 3 shows that subscale correlations were also rather low (range 0.19-0.40; highest correlation between the physical subscales of the JACQ-past and the JACQ-now).

**Table 3. Correlations between scales of JACQ-past and JACQ-now for sample A (n=251).**

<table>
<thead>
<tr>
<th></th>
<th>urge-now</th>
<th>phy-now</th>
<th>temp-now</th>
<th>cogn-now</th>
<th>JACQ-now</th>
</tr>
</thead>
<tbody>
<tr>
<td>urge-past</td>
<td>0.19</td>
<td>0.28</td>
<td>0.21</td>
<td>0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>phy-past</td>
<td>0.20</td>
<td>0.40</td>
<td>0.27</td>
<td>0.30</td>
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</tr>
<tr>
<td>temp-past</td>
<td>0.19</td>
<td>0.28</td>
<td>0.24</td>
<td>0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>cogn-past</td>
<td>0.23</td>
<td>0.33</td>
<td>0.26</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>JACQ-past</td>
<td>0.23</td>
<td>0.37</td>
<td>0.28</td>
<td>0.31</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Abbreviations: urge, urge; phy, physical reactions; temp, temptation to drink; cogn, uncontrolled thoughts; JACQ, Jellinek Alcohol Craving Questionnaire.
All Pearson correlations are significant at the 0.01 level (2-tailed).

**Test-Retest Reliability (n=34)**

For sample A, test-retest reliability of JACQ-past was performed in 34 subjects. The (single measure) ICC for JACQ-past was 0.87, indicating excellent test-retest reliability. The ICCs for the subscales of JACQ-past were also high, ranging from 0.76 to 0.88.

**Relation Between JACQ and OCDS, ACQ-Now and VAS**

In order to estimate convergent validity, JACQ-now and JACQ-past scores were correlated with scores on the OCDS and scores on the ACQ-now in sample A.
Measuring craving

For the OCDS, we used the obsessive and the compulsive subscales presented by Anton et al. (1995). In addition, we used the ‘actual craving’ subscale of the OCDS that was recently proposed by De Wildt et al. (2005), including only OCDS items 1, 2, 4, 5 and 13. For the ACQ-now standard subscales were used.

Table 4a shows that the JACQ-now total score was only moderately correlated with the obsessive, compulsive and ‘actual craving’ OCDS subscales (r=0.57, r=0.61, and r=0.56 respectively). For the JACQ-past, correlations with the OCDS were even lower (r=0.28, r=0.26, and r=0.26 respectively). In contrast to the OCDS, the ACQ-now was highly correlated with all (sub)scales of JACQ-now (r=0.77-0.87).

In sample B, the mean craving score of 3 VAS ratings during cue exposure was highly correlated with the JACQ-now (r=0.79; p<0.01). As expected, the highest correlation with mean VAS score was found for the JACQ-now subscale ‘urge’ since the items are very similar (r=0.84, p<0.01; see Table 4b).

Table 4a. Convergent validity of sample A (n=251): correlations between JACQ and OCDS, JACQ and ACQ.

<table>
<thead>
<tr>
<th></th>
<th>urge-</th>
<th>phy-</th>
<th>temp-</th>
<th>cogn-</th>
<th>JACQ-</th>
<th>urge-</th>
<th>phy-</th>
<th>temp-</th>
<th>cogn-</th>
<th>JACQ-</th>
</tr>
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<tbody>
<tr>
<td>OCDS</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>comp</td>
<td>0.57</td>
<td>0.53</td>
<td>0.54</td>
<td>0.59</td>
<td>0.61</td>
<td>0.23</td>
<td>0.23</td>
<td>0.17</td>
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<tr>
<td>obsess</td>
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<td>0.50</td>
<td>0.59</td>
<td>0.57</td>
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<td>actual</td>
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<td>0.54</td>
<td>0.62</td>
<td>0.62</td>
<td>0.24</td>
<td>0.24</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>desire</td>
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<td>0.77</td>
<td>0.78</td>
<td>0.86</td>
<td>0.22</td>
<td>0.19</td>
<td>0.21</td>
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<tr>
<td>intent</td>
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<td>0.73</td>
<td>0.82</td>
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<tr>
<td>a-pos</td>
<td>0.79</td>
<td>0.64</td>
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<td>0.65</td>
<td>0.76</td>
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<td>0.10</td>
<td>0.19</td>
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<td>a-neg</td>
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<td>0.75</td>
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<td>0.29</td>
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<tr>
<td>control</td>
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<td>total</td>
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<td>0.77</td>
<td>0.83</td>
<td>0.77</td>
<td>0.87</td>
<td>0.29</td>
<td>0.20</td>
<td>0.31</td>
<td>0.30</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Abbreviations: OCDS, Obsessive Compulsive Drinking Scale; ACQ, Alcohol Craving Questionnaire; comp, compulsions; obsess, obsessions; desire, urges and desires to use alcohol; intent, intent to use alcohol; a-pos, anticipation of positive outcome; a-neg, anticipation of relief from withdrawal or negative outcome; control, lack of control over use; JACQ, Jellinek Alcohol Craving Questionnaire.

All Pearson correlations are significant at the 0.01 level (2-tailed).
CHAPTER 4

RELATION AMONG JACQ AND AUDIT, STAI AND MACL

In order to test the divergent validity of the JACQ further, in sample B, all scales of JACQ-now and JACQ-past were correlated with AUDIT scores, subjective pretest stress levels (STAI) and cue-induced mood (MACL) (see Table 4b). Jellinek Alcohol Craving Questionnaire-now showed a high correlation with MACL-stress ($r=0.75$, $p<0.01$) and a moderate correlation with STAI ($r=0.53$, $p<0.001$), moderate negative correlation with MACL-arousal ($r=-0.36$, $p<0.05$), and a moderate correlation with the AUDIT ($r=0.27$, $p<0.10$). In contrast, JACQ-past scores showed a high correlation with AUDIT scores ($r=0.61$, $p<0.01$), a moderate correlation with MACL-stress ($r=0.37$, $p<0.05$) and STAI ($r=0.31$, $p<0.10$), and an insignificant correlation with MACL-arousal.

Table 4b. Convergent and divergent validity of sample B ($n=48$): correlations between JACQ and VAS, AUDIT, STAI, MACL.

<table>
<thead>
<tr>
<th>VAS</th>
<th>urge-now</th>
<th>phy-now</th>
<th>JACQ-now</th>
<th>urge-past</th>
<th>phy-past</th>
<th>temp-past</th>
<th>cogn-past</th>
<th>JACQ-past</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>0.84***</td>
<td>0.67***</td>
<td>0.79***</td>
<td>0.19</td>
<td>0.10</td>
<td>0.28</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>max</td>
<td>0.79***</td>
<td>0.65***</td>
<td>0.76***</td>
<td>0.14</td>
<td>0.11</td>
<td>0.26</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>AUDIT</td>
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<td>0.27*</td>
<td>0.27*</td>
<td>0.60***</td>
<td>0.57***</td>
<td>0.45***</td>
<td>0.61***</td>
<td>0.61***</td>
</tr>
<tr>
<td>STAI</td>
<td>0.50***</td>
<td>0.52***</td>
<td>0.53***</td>
<td>0.28*</td>
<td>0.26</td>
<td>0.26</td>
<td>0.32**</td>
<td>0.31*</td>
</tr>
<tr>
<td>MACL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stress</td>
<td>0.71***</td>
<td>0.73***</td>
<td>0.75***</td>
<td>0.29*</td>
<td>0.38**</td>
<td>0.34**</td>
<td>0.30*</td>
<td>0.37**</td>
</tr>
<tr>
<td>arousal</td>
<td>-0.37**</td>
<td>-0.31**</td>
<td>-0.36**</td>
<td>-0.23</td>
<td>-0.05</td>
<td>-0.25</td>
<td>-0.22</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

Abbreviations: JACQ, Jellinek Alcohol Craving Questionnaire; VAS, Visual Analog Scales; AUDIT, Alcohol Use Disorders Identification Test; STAI, Spielberger State-Trait Anxiety Inventory; MACL, Mood Adjective Checklist.
*Correlation is significant at the 0.1 level.
** Correlation is significant at the 0.05 level.
*** Correlation is significant at the 0.01 level.
The second aim of the study was to find a higher correlation between subjective craving and psychophysiological cue reactivity compared with other craving measures. First, the urge and physical scales of the JACQ-now, which could be filled out quickly during a cue-exposure challenge, were selected. Mood induction was successful with 90.2% of the patients having a score of 4 or higher on the BMIQ.

All psychophysiological parameters (HR, RR, SCL, SCR) were continuously recorded during baseline and cue exposure. It was expected to find a significant cue-induced increase for all parameters in line with previous findings. As expected, for all parameters, a significant increase was found for cue-exposure values compared to baseline values (paired t-test, \( p < 0.05 \)) (see Figure 2a and 2b for the results of HR and SCL). It should be noted that \( \Delta \) peak scores showed even greater effects of cue exposure than suggested by the mean values in the graphs (e.g., the mean \( \Delta \) peak for HR is 11.6 bpm and the mean \( \Delta \) peak for skin conductance level is 0.69 \( \mu \)S).

Although Pearson correlations between \( \Delta \) peaks and JACQ-now and JACQ-past were not significant for physiological parameters SCR, SCL, and RR, moderately positive correlations were found between JACQ-now and HR (\( r = 0.49, p < 0.01 \)) and between the physical scale of the JACQ-past and HR (\( r = 0.31, p < 0.10 \)) (see Table 5). In addition, significant correlations were found between \( \Delta \) peak HR and the stress scale of MACL (\( r = 0.40, p < 0.05 \)), and between \( \Delta \) peak SCL and the stress scale of MACL (\( r = 0.28, p < 0.1 \)). No correlations were found with pretest stress or dependence severity.

Inspection of the scatterplots showed that subjects with no objective cue reactivity (according to HR, RR, SCL, SCR) almost never reported subjective craving, whereas only part of the subjects with objective cue reactivity reported subjective craving (data not shown).

Finally, differences in physiological responses between high-craving and low-craving subjects were estimated by median split on JACQ-now. Using t-tests, there were no significant differences between high-craving and low-craving subjects with respect to baseline values of HR, RR, or SCR. However, the mean baseline levels of skin conductance (SCL) were significantly higher in low craving subjects (\( p < 0.05 \)).

Analyses of covariance were applied for the \( \Delta \) peak of each parameter, in which the baseline value of each parameter was used as a covariate. No significant differences were found between high-craving and low-craving subjects for SCL and SCR. However, a significant between-subjects effect was found for HR.
Figure 2. (A) Mean heart rate during a cue-exposure experiment in sample B (n=41). Error bars show mean ±1.0 SE. (B) Mean skin conductance during a cue-exposure experiment in sample B (n=41). Error bars show mean ±1.0 SE.
Measuring craving

Table 5. Correlations between JACQ scales and endocrinological and physiological measures (n=39).

<table>
<thead>
<tr>
<th>n=39</th>
<th>urge-now</th>
<th>phy-now</th>
<th>JACQ-now</th>
<th>urge-past</th>
<th>phy-past</th>
<th>temp-past</th>
<th>cogn-past</th>
<th>JACQ-past</th>
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</thead>
<tbody>
<tr>
<td>cortisol Δ peak</td>
<td>0.16</td>
<td>0.21</td>
<td>0.19</td>
<td>0.32*</td>
<td>0.30*</td>
<td>0.42*</td>
<td>0.15</td>
<td>0.33*</td>
</tr>
<tr>
<td>HR Δ peak</td>
<td>0.48**</td>
<td>0.46**</td>
<td>0.49**</td>
<td>0.17</td>
<td>0.31*</td>
<td>0.16</td>
<td>0.09</td>
<td>0.22</td>
</tr>
<tr>
<td>RR Δ peak</td>
<td>-0.15</td>
<td>-0.00</td>
<td>-0.09</td>
<td>0.02</td>
<td>0.13</td>
<td>-0.10</td>
<td>-0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>SCR Δ peak</td>
<td>-0.13</td>
<td>-0.07</td>
<td>-0.11</td>
<td>0.04</td>
<td>0.01</td>
<td>0.03</td>
<td>-0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>SCL Δ peak</td>
<td>0.15</td>
<td>0.05</td>
<td>0.11</td>
<td>0.09</td>
<td>0.22</td>
<td>0.09</td>
<td>0.19</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Abbreviations: HR, heart rate; RR, respiration rate; SCR, skin conductance response; SCL, skin conductance level; JACQ, Jellinek Alcohol Craving Questionnaire.
* Correlation is significant at the 0.1 level.
** Correlation is significant at the 0.05 level.

(p<0.05) and RR (p<0.1), with higher Δ peak HR and RR in high-craving subjects.

Relation between JACQ and Cortisol

Cortisol response was defined as a 15% increase relative to baseline with a minimum of 2.5 nmol/l. Only 6 of the 39 subjects (15.4%) showed a response of the HPA axis. Mean JACQ-past scores of the cortisol responders were significantly higher than those of cortisol nonresponders (120.4 versus 99.3; p<0.05). In addition, cortisol responders had slightly higher scores on the subscale 'physical sensations' of JACQ-now (p<0.10). Scores on AUDIT, STAI or MACL were not significantly different for cortisol responders compared with nonresponders.

No significant correlations were found between Δ peak cortisol and JACQ-now. However, a positive correlation was found between the JACQ-past and Δ peak cortisol (r=0.33, p<0.1). The highest correlation was found between subscale 'temptation to actual drinking' and Δ peak cortisol (r=0.42, p<0.01) (see Table 5). Independent t-tests and ANCOVAs were used in order to investigate differences between high-craving subjects (n=21) and low-craving subjects (n=18) for cortisol baseline and cortisol Δ peaks, AUDIT scores, STAI scores (pretest
stress) and MACL scores. Using independent $t$-tests, no differences were found in basal cortisol levels between high-craving and low-craving subjects. The high-craving group included significantly more unmarried inpatients, had higher AUDIT scores and pretest-stress levels ($p<0.05$), but also had higher subjective stress levels after exposure than the low-craving group ($p<0.01$).

In the final step, ANCOVAs were conducted to investigate differences in $\Delta$ 

![Figure 3](image_url)

**Figure 3.** (A) Mean cortisol values for low-craving (left graph) and high-craving subjects (right graph). Definition of the HC group ($n=21$) and LC group ($n=18$) is based on split half of Jellinek Alcohol Craving Questionnaire (JACQ)-short. Error bars show mean ±1.0 SE. (B) Mean cortisol values for low-craving (left graph) and high-craving subjects (right graph). Definition of the HC group ($n=22$) and LC group ($n=16$) is based on split half of JACQ-past. Error bars show mean ±1.0 SE.
peak cortisol between high-craving and low-craving subjects, using the mean baseline cortisol value as a covariate for each parameter (see Figure 3a and 3b). No significant between-subjects effect was found when high-craving and low-craving subjects were defined by the JACQ-now. However, a significant between-subjects effect was found on using JACQ-past ($p<0.05$), indicating that high craving experiences in the past correlate with cortisol $\Delta$ peak.

**Discussion**

In summary, the JACQ appeared to measure 4 distinct aspects of craving, with good internal consistencies and high interscale correlations. General craving showed a low correlation with instant craving. Instant craving had a moderately high association with HR and RR, and general craving had a moderate association with cortisol response. In contrast to our expectations, the physical craving subscale had only a moderate association with psychophysiological indicators of cue reactivity.

The JACQ-now and the JACQ-past appeared to be questionnaires with high interscale correlations. It is therefore questionable whether the concept of craving consists of independent dimensions. The results suggest that the various aspects of craving are empirically highly interrelated, including the self-reported aspect of physiological sensations, which is in contrast with what we predicted. The data suggest that craving exists of one single factor with 4 distinct aspects. In addition to high internal consistencies, the JACQ-past showed excellent test-retest reliability, suggesting that the JACQ-past is a reliable questionnaire.

There was a low correlation between JACQ-now and JACQ-past, suggesting that there is a limited overlap between the constructs of craving-past and craving-now. An alternative explanation for the lack of concordance might be that craving frequency (as measured by the JACQ-past) and craving intensity (as measured by the JACQ-now) are 2 distinct phenomena. This might also explain why most self-report questionnaires on craving-past are not predictive for relapse. Apparently, the trait (craving-past) does not predict the state (craving-now) and may therefore not predict relapse. It would be interesting to study this issue in future research.

The ACQ showed a high correlation with the JACQ-now, which may be due to overlapping items. In contrast, the JACQ-now showed only a moderate correlation with the OCDS and JACQ-past showed only a poor correlation. This finding might be accounted for by the fact that (1) the OCDS primarily consists of cognitive items on alcohol-related obsessions and compulsions and (2) the OCDS measures craving in a different time frame (last week). In line with this, the cognitive subscale of the JACQ showed the highest correlation with the OCDS (see
Table 4a). Consistent with the predictions, craving scores of the JACQ-now showed a significant correlation with the stress scale of STAI. This finding suggests that the level of subjective pretest stress is a predictor of cue-induced craving. In addition, JACQ-now showed a high positive correlation with the stress scale of the MACL, which suggests that stress and craving are highly interrelated phenomena. Furthermore, the JACQ-now was inversely associated with the arousal scale of the MACL, representing a negative association with feelings of alertness, activity or energy after cue exposure. In contrast, JACQ-past showed only a modest correlation with STAI and MACL, but a highly significant one with AUDIT scores, suggesting that the frequency of craving in the past correlates with dependence severity. We do not know whether this is due to the distinct characteristics or predictive values of craving intensity and craving frequency, or the difference in the time frame of these questionnaires.

In general, correlations between physiological cue reactivity and subjective craving have always been rather low (Tiffany, 1990). The average correlation coefficient ranged from $r=0.38$ (if negative correlations were allowed) to $r=0.52$ (if negative correlations were excluded). In an attempt to find a higher correlation than previous studies in the literature, we explicitly included a subjective physical component in the JACQ-now. However, although the $\Delta$ peak HR showed a moderate positive correlation of 0.49 with the JACQ-now, the JACQ-now did not show a significantly higher correlation than in previous studies with other indicators of physiological cue reactivity (i.e., RR, SCL, SCR). The physical scale of the JACQ-past also showed significant correlation with HR, but again this correlation was just as low as the correlations with general craving scales in other studies ($r=0.31$). Although SCLs did not show correlation with craving, it did show moderate correlation with stress after cue exposure, suggesting that RR and HR may be more specifically related to craving and skin conductance to stress. Inspection of the scatterplots showed that subjects with no objective cue reactivity (according to HR, RR, SCL, SCR) almost never reported subjective craving, whereas only a few of the subjects with objective cue reactivity reported subjective craving. Apparently, there are large interpersonal differences in detection or reporting existing levels (especially in SCL and SCR) of physiological cue reactivity. The inability to find a high correlation between physiology and subjective craving therefore does not represent a failure of the JACQ. Apparently, there is no one-to-one relationship between physiological cue reactivity and subjective craving. Our study is the first to show that there are several interpersonal differences in detection or reporting of physiological reactions, leading to rather low and often insignificant correlations between subjective craving and physiological cue reactivity. The concordance of physiological cue reactivity and subjective craving may only be present in a subgroup of alcoholic persons who
are sensitive to the bodily reactions following cue exposure. More research is needed to distinguish between sensitive and nonsensitive patients.

As a result of these individual differences in detection or reporting, (objective) endophenotypic reactions may lead to unclear (subjective) phenotypic characteristics that are less closely related to the underlying neurophysiological processes of addiction. This finding may also explain the inconsistent findings regarding the predictive value of subjective craving for relapse (Rohsenow and Monti, 1999). Although it is recommended to investigate JACQs relapse predicting properties, future research into the predictive value of endophenotypic indicators for relapse is also warranted (Monti et al., 2000). On a small scale, it has been found that endophenotypes can indeed predict relapse independent of phenotypes, e.g., cue-elicited salivation predicted relapse in alcoholic persons (Rohsenow et al., 1994), whereas attentional bias and neurocognitive variables predicted relapse much better than subjective craving and self-reported personality styles in persons addicted to heroin and pathological gamblers (Marissen et al., 2005; Goudriaan et al., 2005). However, the estimation of endophenotypes in daily clinical practice is currently very time consuming and often very expensive. Therefore, we advice future researchers and clinicians to take practical implications of endophenotypes into account as well.

Our endocrinological data do not support effective stimulation of the HPA system after cue exposure in alcoholic persons. Only 6 subjects showed a response of 15% over baseline with a minimum of 2.5 nmol/l, whereas most other subjects showed small cortisol changes within the normal range of their baseline. This raises the question of whether alcohol cue exposure is a stimulus that effectively triggers the HPA system. Perhaps stronger cues accompanied by more psychological stress (such as a priming dose of alcohol) are more effective. In line with this, O’Malley et al. (2002) found that cortisol responses after actual consumption of alcohol correlated negatively and significantly with craving, whereas cortisol levels during the baseline period did not significantly correlate with craving. Another explanation may be that most subjects in our study had diminished HPA axis reactivity, which would be in line with previous findings showing less HPA activation in response to a number of functional tests in alcoholic persons (Berman et al., 1990; Vescovi et al., 1997; Wand and Dobs, 1991).

Although we did not find a significant correlation between JACQ-now and Δ peak of cortisol, we did find a significant positive correlation between the JACQ-past and Δ peak cortisol. The discrepancy of these findings may be due to distinct characteristics and/or predictive values of JACQ-now and JACQ-past, in cue reactivity of the HPA axis. This positive correlation may be explained by the finding that the group with a high frequency of craving experiences in the past (behavioral tendency) may have developed a more sensitive HPA system to the same
amount of induced craving and stress levels during cue exposure (behavioral sensitization). However, this finding is in contrast with the finding by O’Malley, showing a significant negative correlation between Δ peak cortisol (estimated in blood) and craving. A possible explanation for this discrepancy may be that the 18 subjects in O’Malleys study were non-treatment-seeking volunteers, that they actually consumed alcohol during the cue-exposure challenge, and that they used a different questionnaire measuring instant craving. Furthermore, in O’Malley’s study cortisol was measured in serum, which automatically introduces the stress of a needle stick, which may be a confound.

One of the limitations of the study is the low percentage of women in both study populations, and a low percentage of individuals who were employed and/or married. Although this is typical for an alcoholic population, this might have affected the data and should be taken into account when comparing this study with other studies. Another limitation may be that we did not measure salivation production, a reliable physiological indicator of cue reactivity. Because of our measurement of cortisol in saliva, the measurement of salivation production was a practical impossibility. However, since HR and SCL showed a significant increase in response to the cue, representing cue reactivity, it is unlikely that the omission of salivation measurement has seriously jeopardized the validity of the results.

Taken together, the JACQ represents craving as a one-dimensional construct with the following four distinctive aspects: an emotional aspect (feelings of urge), a cognitive aspect (uncontrolled thoughts), a behavior-related aspect (temptation to actual drinking), and a highly correlated physical aspect (physical sensations). Other constructs also showed a high correlation with the core craving concept (e.g., general stress, anticipations of outcome), but they do not represent craving as such. Therefore the JACQ is a theoretically significant craving measure. In addition, this study provides evidence of the importance of the craving measure’s time frame, and differentiation of intensity and frequency of craving experiences.

Furthermore, the study shows that there are only moderately high positive correlations between intensity of craving and psychophysiological indicators of cue reactivity, with the highest correlations between craving and HR and RR. In line with previous studies, the JACQ could not find a substantially high correlation between self-reported craving and physiological cue reactivity despite the presence of a special physical subscale. Apparently, there are large interpersonal differences in detection and/or reporting levels of autonomous cue reactivity, which may explain why findings on the predictive value of subjective craving for relapse are inconsistent.

Although the predictive value of subjective craving is debatable, it does not
mean that the concept of subjective craving will not be of further use as a therapeutic target in the treatment of alcoholism. Subjective craving is reported by a subgroup of patients and will therefore maintain to be important, for example, in the communication with these patients.

With respect to endocrinological measures, cortisol response of the HPA system after cue exposure showed a positive correlation with craving frequency in the past but not with the intensity of craving now, suggesting again that the JACQ-now and the JACQ-past measure distinct concepts. Our findings suggest that, the frequency of craving experiences in the past predicts HPA axis responsivity to cue exposure. However, the findings also indicate that craving is only moderately related to the responsivity of the HPA system.

In conclusion, the low correlations between subjective craving and physiological cue reactivity show that the JACQ does not outperform other questionnaires. In addition, the JACQ shows a high correlation with another craving questionnaire, the ACQ. However, the JACQ has a small improvement over previous questionnaires. The JACQ conceptualizes craving to the core, including an explicit physiological scale. The JACQ may therefore be used for biofeedback treatment, a technique by which patients are made more sensitive to bodily sensations, which can be helpful to recognize objective cue reactivity and to resist drinking when confronted with alcohol cues.

One of the most important findings of this study is that there are large interpersonal differences with respect to detection and/or report levels of physiological cue reactivity. Apparently a substantial number of the alcoholic persons are not sensitive to the detection of cue-related psychophysiological signs as indicators of cue reactivity, or fail to report these bodily sensations. Further research should focus on the nature of these individual differences and the possibilities of making patients more aware of these sensations.

Finally, it would be informative to investigate whether JACQ scores show correlations with subsequent relapse in order to truly determine the utility of the JACQ in predicting relapse. However, in addition to phenotypic indicators (e.g., subjective craving and stress), more attention on endophenotypic indicators (e.g., cue reactivity measures such as HR, RR, cortisol) is needed, and is a necessarily step in the search for predictors of relapse (see also Marissen et al., in press; Goudriaan et al., 2005). Similar recommendations have recently been made for patient-treatment matching (Ooteman et al., 2005). More research is needed on the relative predictive validity of subjective phenotypic indicators of craving (such as self-reported craving) versus objective endophenotypic indicators of craving (such as physiological measures of cue reactivity) in both relapse and treatment effectiveness.
CHAPTER 4

Appendix

JACQ-now (24 item-version, translated from Dutch)

This questionnaire aims at getting an impression of the level of your desire, urge or need for alcohol, or in other words how much you are experiencing ‘craving’ for alcohol RIGHT NOW. The questionnaire contains a few statements (experiences) that ask about the urge or need to drink alcohol. Please indicate to how much you are experiencing each of the following statements right now by placing a circle around one of the numbers. There are no wrong or right answers. For example: number ‘5’ indicates that you are experiencing the statement ‘very much’; number ‘1’ indicates ‘not at all’. We are interested in how much you are craving for alcohol right now as you are filling out the questionnaire. Please read carefully but do not think too long about your answer. Usually your first impression is the best one. Please complete every item.

Right now...

1. I am feeling an urge to drink
2. The thought of alcohol keeps me so busy I cannot think of anything else
3. My heart would beat faster if I saw or smell alcohol
4. It would be difficult for me not to drink if I saw or smell alcohol
5. I would sweat more then usual if I smell or saw alcohol
6. I would like to drink alcohol so bad that I can almost taste it
7. I am thinking of nothing else but drinking alcohol
8. I would not be able to stop if I would taste a little alcohol
9. I would produce more saliva if I saw or smell alcohol
10. I am having a strong desire for an alcoholic drink
11. I am fantasizing how delicious a drink would taste
12. My hands and fingers would tremble if I saw or smell alcohol
13. I am bothered by reoccurring images about drinking alcohol
14. It would be hard for me to turn down a drink
15. I cannot stop or turn away my thought(s) about alcohol
16. It would be difficult to resist the temptation to drink if I saw or smell alcohol
17. My body has a strong need for alcohol
18. I would be drawn a towards alcohol if there would be a drink in front of me
19. I would get a dry mouth if I saw or smell alcohol
20. Drinking alcohol appeals as something very delicious to me
21. I would drink immediately if I would be at home or in a bar
22. My desire to drink alcohol seems overwhelming
Measuring craving

23. My thoughts about alcohol keep me out of my concentration
24. My muscle tension would increase if I saw or smell alcohol

Acknowledgements

We thank Clemens Kirschbaum for his advice and comments on the paper, and Simone Höhner, Lonneke van der Hoeve, Marielle Visser, Femke Bartelds, and Hans Kronemeijer for their assistance.

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CHAPTER 4


94
Measuring craving

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CHAPTER 4


CHAPTER 5

The effect of naltrexone and acamprosate on cue-induced craving and physiological cue reactivity in alcoholics

This chapter is submitted for publication as: Ooteman, W., Koeter, M.W.J., Verheul, R., Schippers, G.M., & Van den Brink, W. The effect of naltrexone and acamprosate on cue-induced craving and physiological cue reactivity in alcoholics.
CHAPTER 5

Abstract

Introduction: Acamprosate and naltrexone have been shown to be effective in relapse prevention of alcoholism. Both medications may act by the reduction of cue-induced craving and physiological cue reactivity, although perhaps through different mechanisms of action. To elucidate these mechanisms, we studied the effect of acamprosate or naltrexone on cue-induced craving and physiological cue reactivity in abstinent alcoholics. It is hypothesized that naltrexone will exert its effects primarily on self-reported cue-induced craving and endocrinological cue reactivity measures (cortisol), whereas acamprosate will exert its effect primarily on physiological cue reactivity measures associated with withdrawal and anxiety (heart rate, skin conductance).

Patients and Methods: A total of 131 abstinent alcoholics participated in a randomized, double-blind, placebo-controlled protocol. Subjects received acamprosate (n=56), naltrexone (n=52) or placebo (n=23) for three weeks. All subjects participated in a cue-exposure session at the day before and at the last day of the medication period. Cue-induced craving was measured on a 10-point Visual Analog Scale (VAS) and with the Jellinek Alcohol Craving Questionnaire (JACQ). Cortisol, heart rate (HR), skin conductance level (SCL) and skin conductance response (SCR) were recorded as measures of physiological cue reactivity.

Results: Consistent with the hypotheses, naltrexone reduced craving more than acamprosate, and reversely, acamprosate reduced heart rate more than naltrexone. No indications were found for a medication effect on changes in cue-induced cortisol production.

Discussion: The findings provide evidence for differential effects of naltrexone and acamprosate: naltrexone exerts its effect, at least partly, by the reduction of cue-induced craving, whereas acamprosate exerts its effect, at least partly, by the reduction of physiological cue reactivity.
Introduction

Relapse prevention is among the most important treatments for alcohol dependence. Over the last 20 years, the role of pharmacotherapy in relapse prevention has become increasingly evident. There are two relatively new compounds that are proven effective (Kranzler, 2000) which are approved in both the United States and Europe, i.e., naltrexone and acamprosate. However, the effect size of these medications is moderate at best and their mechanism of action is not fully understood. In general, it is assumed that both medications prevent relapse though the reduction of craving (i.e., the conscious experience of an urge to drink). However, published correlations between craving and relapse are inconsistent (Rohsenow and Monti, 1999). The current study is the first randomized, double-blind, placebo-controlled study testing the main hypotheses regarding the assumed different mechanisms of action of the two compounds.

Naltrexone is an opioid antagonist that mainly acts at the µ-opioid receptor (Littleton and Ziegla"nsberger, 2003). Naltrexone is hypothesized to prevent relapse by attenuating the self-reported urge for alcohol’s rewarding properties (reward craving) in patients characterized by an opioidergic dysregulation and a reward seeking personality style (Verheul et al., 1999; Koob and LeMoal, 2001, 2005). Several studies have shown that naltrexone is most effective in patients with strong self-reported baseline craving (Jaffe et al., 1996), and that craving can be reduced by naltrexone (e.g., Chick et al., 2000a; Anton et al., 1999; Volpicelli et al., 1992). It is generally believed that naltrexone reduces craving by the blocking of opioid receptors, which in turn leads to an attenuation of the rewarding effect of alcohol (Volpicelli et al., 1995). Other studies found that the anti-craving effect of naltrexone is dependent on the pattern of consumption (Anton et al., 2004) and most effective when at least some alcohol is consumed, e.g., in controlled drinking programs (see for a review: Sinclair, 2001). Some recent studies suggest that naltrexone may also exert its effect on craving through stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in higher baseline cortisol levels and stronger cortisol reactions following cue exposure or alcohol intake (Adinoff et al., 2005; Kiefer et al., 2002; O’Malley et al., 2002).

Since its approval, several trials have been performed investigating naltrexone’s efficacy in relapse prevention. However, the data are somewhat inconsistent and effect sizes are modest at best (see for review studies: Mann, 2004; Srisurapanont and Jarusuraisin, 2005a, 2005b; Roozen et al., 2005). The most consistent finding has been an increase in time to first relapse, although not in all trials, including the largest with 627 veterans (Krystal et al., 2001). Negative findings may be accounted for by inadequate samples sizes, poor medication compli-
Chapter 5

Many studies have examined the effect of naltrexone on craving in non-experimental settings (see for reviews: Srisurapanont and Jarusuraisin 2005a; Roozen et al., 2005). However, only a limited number of studies have included cue-induced craving or measures of physiological cue reactivity in the laboratory as outcome measures. Alcohol-related cues (e.g., negative mood, the sight and smell of alcohol) are generally believed to act as triggers for craving and/or physiological cue reactivity (e.g., Cooney et al., 1997; Kaplan et al., 1985; Niaura et al., 1988). Therefore, cue-induced craving and physiological cue reactivity may be important intermediate outcome measures for naltrexone’s efficacy as well. With respect to the effect of naltrexone on cue-induced craving, the limited number of studies showed inconsistent results. Some studies (Rosenow et al., 2000; O’Malley et al., 2002; Palfai et al., 1999) found a reduction in the level of cue-induced craving after naltrexone treatment, whereas other studies (Modesto-Lowe et al., 1997; Monti et al., 1999) did not. It should be noted, however, that Monti et al. (1999) did find an effect on the number of patients reporting cue-induced craving. The number of studies about naltrexone’s effect on physiological cue reactivity in alcoholics is even smaller. Monti et al. (1999) did not find an effect of naltrexone treatment on measures of physiological cue reactivity (blood pressure and heart rate) in alcoholics. In fact, they found a smaller decrease in blood pressure after naltrexone treatment than after placebo treatment. Others hypothesized that naltrexone’s effect on craving may be related in part to naltrexone’s ability to stimulate the HPA axis and to normalize its suppressed basal activity and blunted response to a number of functional tests (Adinoff et al., 2005; Kiefer et al., 2002; O’Malley et al., 2002). In line with this theory, an increase of baseline cortisol and a negative correlation between craving and alcohol-induced cortisol response was observed after naltrexone treatment (O’Malley et al., 2002).

Acamprosate or calcium-acetyl-homotaurinate is a glutamate antagonist and possible GABA agonist. Although the precise mechanism of action is still unknown, it seems to involve primarily the restoration of a normal N-methyl-D-aspartate (NMDA) receptor tone in glutamatergic systems (Rammes et al., 2001). In general, acamprosate is believed to maintain abstinence primarily by reducing craving. Some investigators hypothesize that acamprosate specifically acts on craving that is mediated through glutamatergic and GABAergic dysregulations of stress, anxiety or withdrawal systems (relief craving), and is thus accompanied by physiological reactions (Littleton, 1995; Koob and LeMoal 2001, 2005; Verheul et al., 1999).

Since its approval, several trials have been performed investigating acamprosate’s efficacy. In most clinical trials, continuous abstinence rather than re-
The effect of naltrexone and acamprosate on cue-induced craving

Lapse or craving has been the primary outcome measure, with a beneficial effect of acamprosate on continuous abstinence rates with a modest effect size (see for a review: Mann, 2004; see for a meta-analysis: Mann et al., 2004). The effects of acamprosate on craving are less consistent. Several trials showed a significant reduction of craving compared to placebo (e.g., Chick et al., 2000b; Pelc et al., 1997; Paille et al., 1995), but other studies did not (Roussaux et al., 1996; Tempesta et al., 2000). Only few studies included cue-induced craving and/or physiological cue reactivity as outcome measures. Weinstein et al. (2003) presented some preliminary results of an uncontrolled pilot study suggesting that acamprosate does alter cue-induced self-reported craving and reaction time to an alcohol-related stimulus. In addition, Agelink et al. (1998) showed improved autonomic neurocardial balance in abstinent alcoholics treated with acamprosate, i.e., following treatment with acamprosate patients showed less disturbances in neurocardiac vagal function.

In summary, it seems that acamprosate and naltrexone exert their effect on relapse via different mechanisms and relate to different aspects of drinking behavior: naltrexone is thought to reduce relapse primarily via the reduction of self-reported craving, possibly through stimulation of the HPA axis, whereas acamprosate is thought to work primarily via the reduction of physiological reactions of the sympathetic nervous system associated with withdrawal and anxiety. However, until now, the literature lacks sufficient empirical evidence on the differential effect of naltrexone and acamprosate on both cue-induced craving and physiological cue reactivity. The aim of the current study is, therefore, to investigate possible mechanisms of action on craving of naltrexone and acamprosate by testing a primary and a secondary hypothesis in a treatment paradigm. The primary hypothesis is that naltrexone and acamprosate exert their effect through different mechanisms: naltrexone will primarily exert its effect on cue-induced craving and endocrinological cue reactivity measures of the HPA axis (cortisol) whereas acamprosate will primarily exert its effect on cue-induced physiological parameters associated with withdrawal symptoms or anxiety (heart rate, skin conductance). The secondary hypothesis is that both naltrexone and acamprosate result in a larger reduction of cue-induced craving and/or physiological cue reactivity than placebo.

Patients and methods

Participants
The study population consisted of both treatment-seeking and non-treatment-seeking alcoholics, that were recruited either at the Jellinek addiction treatment center in Amsterdam or through advertisement in newspapers and radio interviews.
Inclusion criteria were: primary DSM-IV diagnosis of alcohol dependence; minimum age of 18; and no heavy drinking days (≥ 5 units) for a minimum of one week and a maximum of six months. Exclusion criteria were: comorbid cocaine or heroin dependence; cocaine or heroin use in the last 30 days before intake; current use of naltrexone, acamprosate or disulfiram; severe cognitive deficits; insufficient command of the Dutch language; disturbed renal function (creatinine > 120 μmol/l); acute hepatitis (ASAT/ALAT ≥ 3 x normal value); severe liver insufficiency; hypersensitivity for acamprosate and/or naltrexone; pregnancy; lactation; expected medical interventions including pain relief with opioids; severe medical illnesses; active psychosis; current use of antipsychotic medication; and suicidality.

A total of 524 subjects were screened (see Figure 1). Of these, 188 subjects refused to participate at intake and 139 subjects had to be excluded (most important reasons for exclusion: various medical conditions and current use of anti-craving compounds). Of the remaining 197 subjects, 41 subjects filled out baseline questionnaires, but refused further participation before randomization, leaving 156 subjects for the current study. Of these 156 subjects, 25 subjects (16%) (7 in the acamprosate group, 11 in the naltrexone group, and 7 in the placebo group) dropped out after the first cue-exposure session, leaving 131 subjects (84%) who completed the entire study: 56 in the acamprosate group, 52 in the naltrexone group, 23 in the placebo group.

Figure 1. Flow chart: subject progress through study phases.
Table 1. Patient characteristics and alcohol-related variables.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Placebo (n=23)</th>
<th>Naltrexone (n=52)</th>
<th>Acamprosate (n=56)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>45.3 (9.6)</td>
<td>47.2 (10.1)</td>
<td>48.1 (9.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>Men (%)</td>
<td>78.3</td>
<td>78.8</td>
<td>66.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Dutch ethnicity (%)</td>
<td>87.0</td>
<td>88.5</td>
<td>76.8</td>
<td>0.23</td>
</tr>
<tr>
<td>Inpatients (%)</td>
<td>17.4</td>
<td>32.7</td>
<td>25.0</td>
<td>0.36</td>
</tr>
<tr>
<td>In treatment at a clinic (%)</td>
<td>73.9</td>
<td>69.2</td>
<td>64.3</td>
<td>0.68</td>
</tr>
<tr>
<td>Higher education (%)</td>
<td>50.0</td>
<td>28.0</td>
<td>38.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>15.8 (5.0)</td>
<td>13.6 (4.3)</td>
<td>13.4 (3.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>54.5</td>
<td>58.0</td>
<td>57.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Married (%)</td>
<td>22.7</td>
<td>32.0</td>
<td>16.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Alcohol-related variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AUDIT score (SD)</td>
<td>20.5 (4.2)</td>
<td>21.3 (5.1)</td>
<td>20.8 (5.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean age of onset (SD)</td>
<td>32.8 (8.2)</td>
<td>35.9 (10.3)</td>
<td>35.2 (9.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Other substance use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using benzodiazepines (%)</td>
<td>27.3</td>
<td>12.0</td>
<td>13.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Using cannabis (%)</td>
<td>18.2</td>
<td>8.0</td>
<td>18.5</td>
<td>0.26</td>
</tr>
<tr>
<td>Using nicotine (%)</td>
<td>86.4</td>
<td>84.0</td>
<td>92.6</td>
<td>0.39</td>
</tr>
<tr>
<td>Using anti-depressives (%)</td>
<td>40.9</td>
<td>26.0</td>
<td>31.5</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test.

The effect of naltrexone and acamprosate on cue-induced craving

Table 1 shows that most study participants were Dutch, male, unemployed, unmarried and with low education. In the total group, 26.7% of the participants were inpatients, 41.2% were outpatients and 32.1% was currently non-treatment-seeking. Most subjects had moderate to severe levels of alcohol dependence. With the exception of the mean years of education, there were no significant (p<0.20) differences between the groups in baseline characteristics; mean years of education was higher in the placebo than in the active medication conditions.
CHAPTER 5

GENERAL DESIGN
All clients filled out self-report questionnaires on demographics, immediately after inclusion in the study. To assess the severity of their alcohol problems all participants self-administered the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992). All participants were instructed to quit drinking one week before start of the medication period. They were then prepared for a cue-exposure challenge. Based on a Drinking Triggers Interview (Monti et al., 1993a), individualized audiotaped mood induction scripts were prepared (Cooney et al., 1997). The aim of the script was to induce the mood in which the subject was most likely to experience craving.

One day before the start of the medication period, every subject was exposed to a cue-exposure challenge, in which craving and physiological cue reactivity were measured. All subjects then participated in a randomized, double-blind, placebo-controlled protocol: 40% of the subjects received acamprosate, 40% naltrexone and 20% placebo for 21 days, under supervision of a physician. The dosages of naltrexone and acamprosate were given according to current treatment recommendations. For acamprosate, 2.0 g/day was given to patients with bodyweight >60 kg, and 1.3 g/day in patients with bodyweight <60 kg. The recommended dose of naltrexone is 50 mg/day. All tablets (placebo, naltrexone and acamprosate) were identical in appearance. Based on data about the pharmacokinetics of the compounds, 21 days of administration should be sufficient to exclude the possibility that no effect is detected due to a potential latency period for the effect of acamprosate (Wilde and Wagstaff, 1997) or naltrexone (Mason et al., 2002; Yuen et al., 1999).

After three weeks of placebo or medication, all subjects were exposed to a second cue-exposure session according to exactly the same protocol as the first session, with an additional retrospective assessment of medication compliance of the past three weeks. After debriefing and unblinding, a treatment advice was given by the physician. All subjects received three vouchers with a total value of 35 Euro.

PROCEDURE
The cue-exposure paradigm was based on procedures developed by Cooney et al. (1997) and Monti et al. (1993b). First, subjects were screened for alcohol use, connected to electrodes and acclimatized for thirty minutes. Each subject was then asked to relax for four minutes. The subject’s favorite beverage was then poured in the glass in front of the subject. While the pre-recorded mood-induction script was played over the headphone for five minutes, the subject was instructed to sniff the beverage four times (one time at the start of the script and three times at the end of the script). During exposure, craving was assessed four...
times on a VAS scale ranging from 0 to 10 (at the 1st, 3rd, 4th and 5th minute). At the end, a self-report craving questionnaire (JACQ-now; Ooteman et al., 2006a) was filled out and a final assessment with the VAS scale was taken before bringing the participant back to a relaxed state.

**SUBJECTIVE OUTCOME MEASURES**

At baseline and during cue exposure, craving was measured on a 10-point VAS scale (VASa) (‘How strong is your urge or need to drink right now?’). Immediately after cue exposure, subjects were asked to give a rating on a 10-point VAS scale (VASb) (‘How strong was your strongest urge or need to drink alcohol during the session?’). In addition, they were asked to administer the 24-item Jellinek Alcohol Craving Questionnaire (JACQ-now; Ooteman et al., 2006a), a questionnaire with four subscales that measure the core aspects of craving. After the second cue-exposure session, an evaluation form was filled out and medication compliance (defined as the percentage of pills taken by the subject) was retrospectively assessed by self-report.

**PHYSIOLOGICAL AND ENDOCRINOLOGICAL OUTCOME MEASURES**

**Physiological cue reactivity outcome measures**

The following physiological measures were continuously recorded during both cue-exposure challenges: (1) heart rate (HR); (2) skin conductance level (SCL); (3) skin conductance response (SCR). Based on these assessments, mean values of HR, SCL, and SCR as well as $\Delta$ peak values (see statistical analysis) were calculated, since subjects may peak at different moments in time in which case mean values may mask the cue-exposure (and medication) effect.

For HR assessment, ECG (electrocardiogram) electrodes were placed on either side of the participant’s chest. A Contact Precision Instruments analogue-digital converter (ADC) sampled the ECG signal at a rate of 300 Hz and calculated the number of interbeat intervals (IBI’s) during 10-second sampling periods (range 2mV, High Pass 10Hz, Low Pass 200Hz).

For the assessment of SCL and SCR, electrodes were taped to the middle phalanx of the forefinger and the middle finger of the participant’s nondominant hand. The skin conductance signal was amplified by a Contact Precision Instruments skin conductance coupler, sampled at a fixed 40Hz. SCL and SCR count were averaged across a 10-second sampling period. The response criterion for SCR was an increase of 0.0015625 micro Siemens ($\mu$S).
ENDOCRINOLOGICAL CUE REACTIVITY OUTCOME MEASURE

Cortisol production was measured in saliva and sampled ten times during the cue-exposure session. The first baseline sample was taken directly following the resting period, and a second baseline sample was taken 5 minutes after the resting period. A further eight samples were taken 15, 20, 25, 30, 35, 40, 45, and 50 minutes after start of the cue exposure. Saliva was collected using Sarstedt salivettes with a dental cotton roll, frozen at –20 degrees ºC and cortisol analyses were performed at the Department of Psychology, TU Dresden, Germany, (Laboratory Dr. Kirschbaum) using a commercial immunoassay with chemiluminescence detection. The lower sensitivity of the assays is 0.44 nmol/l, intra-assay and inter-assay coefficients of variation are less than 10%.

STATISTICAL ANALYSIS

Despite some drop-outs after randomization, there were no significant (p<0.20) differences in baseline characteristics between the three groups, with the exception of more years of education in the placebo condition. However, in order to improve the power of the study and to prevent residual confounding, AUDIT (Alcohol Use Disorders Identification Test) scores, gender and benzodiazepine use will be used as covariates in all analyses.

Responses at each cue-exposure session on the physiological and endocrinological measures were operationalized as Δ peak values. For craving, two different Δ peak scores were calculated: the first by subtracting the baseline VAS score from the highest VAS score filled out during cue exposure (Δ peak VASa), the second by subtracting the baseline VAS score from the retrospective VAS score ‘How strong was your strongest urge?’ filled out immediately after cue exposure (Δ peak VASb). For HR, SCL and SCR, Δ peaks were calculated by subtracting the average of the last minute of the baseline period from the maximum value during the 5-minutes lasting cue-exposure period. Cortisol Δ peak scores were calculated by subtracting the mean baseline value (sample 1a and 1b were regarded as baseline values since it takes approximately 15-25 minutes before the cortisol reaction becomes apparent following the cue) from the highest cortisol value after cue exposure.

The effect of naltrexone and acamprosate for each of the physiological and endocrinological measures was estimated using univariate ANCOVA (General Linear Model module, SPSS 12), with the difference score in Δ peak value between the first and second cue exposure as dependent variable, medication condition (naltrexone, acamprosate and placebo) as independent variable and Δ peak of the first cue-exposure session, baseline AUDIT scores, benzodiazepine use and gender as covariates. Standardized effect sizes are presented as Cohen's d values. For the primary research question, relatively large samples were included to
compare the acamprosate and naltrexone groups. Significance was tested at the 0.05 level. In order to have an indication of the efficacy of acamprosate and naltrexone in the current study, a relatively small placebo group was included. To take into account the small sample size of the placebo group, multiple testing and type II error, significance was tested at the 0.1 level for the secondary research question.

**Results**

**Medication Compliance**

Self-reported medication compliance in study completers was good. The mean percentage of taken pills was 98.1% in the placebo group, 99.1% in the naltrexone group, and 96.5% in the acamprosate group. These findings were confirmed by data on medication (metabolites) in randomly taken urine samples and by a pill count.

**Effect of Naltrexone and Acamprosate on Craving**

For all craving measures, and for each active medication group, a significant increase in Δ peak value was found during both cue-exposure sessions \((p<0.05)\). In line with our expectations, the reductions in Δ peak craving scores between the sessions in the naltrexone group were significantly larger than the reductions in Δ peak craving scores between the sessions in the acamprosate group for VASb \([p<0.05, d=0.29]\). No significant effects were found for the other craving indicators (VASa and the (sub)scales of the JACQ). In contrast to our expectations, reductions in Δ peak craving scores between the sessions in both the acamprosate and naltrexone group were not significantly larger than in the placebo group, which may be due to the small sample size of the placebo group (see Figure 2).

**Effect of Naltrexone and Acamprosate on Physiological Cue Reactivity**

For all physiological parameters, and for each medication group, a significant increase in Δ peak value was observed during both cue-exposure sessions \((p<0.05)\). In line with our expectations, the decrease in Δ peak HR in the acamprosate was significantly larger than the decrease in Δ peak HR in the naltrexone group \([p<0.05, d=0.15]\). However, in contrast to our expectations, no significant medication effect was found in the reduction of Δ peak SCL between the sessions and a significant smaller reduction between the sessions was found for both active medications compared to the control group on Δ peak SCR \([p<0.01; d=0.06\) for acamprosate and \(d=0.27\) for naltrexone]. In addition, reductions in Δ peak on all physiological measures between the sessions in the naltrexone group were not
Figure 2. Changes over time in $\Delta$ peak values for cue-induced craving measures. Left bar represents cue-exposure session 1, right bar cue-exposure session 2. Error bars show mean $\pm 1.0$ SE.

Abbreviations:
$\Delta$ peak VASa = highest VAS during cue exposure – baseline VAS
$\Delta$ peak VASb = retrospective VAS ‘strongest craving’ – baseline VAS
JACQ, Jellinek Alcohol Craving Questionnaire.

**A** $\Delta$ peak VASa craving score (during cue exposure)

**B** $\Delta$ peak VASb craving score (after cue exposure)
The effect of naltrexone and acamprosate on cue-induced craving

Figure 3. Changes over time in Δ peak values for the physiological cue-reactivity measures.
Left bar represents cue-exposure session 1, right bar cue-exposure session 2. Error bars show mean ±1.0 SE.
Abbreviations: HR, heart rate; SCL, skin conductance level; SCR, skin conductance response.

A Δ peak HR

B Δ peak JACQ-now total craving score
CHAPTER 5

B Δ peak SCL

C Δ peak SCR
The effect of naltrexone and acamprosate on cue-induced craving

**D Δ peak cortisol**

significantly larger than in the placebo group. However, the decrease in Δ peak HR in the acamprosate group was significantly larger than in the placebo group \[ p<0.1, d=0.40 \] (see Figure 3).

**EFFECT OF NALTREXONE AND ACAMPROSATE ON ENDOCRINOLOGICAL CUE REACTIVITY**

No significant cue-induced cortisol Δ peak values were found at the first and second cue-exposure session in each medication group. In contrast to our expectations, no significant effects of naltrexone and acamprosate on reductions in Δ peak cortisol levels were observed. In addition, no significant differences between placebo and active medications were found in basal cortisol levels or in cortisol Δ peaks (see Figure 3d).

**Discussion**

In summary, the effect of naltrexone on cue-induced craving was significantly larger than the effect of acamprosate \( p<0.05; d=0.29 \), although this effect was not statistically significant for the comparison of naltrexone with placebo. With respect to physiological cue reactivity, a small but significant effect was seen for acamprosate versus naltrexone \( p<0.05; d=0.15 \), and a significant but moderate
reduction in Δ peak HR was found in the acamprosate group compared to placebo \( p<0.1; d=0.40 \). No significant medication effects were observed with regard to cortisol responses to cue exposure.

First, it seems that naltrexone has a moderate effect on cue-induced craving compared to acamprosate. This was most strongly present on the VASb scale \( p<0.05, d=0.29 \). The VASb scale may therefore be the most sensitive scale in the current study to detect a reduction in cue-induced craving. An explanation for this may be that the VASb scale is administered directly following the experience of cue-induced craving, combining the advantages that (a) the craving experience is very recent, and that (b) it concerns the highest craving score of the entire cue-exposure period and therefore reduces the risk that the highest score is missed. Since the effect of naltrexone on cue-induced craving is only moderate, it is questionable whether naltrexone exerts its main therapeutic effect on relapse through the reduction of cue-induced craving. This would be in line with studies showing low correlations between craving and relapse (Rohsenow and Monti, 1999). Although we did not find an effect of acamprosate on cue-induced craving at three weeks of medication, acamprosate may exert its effects on cue-induced craving after more than three weeks of medication.

Second, in line with our prediction, a small but significant effect on Δ peak HR was seen for acamprosate versus naltrexone \( p<0.05; d=0.15 \) In addition, acamprosate showed a moderate effect on one of the physiological measures (heart rate) compared to placebo \( p<0.1, d=0.40 \), whereas naltrexone did not. Physiological cue reactivity of the sympathetic nervous system may therefore be a sensitive parameter for acamprosate’s mechanism of action. This is in line with our hypothesis that acamprosate is differentially effective in reducing physiological reactions that are mediated through glutamatergic and GABAergic dysregulations of stress, anxiety or withdrawal systems (Littleton, 1995; Verheul et al., 1999; Koob and LeMoal, 2001, 2005). It is also in line with a study showing improved neurocardial balance (Agelink et al., 1998) and a pilot study showing an effect of acamprosate on another cue reactivity measure (reaction time) (Weinstein et al., 2003). However, despite a moderate effect size for acamprosate compared to placebo \( d=0.31 \), we did not find a significant medication effect on SCL. Moreover, in sharp contrast to our predictions, we found smaller reductions in cue-induced SCR in both medication groups compared to the placebo group \( p<0.1; d=0.06 \) for acamprosate and \( d=0.27 \) for naltrexone. Apparently, not all sympathetic outcome measures in our study are sensitive to the dampening effect of acamprosate. In the current study, naltrexone did not significantly decrease any physiological indicators of cue reactivity. This is partly in line with Monti’s study, showing a smaller decrease of cue-induced arterial pressure in the naltrexone group compared to placebo (Monti et al., 1999). Our finding, however, is not in
The effect of naltrexone and acamprosate on cue-induced craving

line with McCaul’s study in heavy drinkers, showing alcohol-induced heart rate reductions after naltrexone (McCaul et al., 2001). This discrepancy may result from the fact that in McCaul’s study alcohol was actually consumed and heavy drinkers instead of alcohol-dependent subjects were studied.

Third, no significant effects of naltrexone on baseline cortisol and Δ peak cortisol after cue exposure were observed. Our findings, therefore, do not support the hypothesis that naltrexone exerts its therapeutic effect by restoring the blunted basal activity and reactivity of the HPA system in alcohol-dependent subjects. Our finding is not in line with the study of O’Malley et al. (2002) showing a stimulating effect of naltrexone on cortisol (O’Malley et al., 2002). However, in that particular study subjects were exposed to real alcohol (elevating cortisol levels) and cortisol was measured by an invasive method (in serum), which may explain the discrepancies with the current study. Another explanation why we did not find an effect of naltrexone on cortisol might be the poor temporal resolution of the cortisol reaction and subsequently the difficulty of attributing cortisol responses to the cue-exposure period. Since the literature is scarce and not very consistent, further investigation of the effect of naltrexone on the HPA axis in the regulation of craving and relapse is warranted.

Our findings raise the question whether acamprosate and naltrexone are highly effective in the reduction of cue-induced craving and physiological cue reactivity in the short term. In summary, it seems that naltrexone only moderately reduces cue-induced craving (specifically when measured by use of a VAS scale) and that acamprosate only moderately reduces arousal of the sympathetic nervous system (specifically heart rate). Cue reactivity measures may not be sensitive enough to elucidate pharmacologic mechanisms of action, or alternatively, naltrexone and acamprosate may exert their effect by acting on other brain systems. Finally, it is possible that the observed moderate effects on cue-induced parameters reflect the moderate clinical effects on relapse.

The moderate effect sizes in this and other studies on the efficacy of acamprosate and naltrexone are most likely a consequence of inefficient patient-treatment matching, resulting in subgroups of nonresponders who mask the effect of the medication (Verheul et al., 1999; Ooteman et al., 2005). In line with this post-hoc explanation, we found large standard deviations of the mean group values for all outcome measures. The histograms for all outcome measures suggest that subgroups of alcoholics differentially respond to acamprosate or naltrexone (data not shown). One part of the patients seems to benefit with reasonably large effect sizes, whereas another part may even show an effect in the opposite direction. More research is needed on the characteristics of these responders and nonresponders at the phenotypic level (e.g., clinical characteristics), the endophenotypic level (e.g., brain functioning) as well as at the genetic level (e.g.,
gene polymorphisms) (see also: Gottesman and Gould, 2003; Ooteman et al., 2005).

Despite the various strengths of the current study (e.g., explicit hypothesis driven approach; inclusion of two competitive medications; cue-induced craving and physiological cue reactivity as the outcome measures), the current study also has several limitations. First, the study has a relatively small placebo group, which may have masked existing effects of acamprosate and naltrexone when compared to placebo. Second, our study focused on effects after only three weeks of medication. Long-term medication challenges may show different results. For example, in Weinstein’s pilot study a reduction in cue reactivity was found after six weeks of treatment (Weinstein et al., 2003). Perhaps, acamprosate’s immediate effect on physiological cue reactivity is followed by a delayed effect on cue-induced craving. Third, since exactly the same cue-exposure protocol was repeated at the second session, it cannot be excluded that habituation masked existing differences in cue reactivity measures between groups. Fourth, although the participants were instructed not to drink during the medication period, some of the patients may have been drinking alcohol. Although this may account for the nonresponders only, drinking itself has also been hypothesized to affect specifically naltrexone’s mechanism of action (see for a review: Sinclair, 2001). Fifth, in the current study, the reductions in sympathetic arousal are hypothesized to be related to withdrawal and anxiety. However, sympathetic indices are conservatively interpreted as general measures of arousal. For example, cue reactivity theorists have suggested that sympathetic arousal can reflect either appetitive, aversive or cognitive aspects of craving. Our hypothesis, predicting that acamprosate primarily acts on physiological cue reactivity, may therefore be too simple.

Sixth, in the current study we attempted to differentiate medications according to their unique effects on reward and relief aspects of cue reactivity (craving scores and actual physiological reactions respectively). It may have been better to differentiate relief and reward aspects of cue reactivity by using the Alcohol Craving Questionnaire (ACQ) that includes anticipations of positive outcome and relief from negative outcome (Singleton et al., 1994). However, it must be noted that, until now, attempts to differentiate relief and reward concepts at the phenotypic level have been rather disappointing (e.g., Cooper et al., 1995; Ooteman et al., 2006b).

In conclusion, this study shows moderate and differential effects of naltrexone and acamprosate on cue-induced craving and physiological cue reactivity respectively. The results of this study only partly support the efficacy of naltrexone and acamprosate in the reduction of cue-induced craving and physiological cue reactivity. More research is needed on the mechanisms of action of acamprosate and naltrexone on craving, patient-treatment matching, alternative mechanisms
of naltrexone and acamprosate, the implications of these findings for the treatment of alcoholism, the effects of long-term treatment on cue-induced craving and physiological cue reactivity measures and the effects of combined pharmacotherapy.

**Acknowledgements**

We thank Clemens Kirschbaum for his advice on the cortisol data and Hans Kro-nemeijer for his data management, advice and support. We thank Simone Höh-ner, Premal Koning, Ron Baas, Sigrid Wittenberg, Dorine Eeken, Kai Hulstijn, Weena Chen and Gjalt de Vries for their assistance.

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CHAPTER 5


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The effect of naltrexone and acamprosate on cue-induced craving

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CHAPTER 5

CHAPTER 6

Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using phenotypic, endophenotypic and genetic indicators.

This chapter is submitted for publication as: Ooteman, W., Naassila, M., Koeter, M.W.J., Verheul, R., Schippers, G.M., Houchi, H., Daoust, M., & Van den Brink, W. Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using phenotypic, endophenotypic and genetic indicators.
Abstract

CONTEXT: Acamprosate and naltrexone are effective in the prevention of relapse in alcohol dependence. However, effect sizes are modest at best, most likely because of inadequate patient–treatment matching. Based on the three-pathway model for alcoholism, it is hypothesized that naltrexone primarily exerts its effect through reductions in cue-induced craving in reward drinkers, whereas acamprosate exerts its effect primarily through reductions in physiological cue reactivity in relief drinkers.

OBJECTIVE: To test patient–treatment matching hypotheses based on the three-pathway model for alcoholism.

DESIGN: Randomized double-blind controlled study. After assessment of phenotypic, endophenotypic and genetic indicators of relief and reward drinking, subjects were randomly assigned to either acamprosate or naltrexone. Subjects participated in two cue-exposure sessions: the first at the day before and the second at the last day of medication.

SETTING: Addiction treatment center in Amsterdam, The Netherlands.

PATIENTS: After screening of 524 alcohol-dependent patients, 139 did not meet criteria, 188 refused and 41 dropped out before randomization. Of the 126 randomized subjects, 18 dropped out, leaving 108 patients for analysis (naltrexone: n=52; acamprosate: n=56).

INTERVENTIONS: 21 Days oral acamprosate (1333/1996 mg/day) or naltrexone (50 mg/day).

MAIN OUTCOME MEASURES: Reductions between the cue-exposure sessions in cue-induced craving and physiological cue reactivity (heart rate).

RESULTS: No significant matching effects were found for phenotypic indicators. However, significant matching effects were found for cue-induced skin conductance level at baseline and for polymorphisms at the DRD2, GABRA6 and GABRB2 gene (p<0.1). A trend was found for the OPRM1 polymorphism on physiological cue reactivity (p<0.2).

CONCLUSIONS: The study provides strong evidence for the matching potential of endophenotypic and genotypic patient characteristics. Replication in bigger samples with clinical outcome measures is warranted. It is expected that more effective, efficient and cost-effective treatments can be offered when genetic and endophenotypic information is used in patient–treatment matching strategies.
Introduction

Relapse prevention is a cornerstone in the treatment of alcohol dependence. Over the last 20 years, the role of pharmacotherapy in relapse prevention has become increasingly evident. Naltrexone and acamprosate are currently regarded to be the most effective and safest compounds registered for the treatment of alcohol dependence in North America, Australia and Europe. However, the effect size of these and other medications is quite modest with many patients relapsing during treatment (see reviews: Mann, 2004; Srisurapanont and Jarusuraisin, 2005a, 2005b; for meta-analyses see: Mann et al., 2004; Roozen et al., 2005). In addition, a combined treatment seems to be more effective than the treatment with these medications alone (Kiefer et al., 2003). The most likely explanation is that these compounds have different mechanisms of action and that a better matching of patient characteristics and pharmacological interventions may result in larger effect sizes, and thus more effective and efficient treatments. In order to improve matching, information about the different mechanisms of action and individual differences related to such mechanisms is crucial.

With respect to naltrexone, there are indications that this opioid antagonist reduces craving and relapse through blocking of opioid receptors. According to Verheul et al. (1999), reward drinkers benefit from naltrexone. Reward drinkers are in theory characterized by phenotypic indicators such as reward drinking motives, early-onset, and familial alcoholism. At the endophenotypic level they show blunted neuroendocrine cue reactivity (e.g., Adinoff et al., 2005), and have a dysregulated dopaminergic and opioidergic system, which stem from a neurochemical dysregulation and/or a specific dopaminergic and/or opioidergic genotype.

With respect to acamprosate, there are indications that this glutamate antagonist reduces craving and relapse through a reduction of neuronal hyperexcitability (Pierrefiche et al., 2004). According to the matching hypothesis of Verheul et al. (1999), relief drinkers benefit from acamprosate. Relief drinkers are in theory characterized by phenotypic indicators such as relief drinking motives, withdrawal symptoms, late-onset or non-familial alcoholism. At the endophenotypic level they are hypothesized to have strong physiological cue reactivity, and to have a GABAergic or glutamatergic dysregulation, which can be translated into a neurochemical dysregulation or distinct polymorphisms in glutamatergic and GABAergic genes.

Some studies have attempted to test these matching hypotheses. In a review, we concluded that most studies only examined phenotypic indicators, producing inconsistent results (Ooteman et al., 2005). Matching variables for acam-
propane were scarce and limited to the phenotypic level (e.g., non-familial alcoholism). With respect to naltrexone, some support for the matching hypothesis was found. Again, indicators were primarily studied at the phenotypic level (e.g., familial alcoholism). At the genetic level, one promising indicator was found in line with the matching hypothesis: a $\mu$-opioid receptor polymorphism at the OPRM1 gene (Oslin et al., 2003). In addition, some indicators were found which are not included in the matching hypotheses, e.g., active drinking and high baseline craving. Another striking finding was that most studies were conducted in small samples, without competitive medication, and with relapse or craving as the only outcome measures. Studies with cue-induced craving and physiological cue reactivity as the primary outcome measures were scarce. In summary, until now, the matching hypotheses have not been seriously tested and data available only partly confirmed the hypotheses.

The current study is the first randomized double-blind controlled study that uses both naltrexone and acamprosate and simultaneously measures potential matching variables at the phenotypic, endophenotypic, and genetic level, with both cue-induced craving and physiological cue reactivity as outcome measures. In a previous paper on the same sample, we reported that naltrexone primarily exerts its effect on cue-induced craving, whereas acamprosate primarily influenced physiological cue reactivity (heart rate) (Ooteman et al., submitted). As expected, the effect sizes for both compounds were modest, most likely due to inadequate patient-treatment matching.

In order to achieve more efficient matching, the current study will test the following matching hypotheses: naltrexone will primarily exert its effect on cue-induced craving in reward drinkers, whereas acamprosate will primarily exert its effect on physiological cue reactivity (heart rate) in relief drinkers.

**Materials and methods**

**Participants**

The study population consisted of both treatment-seeking and non-treatment-seeking alcoholics recruited either by the Jellinek addiction treatment center in Amsterdam or through newspaper advertisements and radio interviews (see also Ooteman et al., submitted).

Inclusion criteria were: primary DSM-IV diagnosis of alcohol dependence; minimum age of 18 year; and no heavy drinking days ($\geq 5$ units) for a minimum of one week and a maximum of six months. Exclusion criteria were: comorbid cocaine or heroin dependence; cocaine or heroin use in the last 30 days; current use of naltrexone, acamprosate, or disulfiram; severe cognitive deficits; insufficient command of the Dutch language; disturbed renal function (creatinine >
Predicting the effect of naltrexone and acamprosate

120 µmol/l); acute hepatitis (ASAT/ALAT ≥ 3 x normal value); severe liver insufficiency; hypersensitivity for acamprosate and/or naltrexone; pregnancy; lactation; severe medical illnesses; active psychosis; current use of antipsychotic medication; and suicidality.

A total of 524 subjects were screened. 188 Subjects refused participation and 139 were excluded (most important reasons: medical conditions and use of anti-craving compounds). Of the 197 subjects, 41 filled out questionnaires, but refused further participation leaving 156 subjects for randomization. Of these 156 subjects, 30 were randomly assigned to placebo and were not included in the current analyses. The remaining 126 subjects were randomly assigned to acamprosate or naltrexone. 18 Subjects (14%) (seven in the acamprosate group, eleven in the naltrexone group) dropped out after the first session, leaving 108 subjects

Figure 1. Flow chart: subject progress through study phases.
(86%) who completed the study: 56 in the acamprosate group, 52 in the naltrexone group (see Figure 1). Only treatment completers were included in the analysis. Table 1 shows the sample characteristics. Most participants were Dutch, male, unemployed, unmarried, and had low education. On average, 28.7% was inpatient, 38.0% outpatient and 33.3% non-treatment-seeking. Most subjects had moderate to severe levels of alcohol dependence. Groups were comparable with respect to the mean number of days without heavy drinking (≥ 5 units) (respectively 30.4 and 19.4 days for the naltrexone and the acamprosate group). Gender and benzodiazepine use may be potential confounders of the relationship be-

| Table 1. Patient characteristics and alcohol-related variables. |
|-----------------|-----------------|-----------------|-----------------|
| Patient characteristics | Naltrexone (n=52) | Acamprosate (n=56) | P-value |
| Mean age in years (SD) | 47.2 (10.1) | 48.1 (9.8) | 0.62 |
| Men (%) | 78.8 | 66.1 | 0.14 |
| Dutch ethnicity (%) | 88.5 | 76.8 | 0.11 |
| Inpatients (%) | 32.7 | 25.0 | 0.38 |
| In treatment at a clinic (%) | 69.2 | 64.3 | 0.59 |
| Higher education (%) | 28.0 | 38.9 | 0.24 |
| Mean years of education (SD) | 13.6 (4.3) | 13.4 (3.9) | 0.77 |
| Employed (%) | 58.0 | 57.4 | 0.95 |
| Married (%) | 32.0 | 16.7 | 0.07 |
| Alcohol-related variables |
| Mean AUDIT score (SD) | 21.3 (5.1) | 20.8 (5.4) | 0.61 |
| Mean age of onset (SD) | 35.9 (10.3) | 35.2 (9.7) | 0.74 |
| Other substance use |
| Using benzodiazepines (%) | 12.0 | 13.0 | 0.88 |
| Using cannabis (%) | 8.0 | 18.5 | 0.12 |
| Using nicotine (%) | 84.0 | 92.6 | 0.17 |
| Using anti-depressives (%) | 26.0 | 31.5 | 0.54 |

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test.
between the use of certain medications and changes in cue-induced craving and physiological cue reactivity, and therefore these variables will be used as covariates in all analyses.

**GENERAL DESIGN**

All subjects filled out self-report questionnaires immediately after inclusion in the study. In addition, blood was drawn for genotyping. Table 2 shows a schematic overview of the assessed indicators of relief and reward drinking. The selection was based on their fit with the concepts of relief and reward drinking, the validity of their measurement, and their association with the pharmacological mechanism of action of naltrexone and acamprosate. All subjects subsequently participated in a randomized, double-blind, controlled protocol: the subjects received 21 days acamprosate or naltrexone under supervision of a physician. The dosages of naltrexone and acamprosate were given according to current treatment recommendations. For acamprosate, 2.0 g/day was given to patients with bodyweight >60 kg, and 1.3 g/day in patients with bodyweight <60 kg. The recommended dose of naltrexone is 50 mg/day. All tablets were identical in appearance.

All subjects were exposed to two cue-exposure sessions with the same protocol: the first at the day before and the second at day 21 of the medication period. In addition, a retrospective assessment of medication compliance was performed. After unblinding, a treatment advice was given by the physician. All subjects received vouchers with a total value of €35 (~ $28).

**CUE EXPOSURE PROCEDURE**

After inclusion in the study, subjects were prepared for a cue-exposure challenge. Based on a Drinking Triggers Interview (DTI; Monti et al., 1993a), individualized audiotaped mood induction scripts were prepared (Cooney et al., 1997). The aim of the script was to induce the mood in which the subject was most likely to experience craving. One day before the start of the medication period, a cue-exposure challenge was followed by the assessment of cue-induced craving and physiological cue reactivity (Cooney et al., 1997; Monti et al., 1993b). First, subjects were screened on alcohol use and connected to electrodes and acclimatized for thirty minutes. Each subject was then asked to relax for four minutes. The subject’s favorite beverage was then poured in the glass in front of the subject. While the pre-recorded mood-induction script was played over the headphone for five minutes, the subject was instructed to sniff the beverage four times. At the end of the cue-exposure session, craving was measured with a Visual Analogue Scale (VAS) before bringing the participant back to a relaxed state.
Chapter 6

Table 2. Potential phenotypic, endophenotypic and genetic indicators of relief- and reward drinkers for matching with acamprosate and naltrexone.

<table>
<thead>
<tr>
<th>Potential indicators</th>
<th>Relief drinkers</th>
<th>Reward drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypic</td>
<td>Relief drinking motives subscale 'vulnerability'</td>
<td>Reward drinking motives subscale 'stimulation seeking'</td>
</tr>
<tr>
<td></td>
<td>Late-onset alcoholism</td>
<td>Early-onset alcoholism</td>
</tr>
<tr>
<td></td>
<td>Negative family history of alcoholism</td>
<td>Positive family history of alcoholism</td>
</tr>
<tr>
<td></td>
<td>Low withdrawal symptoms</td>
<td>High withdrawal symptoms</td>
</tr>
<tr>
<td>Endophenotypic</td>
<td>High baseline cue-induced HR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High baseline cue-induced SCL</td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td></td>
<td>OPRM1 polymorphism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRD1 polymorphism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRD2 polymorphism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABRA6 polymorphism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABRB2 polymorphism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABRG2 polymorphism</td>
</tr>
</tbody>
</table>

Reference: adapted from Verheul et al., 1999.
Abbreviations: HR, Heart Rate; SCL, Skin Conductance Level.

Baseline Matching Indicators

Phenotypic self-report indicators
At baseline, the following assessments were completed as phenotypic indicators of relief and reward drinking: the reward motives subscale ‘stimulation seeking’ and the relief motives subscale ‘stress and vulnerability’ of the Alcohol Motives for Drinking Scale (AMDS) (Ooteman et al., 2006a), and a series of self-constructed items to assess withdrawal symptoms at baseline, the family history of alcoholism (FH), and age of onset. A positive family history was defined as at least one first degree relative (parents or siblings) having (had) an alcohol problem.

Endophenotypic indicators
As potential endophenotypic matching indicators, the following physiological
cue reactivity measures were continuously recorded during the first cue-exposure challenge: (1) heart rate (HR); and (2) skin conductance level (SCL). Based on these assessments, Δ peak values (see statistical analysis) were calculated.

For HR assessment, ECG (electrocardiogram) electrodes were placed on either side of the participant’s chest. A Contact Precision Instruments analogue-digital converter (ADC) sampled the ECG signal at a rate of 300 Hz and calculated the number of interbeat intervals (IBI’s) during 10-second sampling periods (range 2mV, High Pass 10Hz, Low Pass 200Hz).

For the assessment of SCL, electrodes were taped to the middle phalanx of the forefinger and the middle finger of the participant’s nondominant hand. The skin conductance signal was amplified by a Contact Precision Instruments skin conductance coupler, sampled at a fixed 40Hz. SCL was averaged across a 10-second sampling period.

Genetic indicators

As genetic indicators of reward drinking the following polymorphisms were tested: µ-opioid receptor (gene: OPRM1; alleles A+/118G); D1 dopamine receptor (gene: DRD1; alleles: D2+1405Dr) and D2 dopamine receptor (gene: DRD2; alleles: TaqI A1/A2) (TaqAI). As genetic indicators for relief drinking the following polymorphisms were tested: GABAA alpha6 subunit (gene: GABRA6; alleles: T+1519C); GABAA-receptor beta2 subunit (gene: GABRB2; alleles: C+1412T) (BanI); and GABAA-receptor gamma2 subunit (gene: GABRG2; alleles: G+3154A). Genomic DNA was extracted from blood samples by standard commercial protocol using the kit from Qiagen. Most PCR (Polymerase Chain Reaction) amplifications were carried out in a total volume of 25 ml with 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 0.4–1.4 mM MgCl2, 10–30 pM of each deoxyribonucleoside triphosphate (GIBCOBRL), 1.0–2.5 U Taq DNA polymerase (New England Biolabs), 10–30 pmol of each primer (Eurogentec, Belgium) and 10–100 ng of genomic DNA. For specific regions with a high G+C content, 16 mM (NH4)2SO4, and 5% DMSO were added with the other parameters unchanged. Amplifications were carried out in an Eppendorf Mastercycler and cycling conditions were performed according to a specific protocol for each polymorphism (available on request). Amplified fragment was digested for 16h and RFLP products were loaded onto 2-3% agarose gels.

Outcome measures

Cue-induced self-report outcome measure

At baseline craving was measured on a 10-point VAS scale (‘How strong is your urge or need to drink right now?’). Immediately after cue exposure, subjects were
asked again to give a rating on a 10-point VAS scale (‘How strong was your strongest urge or need to drink alcohol during the session?’). For both test sessions, cue-induced craving scores (Δ peak values) were calculated and then subtracted (see statistical analysis).

**Physiological cue reactivity outcome measure**

Heart rate (HR) was continuously recorded during both cue-exposure challenges. Based on these assessments, Δ peak values were calculated for both sessions and then subtracted (see statistical analysis).

**Statistical analysis**

Responses to each cue-exposure session were operationalized as Δ peak values. For craving, a Δ peak score was calculated by subtracting the baseline VAS score (i.e., before the cue exposure) from the VAS score filled out immediately after cue exposure (Δ peak VAS). For HR and SCL, Δ peaks were calculated by subtracting the average of the last minute of the baseline period from the maximum value during the five minutes lasting cue-exposure period. Delta peaks for VAS and HR were calculated both for the cue-exposure session before the start of the medication and the cue-exposure session at the end of the medication three weeks later. The differences in pre and post medication Δ peak scores (ΔΔ peaks) were used as outcome measures. A matching effect can statistically be translated as a significant interaction between the medication condition and the potential matching indicator in regression models with medication condition and matching variables as independent variables and ΔΔ peak VAS and HR as dependent variables. The matching properties of all indicators were estimated by using univariate ANCOVAs (General Linear Model, SPSS 12), with differences in Δ peak scores between the first and second cue-exposure session as dependent variable, medication as a fixed factor, 13 potential matching indicators, gender and benzodiazepine use as covariates, and the 13 interactions between medication and potential matching indicator as indications for the matching effect. To adjust for regression to the mean effects in ΔΔ peak scores, the pre-medication Δ peak score was also added as covariate to each model. Based on the sample size, the related risk of type II errors and the relatively low power of tests for interaction terms (compared to tests for main effects) α was set at 0.10. Effects with p-values between 0.10 and 0.20 were regarded trends.
Results

Medication Compliance
The mean percentage of taken pills during the 21 days was 99.1% in the naltrexone group, and 96.5% in the acamprosate group. These findings were confirmed by data on medication (metabolites) in randomly taken urine samples and by a pill count.

Matching Properties of Phenotypic Indicators
With respect to the phenotypic indicators of relief and reward drinking, no significant indicator by treatment condition interactions were found. P-values ranged from 0.30 to 0.97 for ΔΔ peak VAS and from 0.42 to 0.90 for ΔΔ peak HR.

Table 3a. Significant matching variables with their parameter estimates of the regression analyses in General Linear Model and ΔΔ peak VAS as outcome measure.

<table>
<thead>
<tr>
<th>Type of indicator</th>
<th>Effect</th>
<th>β-Coefficient</th>
<th>Standard error</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reward indicators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD2 frequency A1</td>
<td>Interaction</td>
<td>1.220</td>
<td>0.702</td>
<td>0.086</td>
</tr>
<tr>
<td>DRD2 frequency A2</td>
<td>Interaction</td>
<td>-1.220</td>
<td>0.702</td>
<td>0.086</td>
</tr>
<tr>
<td>DRD2 A1A1/A1A2 vs A2A2</td>
<td>Interaction</td>
<td>-1.330</td>
<td>0.877</td>
<td>0.133</td>
</tr>
<tr>
<td>DRD2 A2A2/A1A2 vs A1A1</td>
<td>Interaction</td>
<td>2.544</td>
<td>1.843</td>
<td>0.171</td>
</tr>
<tr>
<td><strong>Relief indicators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ peak SCL at first CE session</td>
<td>Interaction</td>
<td>1.381</td>
<td>0.750</td>
<td>0.069</td>
</tr>
<tr>
<td>GABRB2 CC/TT versus CT</td>
<td>Interaction</td>
<td>2.895</td>
<td>1.491</td>
<td>0.055</td>
</tr>
<tr>
<td>GABRA6 CC/TT versus TT</td>
<td>Interaction</td>
<td>-1.768</td>
<td>0.975</td>
<td>0.073</td>
</tr>
<tr>
<td>GABRA6 frequency T</td>
<td>Interaction</td>
<td>-1.085</td>
<td>0.582</td>
<td>0.066</td>
</tr>
<tr>
<td>GABRA6 frequency C</td>
<td>Interaction</td>
<td>1.085</td>
<td>0.582</td>
<td>0.066</td>
</tr>
</tbody>
</table>

β-Coefficients, pertain to indicator by treatment interaction terms in a GLM with treatment condition, indicator and treatment by indicator as dependent variables, standard errors and p-values are presented for those indicator by treatment interaction terms with \( p<0.1 \) and \( p<0.2 \) (trends). Abbreviations: SCL, Skin Conductance Level; CE, Cue Exposure.
No significant interactions with treatment condition were found for ∆peak HR at baseline. However, a significant interaction effect was found for ∆peak SCL at baseline, showing a larger decrease in ∆peak VAS at the second cue-exposure session in the acamprosate group, when ∆peak SCL at baseline was high (p < 0.1). (see Table 3). A trend was found for ∆peak SCL at baseline on ∆∆peak HR.

These findings are partly in line with the matching hypotheses.

MATCHING PROPERTIES OF ENDOPHENOTYPIC INDICATORS
No significant interactions with treatment condition were found for ∆peak HR at baseline. However, a significant interaction effect was found for ∆peak SCL at baseline, showing a larger decrease in ∆peak VAS at the second cue-exposure session in the acamprosate group, when ∆peak SCL at baseline was high (p < 0.1) (see Table 3). A trend was found for ∆peak SCL at baseline on ∆∆peak HR. These findings are partly in line with the matching hypotheses.

MATCHING PROPERTIES OF GENETIC INDICATORS
With respect to the genetic indicators, no significant interaction effects were found for the DRD1 and GABRG2 genotypes (data not shown). However, significant effects were found for the DRD2, the GABRA6, and the GABRB2 genotype (see Table 3, Figures 2 and 3). GABRB2 showed a significant effect with treatment condition on both ∆∆ peak VAS and ∆∆ peak HR (p < 0.1). With respect to ∆∆ peak VAS, naltrexone outperformed acamprosate when the GABRB2 gene was homozygous (CC or TT; the more frequent genotypes, 90% of the sample), but
Predicting the effect of naltrexone and acamprosate

not when the GABRB2 gene was heterozygous. With respect to HR, acamprosate outperformed naltrexone in the homozygous TT group (11% of the sample).

In addition, significant interaction effects were found for the DRD2 and the GABRA6 genotypes on Δ Δ peak VAS (p<0.1), but not on Δ Δ peak HR. With respect to the DRD2 gene, naltrexone outperformed acamprosate in patients homozygous for the A2-allele (60% of the sample), whereas acamprosate outperformed naltrexone in patients homozygous for the A1-allele (6% of the sample). Efficacy of both treatments was similar in heterozygous patients (34% of the sample). With respect to the GABRA6 genotype and Δ Δ peak VAS, acamprosate outperformed naltrexone in patients homozygous for the C-allele (29% of the sample), whereas naltrexone outperformed acamprosate in heterozygous patients (46% of the sample) and in patients homozygous for the T-allele (25% of the sample).

In line with our prediction, a trend was found for the OPRM1 genotype on Δ Δ peak HR (p=0.18). Naltrexone outperformed acamprosate in G-allele carriers (GG or AG; 18% of the sample) at the OPRM1 gene, whereas acamprosate outperformed naltrexone in the A-allele homozygous group (82% of the sample). However, this trend for the µ-opioid receptor was not found with Δ Δ peak VAS as the outcome measure.

Figure 2. Genetic indicators: effect on cue-induced craving. Error bars show mean ±1.0 SE.

Abbreviations: Δ Δ VAS=delta delta peak VAS.

A A1-allele frequency at the DRD2 gene (p=0.086)
CHAPTER 6

B C-allele frequency at the GABRA6 gene ($p=0.066$)

C Heterozygous versus homozygous at the GABRB2 gene ($p=0.055$)
Predicting the effect of naltrexone and acamprosate

D C-allele frequency at the GABRB2 gene ($p=0.53$)

Figure 3. Genetic indicators: effect on cue-induced heart rate. Error bars show mean ±1.0 SE.

Abbreviations: $\Delta \Delta$ HR=delta delta peak heart rate.

A Weight of the G-allele at the OPRM1 gene ($p=0.18$)
CHAPTER 6

B G-allele frequency at the OPRM1 gene ($p=0.39$)

C C-allele frequency at the GABRB2 gene ($p=0.014$)
Summarizing our results, no significant matching effects were found with regard to the phenotypic indicators of relief and reward drinking. At the endophenotypic level, a significant interaction effect was found on $\Delta \Delta$ peak VAS for $\Delta$ peak SCL at baseline. With respect to the genetic indicators, significant interaction effects on $\Delta \Delta$ peak VAS were found for polymorphisms at the DRD2 and GABRA6 gene, whereas this was also true for $\Delta \Delta$ peak VAS and HR for polymorphisms at the GABRB2 gene. A trend was found for the OPRM1 polymorphism on $\Delta \Delta$ peak HR.

First, at the phenotypic level no evidence was found that could support the hypotheses. Therefore it is questionable whether phenotypic indicators of reward and relief drinking are useful matching variables. This conclusion is in line with a recent review (Ooteman et al., 2005), generally showing that phenotypic characteristics have not been found to be effective matching indicators and that endophenotypic and genetic indicators may be more promising.

Second, at the endophenotypic and genetic level a number of significant interactions were found, generally in line with the matching hypotheses: depending on the specific polymorphism acamprosate or naltrexone was more effective. Thus regarding the GABA\(_A\) receptor subunit genes, the efficacy of acamprosate
on ΔΔ peak VAS is enhanced depending on the C-allele frequency of the GABRA6 gene, whereas the efficacy of naltrexone is enhanced by the frequency of the T-allele. In addition, the efficacy of acamprosate is enhanced on ΔΔ peak HR in T-allele homozygotes for the C+1412T polymorphism of the GABRB2 gene. No effect was found for the G+3145A polymorphism of the GABRG2 gene. Regarding the dopamine receptors, no effect was found for the D2+1403D1 polymorphism of the DRD1 gene, but interestingly for the polymorphism Taq1A of the DRD2 gene, when homozygous genotypes were compared, acamprosate outperformed naltrexone in A1-allele carriers whereas naltrexone outperformed acamprosate in A2-allele carriers. Both treatments displayed equal efficacy in subjects heterozygous for this polymorphism. In line with our findings, the A1 allele of the DRD2 Taq1A polymorphism has previously been associated with alteration of brain opiate receptors (Ritchie and Noble, 1996). It was shown that [3H]naloxone binding in the caudate nucleus was lower in brain regions of alcoholic subjects with the A1 allele than in those without this allele. This is in line with our finding that the efficacy of naltrexone in the A1-allele homozygotes is decreased compared to the A2-allele carriers, suggesting that treatment outcome with opioid antagonists maybe related to the polymorphic pattern of the DRD2 gene. Taken together, these data show that the benefit of each treatment is dependent upon (a combination of) polymorphisms of the studied candidate genes.

Third, we found a trend for the OPRM1 polymorphism on ΔΔ peak HR. The observed trend indicated that naltrexone’s efficacy was enhanced in G-allele carriers; a finding that is in line with our hypotheses and the findings of the study by Oslin et al. (2003) showing that naltrexone’s efficacy in preventing relapse in alcohol-dependent patients was greater in G-allele carriers. In line with this, it has previously been found that individuals with the G-allele may have more efficient binding of naltrexone to the µ-opioid receptor (Bond et al., 1998). Another study has shown that G-allele carriers displayed greater subjective feelings of intoxication and greater sensitivity to the sedating and stimulating effects of alcohol (Ray and Hutchison, 2004).

Fourth, we expected that naltrexone would differentially exert its affect in reward drinkers at cue-induced craving and acamprosate in relief drinkers at cue-induced heart rate (Ooteman et al., submitted). We could only partly confirm the differential effects of naltrexone and acamprosate on cue-induced craving and heart rate respectively.

The finding that genetic and endophenotypic indicators of reward and relief drinking have more matching potential in this study than phenotypic indicators, may be a consequence of the fact that they are more closely related to the neurobiological disease process (Gottesman and Gould, 2003).
endophenotypes often show low correlations (Tiffany, 1990); a finding that was recently illustrated by our own study showing that craving (phenotype) correlates low with physiological cue reactivity (endophenotype) because of individual differences in detection or report of physiological reactions (Ooteman et al., 2006b). As a result of these individual differences in detection or report, endophenotypic reactions may lead to rather fuzzy phenotypic characteristics that are less closely related to the underlying neurobiological mechanisms of addiction.

A strength of the study is that it is the first controlled study that includes variables at the phenotypic, endophenotypic and genetic level, as well as phenotypic and endophenotypic outcome measures. As a result, this is the first study that shows matching opportunities for the different levels of patient characteristics for biological changes in the disease process (e.g., physiology) and intermediate disease outcomes (e.g., craving).

The study also has limitations. The sample size is relatively small, especially for the discovery of significant interaction effects. In order to prevent type II errors and the premature closure of important new opportunities for improvements in treatment allocation and treatment efficiency, it was decided to restrict the collection of data to those variables with a clear position in a theoretical framework, not to correct for multiple testing, and to test at a significance level of $p < 0.10$. The downside of this strategy is the increased risk of type I errors and, therefore, we emphasize the need for replications of the current findings in new trials with larger samples and a limited number of matching variables, e.g., only those that have shown to be promising in earlier studies such as the current one. Another important limitation is the fact that treatment lasted only three weeks and outcome was defined in terms of changes in cue-induced craving and physiological cue reactivity and not in terms of relapse into (uncontrolled) use of alcohol. It should be noted, however, that the trend that was observed with regard to the OPRM1 gene has a direct translation in the findings of the study by Oslin et al. (2003), showing significant better drinking outcomes in patients with the AG and GG alleles on the OPRM1 gene treated with naltrexone. We are, therefore, confident that the results of the current short term study have potential for the future planning of patient allocations and the increase of treatment effectiveness, treatment efficiency, and finally also the cost-effectiveness of addiction treatment strategies.

In conclusion, this study shows promise at the genetic and endophenotypic level for matching of certain patients to specific treatments. More research is needed to replicate the findings in bigger samples, longer treatments and follow-up periods using drinking parameters as the primary outcome variables.

Although we found no phenotypic matching indicators of relief and reward
drinking, it does not exclude that phenotypes that are not related to these concepts (e.g., craving level at baseline) will show matching properties. It is therefore suggested for future research to also test models for matching that are not related to the concept of relief and reward. Since endophenotypic and genetic indicators now seem to be more promising, it is warranted that future (adapted) models for matching research and relapse prevention strongly focus on these indicators.

Acknowledgements

We thank Clemens Kirschbaum for his advice on the cortisol data and Hans Kronemeijer for his data management, advice and support. We thank Simone Höhner, Premal Koning, Ron Baas, Sigrid Wittenberg, Dorine Eeken, Kai Hulstijn, Weena Chen and Gjalt de Vries for their assistance.

References

Predicting the effect of naltrexone and acamprosate

CHAPTER 7

Summary and General Discussion
Summary and General Discussion

In this final chapter, a summary and general discussion is provided of the results of the current study. The chapter will end with clinical implications and some directions for future research in this field.

Research questions

This thesis started with the assumption that the relatively small effect sizes of anti-craving medications are due to poor patient-treatment matching. It was stated that alcohol-dependent patients can effectively be treated with anti-craving medications such as the opioid antagonist naltrexone and the glutamate antagonist acamprosate. However, effect sizes are generally rather small (NNT=7) and many patients do not seem to benefit from these medications (Mann, 2004; Mann et al., 2004; Srisurapanont and Jarusuraisin, 2005a, 2005b). It was further stated that these moderate effect sizes are probably owing to inadequate patient-treatment matching, i.e., patients do not always receive the medication that is most appropriate for their specific problem.

The research questions of this thesis are primarily based on the three-pathway model of craving (Verheul et al., 1999). The model describes a typology of drinkers that starts off from different, theoretical types of motives to drink alcohol such as relief and reward motives. In addition, the model assumes a high and direct relation between physiological cue reactivity and craving. However, at the time the hypothetical three-pathway model was presented, no valid questionnaires were developed to test these assumptions.

In this thesis, the matching properties of phenotypic, endophenotypic, and genetic indicators of relief and reward drinkers were studied in alcohol-dependent patients treated with naltrexone or acamprosate. As such, the main aim of this thesis was to improve the treatment efficacy of naltrexone and acamprosate through the identification of matching variables for the effect of naltrexone and acamprosate on the intermediate outcome variables cue-induced craving and physiological cue reactivity. However, before the main study could be started, new assessment instruments had to be developed to adequately measure drinking motives and craving in alcohol-dependent patients.

The thesis attempted to find answers to the following research questions:
CHAPTER 7

1. Can reward and relief drinkers be distinguished based on their drinking motives?
2. What is the relationship between cue-induced craving and physiological cue reactivity?
3. Are naltrexone and acamprosate differentially effective with respect to the reduction of cue-induced craving and physiological cue reactivity?
4. Does naltrexone exert its anti-craving effect primarily in reward drinkers, whereas acamprosate exerts its anti-craving effect primarily in relief drinkers? This question can also be phrased in the following – clinically more relevant – way: can we identify potential matching indicators of reward and relief drinking for naltrexone’s and acamprosate’s efficacy in the reduction of cue-induced craving and physiological cue reactivity?

Summary of the findings

Chapter 2 provided a literature review on the matching properties of patient characteristics that modify the effect of acamprosate, naltrexone, and serotonergic medications on craving and relapse in alcoholics. It is concluded that studies using phenotypic matching variables have produced inconsistent and rather disappointing results. In contrast, genetic matching variables seemed to be quite promising (e.g., μ-opioid receptor polymorphism). No studies that looked at endophenotypic matching variables could be identified. It was concluded that phenotypic matching variables might be too distal, i.e., too far removed from the pathogenic mechanisms, and that matching research should shift its attention towards indicators that are more proximal to the pathogenic process, i.e., genetic and endophenotypic variables.

Chapter 3 reported on the development and validation of a questionnaire that was supposed to distinguish relief and reward drinkers at the phenotypic level: the Amsterdam Motives for Drinking Scale (AMDS). The AMDS reliably measured relief and reward drinking motives, but these scales were highly correlated. Only at subscale level, lower correlations were found. It therefore seems that most treatment-seeking alcoholics have both relief and reward motives for their drinking. With respect to matching, it was recommended to conduct more research on the relation with other phenotypic, endophenotypic, and genetic indicators of relief and reward drinking, and on appropriate cut off points to distinguish both groups.

In chapter 4, the results of a study on the development of a novel craving questionnaire (the Jellinek Alcohol Craving Questionnaire; JACQ) were reported with the objective to better connect cue-induced craving and physiological cue reactivity. The JACQ reliably measured one dimension including four aspects of
craving for distinct time frames. Despite the presence of a special subscale for physical sensations, only moderate correlations were found between self-reported craving and physiological indicators of cue reactivity. It was concluded that the lack of strong associations between craving and physiological cue reactivity can not be attributed to differences in content, but that the observed low correlations are the result of individual differences between alcoholics in their awareness and/or reporting of physiological cue reactivity. Further research should focus on the nature of these individual differences. In addition, it was recommended to conduct more research on the relative predictive validity of self-reported cue-induced craving versus physiological measures of cue reactivity in the prediction of relapse.

In chapter 5, the differential effect of acamprosate and naltrexone on cue-induced craving and physiological cue reactivity was studied. Consistent with the hypotheses, naltrexone reduced craving more than acamprosate, and reversely, acamprosate reduced heart rate more than naltrexone. No indications were found for a medication effect on changes in cue-induced cortisol production. The findings provided evidence that naltrexone exerts its effects, at least partly, by the reduction of cue-induced craving, whereas acamprosate exerts its effects, at least partly, by the reduction of physiological cue reactivity.

Finally in chapter 6, the results of a study on matching indicators of relief and reward drinkers for the treatment with acamprosate and naltrexone were reported. No matching indicators of relief and reward drinking were found at the phenotypic level. However, a significant matching effect was found for baseline physiological cue reactivity at the endophenotypic level (skin conductance) and significant matching results were found at the genetic level for polymorphisms of the DRD2, GABRA6 and GABRB2 genes. A trend in the expected direction was found for a polymorphism of the OPRM1 gene. It was concluded that the matching hypotheses by Verheul et al. (1999) were only partly confirmed. It was recommended to elaborate on the endophenotypic and genetic findings in larger samples.

Discussion

Based on the findings of the literature review (chapter 2) and the findings described in the matching study (chapter 6), it can be concluded that endophenotypic and genetic indicators may be more promising as matching variables than phenotypic indicators. Since phenotypic matching indicators are scarce despite the amount of research on phenotypes, for future matching research, a careful shift in attention from phenotypic indicators to endophenotypic and genetic indicators may be the most promising next step. Phenotypic indicators can also be
referred to as *explicit* measures, which means that people are asked directly to introspect about the causes of their behavior (e.g., 'Why do you drink?'), usually through traditional self-report questionnaires (Wiers and Stacy, 2006). Endophenotypic indicators, on the contrary, are also referred to as *implicit* measures, defined as 'introspectively unidentified (or inaccurately identified) traces of past experiences that mediate feeling, thought or action' (Greenwald and Banaji, 1995). The assessment of implicit indicators has several potential benefits (e.g., Wiers and Stacy, 2006): (1) implicit measures may assess cognitive processes that are not available through introspection (detection bias); (2) implicit measures are often less sensitive to self-justification and social desirability (report bias); (3) implicit indicators often explain a unique part of the variance of different aspects of behavior; (4) implicit measures may be closer to the biological disease process; and (5) implicit indicators provide a new and important bridge between different disciplines as well as between human and animal research on addiction. The proposed shift in attention to the *implicit* endophenotypic and the genetic level does, however, does not necessarily imply that phenotypes should never be studied in matching research. For example, the literature review (chapter 2) shows that phenotypic matching indicators that are not related to relief and reward drinking can be promising (e.g., baseline self-reported craving levels, active drinking).

In chapter 3, we developed and evaluated a new phenotypic measure of relief and reward motives for drinking, because according to our model a subdivision of alcoholics in reward and relief drinkers would be promising for patient-treatment matching strategies. However, the Amsterdam Motives for Drinking Scale (AMDS) that was especially developed for this purpose failed to distinguish reward and relief drinkers. The two scales of the AMDS were highly correlated. Apparently, the AMDS cannot distinguish reward and relief drinkers and therefore has currently no role in patient-treatment matching strategies. Although we expected to find lower correlations between relief and reward motives because of clearly defined concept definitions, our results are in line with previous studies (e.g., Kiefer et al., 2003) showing that most alcohol-dependent patients mention both relief and reward motives for their alcohol intake. How can this be explained? Although awareness of explicit drinking motives is a prerequisite for the valid administration of the AMDS, low awareness of the real motives for drinking is not the most likely explanation for the high correlation between relief and reward motives for drinking. If awareness had been low, we would have expected a low correlation as a result of lower variance. A more likely explanation may be that alcoholics in the current study have developed both reward and relief motives in the course of their addiction: patients may have started off with reward motives but in the course of their addiction may have developed additional relief...
motives for drinking as a consequence of repeated withdrawal episodes and chronic mood disorders due to long periods of excessive drinking (Compton et al., 2000; Clark and Bukstein, 1998; Becker, 1998; Littleton, 1998). In addition, relief motives may become more prominent than reward motives especially at higher levels of drinking (Farber et al., 1980; Carey and Carey, 1995). This post-hoc explanation should be tested in studies that follow social drinkers during the development of their drinking career. It may still be possible that relief and reward drinkers can be distinguished at the phenotypic level in nondependent recreational or problematic users. It must be noted, however, that a study by Cooper et al. (1995) was not able to find low correlations between relief and reward motives in an adult and adolescent group of social drinkers (r=0.59).

In chapter 4 of this thesis, the relation between a phenotypic matching and outcome measure (cure-induced craving) and an endophenotypic matching and outcome measure (physiological cue reactivity) was studied. Self-reported cue-induced craving and physiological cue reactivity showed a lack of concordance: subjects with no physiological cue reactivity almost never reported craving, whereas only part of the subjects with physiological cue reactivity reported craving. Although we expected to find a higher correlation between the specially designed physical subscale of the craving questionnaire and physiological cue reactivity, we found a rather low correlation that was very similar to those found in previous studies (see for a review: Tiffany, 1990). It was concluded that the absence of a substantial correlation was probably due to individual differences between alcoholics in terms of their awareness (detection levels) or report (social desirability) of cue-induced physical reactions. In line with the first explanation, Monti et al. (1987, 1993) found craving to be significantly correlated with sensory awareness (r=0.47). With regard to the second explanation, Marissen et al. (2005) found that social desirability was negatively associated with craving but not with physiological cue reactivity, but social desirability did not modify the relationship between craving and physiological cue reactivity. Others found that the level of concordance between craving and physiological cue reactivity is a function of severity of alcohol dependence (Kaplan et al., 1983, 1985). It can be concluded that the relation between distinct phenotypes (e.g., craving) and endophenotypes (e.g., physiological cue reactivity) is mediated by several factors, which should be taken into account in future studies that attempt to connect these important phenomena. The results and their interpretation also indicate that no further efforts should be made to develop craving questionnaires with subscales that are strongly correlated with indicators of physiological cue reactivity.

In chapter 5, a differential effect was found for acamprosate and naltrexone with respect to physiological cue reactivity and cue-induced craving. These findings are in line with the matching hypotheses of Verheul et al. (1999), predicting
that acamprosate exerts its effect mainly through a reduction in cue reactivity in patients with high physiological arousability. They are also in line with the literature review (chapter 2) showing that naltrexone exerts its effects mainly through a reduction in craving in patients with high levels of baseline craving. The moderate effect sizes for acamprosate as well as for naltrexone in this brief medication trial of 21 days were in line with most of the existing effect studies with 3 to 12 months treatment duration (Mann, 2004; Srisurapanont and Jarusuraisin, 2005a, 2005b). However, most of the other studies did not use cue-induced craving and physiological cue reactivity as their primary outcome measure, but in stead used non-induced craving or drinking related outcome measures (e.g., relapse). Despite these differences in outcome measures, effect sizes were very similar in all studies, including the 21-day medication challenge in the current study. One of the explanations for these moderate effect sizes is inadequate patient-treatment matching. In line with this theory the scatterplots of the study in chapter 5 showed that subgroups of alcoholics differentially responded to acamprosate or naltrexone. One part of the patients seemed to benefit with reasonably large effect sizes, whereas another part may even show an effect in the opposite direction. Obviously, different patients respond differently to the same and alternative treatment strategies, indicating the need for a better match between patients and treatments.

In chapter 6, the matching hypotheses of Verheul et al. (1999) were tested, and only partly confirmed. At the phenotypic level no significant matching indicators were found. Given the available literature, this should come as no surprise. Despite a reasonable amount of research on phenotypes, only few phenotypic indicators (and these were no indicators of relief and reward drinking) appeared to have some matching potential (e.g., high baseline craving, active drinking; see chapter 2) and some previous studies in large patient populations did not find any phenotypic matching indicators (e.g., Verheul et al., 2005). Fortunately, we did find one endophenotypic patient characteristic for matching with acamprosate and nalrexone (high baseline cue reactivity of skin conductance), which was in line with the matching hypotheses. The other endophenotype we tested (baseline cue reactivity of heart rate) did not show a significant interaction effect. Apparently, not all physiological indicators of relief and reward drinking have matching potential. On the other hand, there may be other endophenotypic indicators of relief and reward drinking which have not yet been tested, e.g., attentional bias with respect to images related to reward and relief drinking, cue modulated startle responses (CMSR), brain activation following reward and relief related stimuli (fMRI) or availability, distribution, density, activation and binding sensitivity of receptors in the dopaminergic, opioidergic, glutamatergic or GABAergic system (PET or SPECT). Although these endophenotypes have
been studied in relation to alcohol/drug dependence and the processing of alcohol/drug cues or craving (e.g., Franken et al., 2004, 2005; Heinz et al., 2004), they are not yet studied in relation to matching with acamprosate and naltrexone. However, this relatively unexplored area of endophenotypic indicators may have considerable matching potential.

With respect to the genetic findings of the matching study in chapter 6, the findings show limited supportive evidence for the matching hypotheses. We did find significant interaction effects for polymorphisms at the DRD$_2$, GABRA6, and GABRB2 gene but not at the DRD$_1$ and GABRG2 gene, showing that only distinct genotypes have good matching properties. Also a trend for the matching potential of the polymorphisms at the OPRM1 gene was found, which is in line with the study of Oslin et al. (2003). However, in Oslin's study, drinking behavior was the outcome measure, and naltrexone was compared with placebo. In our matching study, the strongest interaction effects were found for polymorphisms at the GABRB2, GABRA6, and DRD2 gene. Although no previous studies are known that investigated their matching properties, a number of genetic studies showed a relation of these genes with alcohol dependence (e.g., Loh and Ball, 2000; Sander et al., 1999; Connor et al., 2002). Interestingly, the genes appeared to be predictive for both acamprosate and naltrexone’s effectiveness, with the direction of the effect depending on the polymorphism; a finding that is not directly related to the matching hypotheses of Verheul et al. (1999). A post-hoc explanation for this finding may be that both acamprosate and naltrexone act on the glutamatergic/GABAergic system and the dopaminergic/opioidergic system or that one system interacts with the other or provides feedback.

The strengths and limitations of the studies

In chapter 2, we concluded that most studies that have attempted to test the matching hypotheses by Verheul et al. only examined phenotypic indicators, producing inconsistent results. Another striking finding was that most studies were conducted in small samples of outpatients, without competitive medications, and with relapse or craving as the only outcome measures. Studies with cue-induced craving and physiological cue reactivity as the primary outcome measures were scarce. One of the strengths of the current study is therefore that it is the first controlled study that uses both medications and simultaneously measures potential effect modifiers at the phenotypic, endophenotypic, and genetic level with both cue-induced craving and physiological cue reactivity as outcome measures. A second strength of the study is that we tested the matching hypotheses of Verheul et al. (1999) in a heterogeneous sample of alcohol-dependent patients. The fact that the study is testing matching hypotheses that are based on
Chapter 7

A theoretical model is a third strength of the study. Furthermore, the self-reported medication compliance (especially for chapter 5 and 6) was high and confirmed by data on medication (metabolites) in randomly taken urine samples and by a pill count; objective indicators of medication compliance that will be published elsewhere.

Our studies also had some limitations. As a first limitation, it must be noted that the matching hypotheses by Verheul et al., were based on a typology of drinking motives that was not validated at the time we started our study. Moreover, this typology did not substantiate in our own study (chapter 3). In addition, we did not include all different types of drinkers included in the three-pathway model: obsessive drinkers were not distinguished from other types of drinkers. We also did not include all the indicators of relief and reward drinking as potential matching variables. Instead, we selected the most important indicators, and those that were best fitting the model. It cannot be excluded that (in retrospect) some of these decisions were less fortunate.

A second limitation, especially in chapter 5 and 6, is that some patients dropped out after randomization, resulting in smaller sample sizes and less statistical power. However, this dropout was not selective for medication condition and therefore did not seriously jeopardize randomization and internal validity. In order to prevent (residual) selection bias most of the analyses were controlled for baseline differences between the medication groups in terms of benzodiazepine use, gender, or dependence severity.

A third limitation (especially for chapter 5) is the fact that we had a relatively small placebo group and thus limited power.

A fourth limitation (especially for chapter 4, 5 and 6) is that subjects in the experimental study did not receive a neutral cue (e.g., the smell and sight of a glass of water) in addition to the alcohol cue in our cue-reactivity paradigm. This means that we cannot be entirely sure that the increase in physiological and subjective parameters is solely a result of the alcohol cue. However, many studies validated this paradigm, showing that an alcohol stimulus produces significantly higher physiological cue reactivity and cue-induced craving than a non-alcohol-related stimulus (e.g., Cooney et al., 1997; Kaplan et al., 1985). Therefore, it is very likely that the reactivity we measured is primarily induced by our alcohol cues. In addition, with respect to the cue-reactivity measures, the results indicate that there is a significant increase compared to resting baseline. In fact, the increases in for example mean heart rate and VAS score after cue exposure in chapter 4 are even slightly higher than the increases from baseline in the studies of Cooney et al. (1997) and Kaplan et al. (1985). Therefore it is not very likely that the observed significant changes are not a result of alcohol exposure or that they are solely 'noise'.
A fifth limitation is that outcome was only defined in terms of changes in cue-induced craving and physiological cue reactivity without an additional outcome variable pertaining to relapse into (uncontrolled) use of alcohol. Although the patients were instructed not to drink, we cannot exclude that some patients have been drinking during the medication period. Alcohol consumption is not only the most relevant clinical indicator of treatment success, it may also have interacted with the working mechanism of the medications, especially naltrexone (see for a review: Sinclair, 2001).

It should be noted, however, that the trend that was observed in chapter 6 with regard to the OPRM1 gene has a direct translation in the findings of the study by Oslin et al. (2003), showing significant better drinking outcomes in patients with the AG and GG alleles on the OPRM1 gene treated with naltrexone. We are, therefore, confident that the results of the current study have potential for the future planning of patient allocations and the increase of treatment effectiveness, treatment efficiency, and finally also the cost-effectiveness of addiction treatment strategies.

A final limitation is that the evaluation of the medication effect was performed already after three weeks with craving and physiological cue reactivity as the main outcome variables, whereas acamprosate and naltrexone are prescribed as medications for long-term relapse prevention. This is especially important since the relation between craving and relapse is still on debate and since it can not be excluded that these so-called anti-craving medications (O’Brien, 2005) exert their action through some other mechanism(s) of action. However, the observed effects and the matching potentials that were shown do lend support that at least part of the effects of acamprosate and naltrexone are obtained by their influence on physiological cue reactivity and cue-induced craving. In addition, the trend that was observed for the pharmacogenetic effect of the OPRM1 gene in the current study closely paralleled the matching effect of the OPRM1 gene in the treatment study of Oslin et al. (2003) with alcohol relapse as the main outcome.

**Clinical implications**

In addition to a better understanding of the differential mechanisms of action of naltrexone and acamprosate, the findings in this thesis have some important implications for daily clinical practice. Although serotonergic compounds still have an experimental character in alcohol relapse prevention, naltrexone and acamprosate have consistently shown to be moderately effective in a group of alcoholics and therefore these compounds are regarded to be the best and safest pharmacological options in alcohol relapse prevention currently available (chapter 2). Although there are no phenotypic indicators yet for acamprosate, it
is suggested that naltrexone should be prescribed to patients with the phenotypic characteristic of high baseline craving and active drinking behavior (see literature review: chapter 2). Other predictors for naltrexone may be positive family history, although this was not replicated in our study (see literature review in chapter 2 and matching study in chapter 6). It should be noted, however, that naltrexone generally does not lead to total abstinence (e.g., Garbutt et al., 2005) and that the effect seems to only last as long as the medication is continued (Mann, 2004). On the other hand, when total abstinence is the treatment goal, acamprosate may be the best treatment option currently available. In addition, there are some indications that the effect of acamprosate remains even months after discontinuation (Mann, 2004). It seems, therefore, that currently, the choice between acamprosate and naltrexone should be based on the intended treatment goal, the expected side effects and contraindications, and finally some preliminary patient-treatment characteristics such as the level of baseline craving and the actual drinking status.

Our findings do not support the matching properties of relief and reward motives for drinking at the phenotypic level, but the endophenotype ‘high baseline physiological cue reactivity’ (chapter 6) and genetic polymorphisms (chapter 6; Oslin et al., 2003) seem to be very promising. However, before these findings can be implemented, more research is needed to replicate these results. In addition, more research is needed on potential practical and financial aspects. At this moment, assessment of endophenotypes and genotypes may create logistic problems and be more time-consuming and expensive than assessment of phenotypes. However, the development of more efficient and less expensive technologies is rapidly progressing. It is therefore expected that more effective, efficient and cost-effective treatments can be offered when genetic and endophenotypic information is used in future patient-treatment matching strategies.

A final suggestion for clinical practice is to consider the option of combining acamprosate with naltrexone (Kiefer et al., 2003; Mason, 2005) or acamprosate with disulfiram (Besson et al., 1998).

How to integrate our findings in the three-pathway model and the matching hypotheses?

It has repeatedly been stated that the findings of the current study only partly confirm the matching hypotheses based on the three-pathway model of craving for alcohol (Verheul et al., 1999). Therefore, the question arises what these findings mean for the validity of the original model and for the need of subsequent adaptations of matching hypotheses.

With regard to the relief and reward drinking typology, this thesis (chapter 3)
pointed out that we were not able to distinguish reward and relief drinkers at the phenotypic level. This is in line with other studies showing that most nonalcoholic social drinkers describe both reward and relief motives for their alcohol intake (Cooper et al., 1995) and with studies showing this also accounts for most alcohol-dependent patients (Kiefer et al., 2003). Others found that relief motives become even more prominent than reward motives in an alcoholic sample (Farber et al., 1980; Carey and Carey, 1995). These findings do not support the validity of the three-pathway model, since this model starts off from a phenotypic typology based on two or three different types of drinking motives in alcoholic patients, arguing back from there to a more neurobiological level. Another finding that is problematic for the three-pathway model is described in the fourth chapter of this thesis: cue-induced craving and physiological cue reactivity did not highly correlate. This finding is in line with previous studies showing average correlations of around \( r = 0.40 \) (see for a review: Tiffany, 1990), but the three-pathway model hypothesizes a stronger conceptual overlap and therefore a higher correlation was expected based on the model. Furthermore, a recent study by Heinz et al. (2003a) could only partly confirm the three-pathway model at the phenotypic level, since conditioned withdrawal correlated with drinking not only in negative but also in positive situations. For these reasons the validity of the model is seriously questioned.

Genotypes and endophenotypes are more closely related to the original neurobiological disease mechanisms of alcoholism (chapter 2) and for this reason may also have better matching potential compared to phenotypes (chapter 6). Gottesman and Gould (2003) have reviewed the etymology and strategy behind the use of endophenotypes in neuropsychiatric research, including a brief description of some possibilities in schizophrenia research as salient examples. Figure 1 shows a schematic representation of gene regions, genes and putative endophenotypes implicated in a biological systems approach in schizophrenia research (Gottesman and Gould, 2003). The reaction surface suggests the dynamic developmental interplay between genetic, environmental, and epigenetic factors that produce cumulative liability to developing schizophrenia. Since different genes may relate to an endophenotype, multiple interacting endophenotypes may relate to a phenotype, and many more genes and candidate endophenotypes remain to be discovered, the figure also illustrates the complexity in the development of a chronic psychiatric disorder (Gottesman and Gould, 2003). Another recent review presented a strategy constructed to improve the phenotypic definition of another chronic psychiatric disorder (bipolar disorder) by elucidating candidate endophenotypes (Hasler et al., in press). Based on these reviews and the findings in this thesis, it may be a useful and necessary step to define processes in the development of alcohol disorders in a similar multi-dimen-
sional way and not as a one-dimensional model with two or three parallel pathways that start out from the phenotype. It is therefore suggested to generate a model that is adapted from the model for schizophrenia of Gottesman and Gould (2003; see also Van Nimwegen et al., 2005), evolving from genotypes and endophenotypes related to relapse to drinking and/or alcoholism.

Figure 2 shows a preliminary version of this nondefinitive and nonexhaustive heuristic model for the development of alcohol disorders, which may be useful for further modeling and future hypotheses generation. The model shows the dynamic development of alcoholism from the genotype, through the endophenotype to the final stage: the pathological phenotype (alcoholism). The genes at the bottom of the figure have all been studied in relation to alcohol dependence. For example, the genes that have been studied in this thesis with respect to their matching potential for acamprosate and naltrexone have previously been associated with alcohol dependence (e.g., Connor et al., 2002; Wernicke et al., 2003; Bart et al., 2005; Town et al., 1999; Sander et al., 1999; Loh and Ball, 2000). Other genes that have also been associated with alcohol dependence are for example the gene of the Cannabinoid receptor 1 (CNR1), Monoamine oxidase A (MAOA), Catechol-O-methyl transferase (COMT), the Serotonin receptor 1B and 2A (HTR1B, HTR2A) and the Serotonin transporter (SERT) (see for a review: Kreek et al., 2005). These genes were not studied in this thesis, since we were especially searching for genetic matching indicators for acamprosate and naltrexone, which are compounds that primarily aim at respectively the glutamate/GABA system and the opiate/dopamine system.

Most neurotransmitter systems in the brain have been associated with multiple endophenotypes that play a role in the development of alcoholism, not just one. For example, dopamine has been associated with reward deficiency, but also with conditioning, automatic processing (habit formation), and implicit cognitions such as attentional bias (e.g., Van den Brink and Van Ree, 2003; Van Ree et al., 2000; De Vries and Shippenberg, 2002; Kreek et al., 2002; Kosten et al., 2002; Koob, 2003). In line with this, it is expected that the genes related to these neurotransmitters are also associated with multiple endophenotypes.

Some other examples of endophenotypes that may play a role in the development of alcoholism and which may have a link to one or more receptor genes are: low level of response to alcohol (e.g., Schuckit et al., 2004; Hinckers et al., 2006; Schuckit and Smith, 2006), implicit associations (e.g., Stacy, 1997; Wiers et al., 2002; Goldberg and Weinberger, 2004), dysregulated stress responsivity (e.g., Kreek et al., 2005; O’Malley et al., 2002), response disinhibition (e.g., Jacob et al., 2005; Hellemans et al., 2005; Kamarajan et al., 2005a, 2005b; Kreek et al., 2005; Twitchell et al., 2001), and (incentive) sensitization (e.g., Robinson and Berridge, 1993; Heinz et al., 2003b). The presented genes and endophenotypes in figure 2
are not definitive. In addition, the figure does not attempt to be comprehensive with respect to the interactions among endophenotypes, and between genotypes and the environment. Instead, it attempts to give an impression of the many interacting phenomena that may exist in the development of alcoholism.

An endophenotype may evolve into one or more phenotypes that enhance vulnerability such as stress sensitivity, reward seeking, risk taking, impulsivity, alcohol expectancies and finally into one or more symptoms of alcoholism such as tolerance, withdrawal, lack of control over use, conditioned addictive behavior and self-reported craving (not shown in the figure) (see also Heinz et al., 2003b). The top of the figure shows the liability to alcoholism and the influence of environmental factors (which can be harmful or protective), cumulating at the reaction surface (adapted from Gottesman and Gould, 2003).

With regard to the matching hypotheses of Verheul et al. (1999), we did not find any evidence at the phenotypic level. At the endophenotypic level, the hypotheses were only partly confirmed: baseline skin conductance cue reactivity, but not heart rate cue reactivity appeared to be good matching variables. At the genetic level, we did find significant results in some of the selected genes (three out of six genes showed significant results). Although the selection of genes was based on the matching hypotheses, the direction of the effects was not always in line with the hypotheses, e.g., polymorphisms at the DRD2 gene were beneficial for acamprosate when homozygous for the A1-allele, but beneficial for naltrexone when homozygous for the A2-allele. Apparently, the efficacy of both medications is related to the DRD2 genotype and depends on the specific polymorphism. This raises the question whether acamprosate solely interacts with the glutamate and GABA system, and whether naltrexone solely interacts with the dopaminergic and opioidergic system, as originally hypothesized (Verheul et al., 1999). It is known that neurotransmitter systems are not operating in the brain as isolated islands, but can intensely interact (e.g., Ronken et al., 1993; Schoffelmeer et al., 2000). Matching hypotheses that link distinct medications to distinct types of neurotransmitter systems may therefore be too simple. It is suggested not to solely focus on the different types of neurotransmitters, but rather to look at their specific polymorphisms, and their relation to the working mechanisms of acamprosate and naltrexone at the receptor level (e.g., receptor binding properties) (Ray and Hutchison, 2004; Ritchie and Noble, 1996; Bond et al, 1998).

In conclusion, this thesis provides only limited evidence for the three-pathway model and its related matching hypotheses. We therefore recommend a careful shift in attention to the genetic and the endophenotypic level in the construction of future models on relapse and/or alcoholism and related matching hypotheses for current relapse prevention strategies (e.g., acamprosate and naltrexone) and future relapse prevention strategies (e.g., topiramate, rimonabant). This does not
mean, however, that phenotypic indicators should never be investigated. It is suggested that some phenotypic indicators (e.g., baseline craving level or drinking patterns) may still have matching potential (see also chapter 2). In addition, since our study did not include clinical outcome measures that are directly related to drinking (in general the most important indicators of treatment success), more attention on outcome measures such as relapse is warranted in future studies. Finally, modifying factors that possibly connect endophenotypes and phenotypes should be taken into account as well: e.g., awareness and social desirability (see also chapter 4).

**Summary and General Discussion**

**Figuur 2.** A preliminary heuristic model on the development of alcoholism. Adapted from figure 1; Gottesman and Gould, 2005 and personal communication, 2006.

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**Recommendations and directions for future research**

As a first topic for future research, it is recommended to replicate the significant matching properties of the endophenotypes and genotypes as described in chapter 6 in bigger samples, with relapse as an additional outcome measure and taking into account long term effects of acamprosate and naltrexone. In addition, more (explorative) research is warranted on other potential genotypes for matching strategies, e.g., polymorphisms of other GABA receptor subunits, the serotonin receptors or transporters, noradrenergic receptors or the cannabinoid
receptors. Further, more research is needed on other potential endophenotypic indicators of addiction such as attentional bias (e.g., Franken, 2003), response disinhibition (e.g., Goudriaan, 2005; Kreek et al., 2005), reward and punishment sensitivity (Goudriaan, 2005), error and conflict monitoring (Botvinick et al., 2001), direct brain functioning measures using fMRI and SPECT/PET (e.g., Dom et al., 2005; Grusser et al., 2004) or gene expression indicators such as dopamine or µ-opioid receptor density measures obtained through SPECT and PET (e.g., Heinz et al, 2004, 2005a, 2005b).

Second, it is recommended to carefully shift attention from explicit phenotypic indicators to implicit endophenotypic and genetic indicators in matching research (e.g., Wiers and Stacy, 2006). However, phenotypes should not be left out of these studies. Chapter 2 shows that phenotypes, although the evidence is limited, can have predictive value and therefore can still be clinically relevant.

Third, since the matching hypotheses of Verheul et al. are only partly confirmed, it can be questioned to what extend future research should be restricted to the test of this model. Although the model has been instrumental in the formulation of a series of testable hypotheses, the findings of the current study raise serious doubts with respect to some of the basic assumptions of the model such as the possibility to make a valid distinction between reward and relief drinking at the phenotypic level. We, therefore, are confident that an alternative model has to be developed. In the previous paragraph we have made an attempt to describe some elements of such a new model.

Fourth, as already mentioned, individual differences in the detection (or awareness) of underlying mechanisms or processes (detection bias) may connect phenotypes with endophenotypes. Apparently, a substantial part of the alcoholics are not sensitive for the signs of physiological processes and never become aware of changes in their somatic state (Damasio, 1996) and thus fail to report them (chapter 4). Further research should focus on the nature of these individual differences, the possibilities to make patients more aware of underlying endophenotypic processes (e.g., by use of biofeedback therapy) and the effect of this increased awareness on drinking behavior (e.g., Wiers et al., 2006). In line with this, a recent study (Field and Eastwood, 2005) investigated whether experimental manipulation of attentional bias (an endophenotypical indicator of addiction) produces changes in craving and drinking behavior (phenotypes). Indeed, the results suggested that the group with potentiated attentional bias for alcohol related cues showed an increase in craving and alcohol consumption, whereas the group that was trained to direct their attention away from the alcohol-related cues did not. This is also in line with previous studies showing that experimental manipulations of craving can produce increases in attentional bias (see for a review: Franken, 2003).
Fifth, it is recommended to investigate alternative mechanisms of action for acamprosate and naltrexone in relapse prevention. A first argument to do this is because the findings regarding the relation between craving and relapse are inconsistent and generally rather weak (Rohsenow and Monti, 1999). In addition, the relation between endophenotypes (such as attentional bias and physiological cue reactivity) and relapse is rarely investigated and needs further research. Rohsenow et al., for example found that cue-induced salivation predicts relapse in alcoholics (Rohsenow et al., 1994). Furthermore, although the evidence is limited, some studies in nonalcoholic addicts show strong predictive value of endophenotypes for relapse (Marissen et al., in press; Goudriaan et al., 2005). Another argument to investigate alternative mechanisms is that the moderate effects on craving in chapter 5 and other studies may not solely be explained by inadequate patient-treatment matching. Perhaps, acamprosate and naltrexone only partly exert their effect on relapse through the reduction of craving and physiological cue reactivity, even when the patients are well matched to the compounds. It would, therefore, be interesting to investigate alternative working mechanisms that are not (directly) related to craving. For example, it has been postulated that naltrexone may affect the reactivity of the HPA axis (O’Malley et al., 2002). Although our study did not support this, it cannot be excluded that naltrexone has a stimulating effect on the (dysregulated) HPA system of alcohol-dependent patients. Naltrexone may exert its effect on relapse by blocking the ‘kick’ effect of alcohol, but this does not necessarily mean that it decreases the craving for this kick. The patient may stop drinking because the alcohol does not give the craved effect, and not because the craving is not there anymore. Of course, due to a learning effect while actively drinking, this mechanism may eventually decrease craving in actively drinking subjects, but this is not a prerequisite. Another alternative mechanism for naltrexone, suggested by one of the physicians of the Jellinek, may be that naltrexone makes a patient too numb and inactive to actually act on their craving. With respect to acamprosate an often heard remark during our study and by physicians of the Jellinek is that ‘acamprosate gives rest in the head’ or that ‘acamprosate clears the head’. These examples show that the input of both patients and physicians should not be forgotten and can inspire to new insights.

But what if future matching indicators have limited power and are not useful for daily clinical practice, or in other words what if matching is not the best answer to more efficient treatments? In that case the combination of medications or the combination of medication with certain types of psychotherapy may be a good alternative option, although studies on these topics are still scarce and need to be replicated (e.g., De Wildt et al., 2002; O’Malley et al., 1992). In addition, it is good to keep an open mind to new anti-relapse medications, to further investi-
gations of serotonergic compounds for subgroups and to novel compounds that show promise in related disorders and animal research such as topiramate, baclofen, and aripiprazole (Ait-Daoud et al., 2006; Kranzler et al., 2006).

But even if matching is not the only key to treatment success, this thesis has shown that inadequate matching is likely to play a role in the limited efficacy ofacamprosate and naltrexone. In addition it shows that individual differences in the treatment of alcoholism cannot be disregarded. Not only with respect to human research, but also animal research in the addiction field, individual differences have shown to be important for treatment success. For example, a study by Homberg et al. (2004) showed that serotonergic anxiolytics abolish the pre-existing individual differences in cocaine self-administration between high grooming and low grooming rats, which show differences in the reactivity of serotonergic neurons. This suggests that the effectiveness of pharmacological interference may depend on the neurochemical and motivational state of the individual. Animal studies enable the researcher to control most confounders and to create large samples. As a final suggestion for future research, it is therefore suggested to relate human studies to animal studies and visa versa. Interdisciplinary and translational research may be necessary bridges in the development of efficient pharmacological treatment strategies.

In conclusion, this study shows great promise at the genetic and endophenotypic level for matching. More research is needed to replicate the findings in bigger samples, longer treatments and follow-up periods using drinking parameters as the primary outcome variables.

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160
Summary and General Discussion


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Summary and General Discussion


Samenvatting [Summary in Dutch]
Inleiding

Alcohol is een verslavende stof, wat wil zeggen dat het een direct belonend karakter heeft en herhaaldelijk excessief gebruik kan leiden tot een overweldigende drang om te gebruiken en controleverlies. Daarnaast kunnen tolerantie, onthoudingsverschijnselen, toxiciteit en een verscheidenheid aan ziekten optreden. Zwaar alcoholgebruik (> 35 glazen per week voor vrouwen en >50 voor mannen) komt voor in 1.6% van de bevolking: bij 2.4% van de mannen en bij 0.8% van de vrouwen. Alcohol misbruik en alcohol afhankelijkheid komt respectievelijk in 4.6% en 3.7% van de bevolking voor (V erdurmen et al., 2003).

Eén van de belangrijke symptomen van alcoholafhankelijkheid is ‘craving’, dat wil zeggen de subjectieve beleving van een sterke of overweldigende drang om te willen drinken (American Psychiatric Association). Over het algemeen gaat men ervan uit dat craving een centrale rol speelt bij de ontwikkeling van alcoholafhankelijkheid en bij terugval na een periode van abstinentie; het verminderen van craving is dus essentieel voor de behandeling van alcoholisme en het voorkomen van terugval (o.a. Wise, 1988; Anton e.a., 1996; Volpicelli e.a., 1992; O’Brien, 2005). Echter, er zijn een aantal onopgeloste problemen ten aanzien van het concept van craving en de rol die craving speelt bij het ontwikkelen van alcoholverslaving. Zo zijn er bijvoorbeeld tegenstrijdige bevindingen als het gaat om de relatie tussen craving en terugval. Deze tegenstrijdigheden zijn waarschijnlijk het gevolg van een aantal, elkaar samenhangende, problemen. Zo is er weinig consensus ten aanzien van de definitie van craving en is er in de literatuur meestal slechts een zwakke samenhang tussen craving en fysiologische cue-reactiviteit, dat wil zeggen lichamelijke reacties op een alcoholgerelateerde stimulus (bijvoorbeeld zweetsecretie of hartslagverhoging bij het ruiken of zien van alcohol).

Hoewel nog onduidelijk is welke rol craving speelt bij het ontwikkelen van alcoholafhankelijkheid, zijn er de laatste jaren een aantal bewezen effectieve medicijnen voor de behandeling van alcoholafhankelijkheid ter beschikking gekomen. Deze pretenderen allemaal dat ze de craving naar alcohol verminderen en op die manier de kans op terugval na abstinentie kunnen verkleinen (O’Brien, 2005). Een probleem is dat de grootte van het effect van deze nieuwe geneesmiddelen tamelijk beperkt is met een verschil in abstinentie van ongeveer 15% tussen
het geneesmiddel en een placebo, waardoor er ongeveer zeven alcoholisten met het medicijn moeten worden behandeld om er een extra beter te maken (Mann, 2004; Mann e.a., 2004; Srisurapanont en Jarusuraisin, 2005; Roozen e.a., 2005). In dit proefschrift wordt ervan uitgegaan dat deze relatief kleine effecten van anti-craving medicijnen het gevolg zijn van een slechte afstemming tussen de kenmerken van de patiënt en de farmacologische eigenschappen van het medicijn, de zogenaamde ‘patient-treatment matching’. Echter, in de literatuur zijn hier weinig duidelijke hypothesen over te vinden.

Om de effectiviteit van anti-craving medicijnen te verhogen, is betere afstemming nodig tussen patiëntkenmerken en de farmacologische kenmerken van de medicijnen. We moeten daarom meer weten over de relatie tussen beide en dus meer weten over de belangrijkste patiëntkenmerken. Hierbij zijn voornamelijk die patiëntkenmerken van belang die te maken hebben met de manier waarop patiënten verslaafd zijn geraakt en de manier waarop craving zich heeft ontwikkeld. Daartoe is in dit proefschrift gebruik gemaakt van het zogenaamde drie-pad model voor craving, dat is ontwikkeld door Verheul c.s. (1999). Dat model beschrijft een typologie van drinkers uitgaande van verschillende typen motieven om alcohol te drinken: ‘relief’ motieven (= drinken om verlichting van lijden te bewerkstelligen), ‘reward’ motieven (= drinken om de te verwachten beloning) en ‘obsessieve’ motieven (= drinken door gebrek aan controle). Het model voorspelt dat naltrexon de craving vermindert in patiënten met kenmerken die samenhangen met reward-drinken, acamprosaat in patiënten met kenmerken die samenhangen met relief-drinken en serotonerge medicijnen in patiënten met kenmerken die samenhangen met obsessief drinken. Bovendien gaat het model uit van de veronderstelling dat er een sterke en directe relatie is tussen fysiologische cue-reactiviteit en craving, dat wil zeggen dat mensen die weinig fysiologische reacties hebben, weinig craving ervaren, en dat mensen met hevige fysiologische reacties hevige craving ervaren.

De voorspellende patiëntkenmerken (matchingsindicatoren) van het drie-pad model kunnen geconceptualiseerd en gemeten worden op drie niveaus: (1) fenotypische indicatoren, (2) endofenotypische indicatoren, en (3) genetische indicatoren (Gottesman en Gould, 2003). Fenotypische indicatoren zijn subje
tieve belevingen en direct observeerbare klinische kenmerken die het eindproduct zijn van genetische- en omgevingsfactoren. Endofenotypische indicatoren zijn niet direct observeerbare en vaak onbewuste kenmerken zoals bijvoorbeeld fysiologische reacties of hersenactiviteit. Er is meestal bijzondere apparatuur nodig om de aanwezigheid van deze kenmerken vast te kunnen stellen (bijvoorbeeld ECG, EEG, fMRI). Genetische indicatoren zijn kenmerken op gen-niveau, zoals de verschijnselvorm van een gen (polymorfisme). De belangrijkste fenotypische indicatoren van Verheul’s model waren drink-motieven, familair alco-
holisme, onthoudingsverschijnselen, en de leeftijd waarop de problemen begonnen. Een endofenotypische indicator was fysiologische hyperarousabiliteit, die geoperationaliseerd kon worden als fysiologische cue-reactiviteit, dat wil zeggen een lichamelijke reactie (bijvoorbeeld een verhoogde hartfrequentie) op een alcoholgerelateerde stimulus. Genetische indicatoren van het model waren genotypen die van belang zijn voor onregelde of (on)gevoelige receptoren van het GABA, glutamaat, dopamine en opioid systeem. De genen die coderen voor deze receptoren (zoals o.a. GABRA6, GABRB2, DRD2) spelen allen een rol bij het ontstaan van verslaving en elk van deze genen stuurt een ander biologisch proces aan waardoor effecten van medicijnen op het beloop van de stoornis per patiënt duidelijk kunnen verschillen.

Toen het drie-paden model werd geïntroduceerd was nog maar weinig bekend over de voorspellende waarde van fenotypische, endofenotypische en genetische patiëntkenmerken die samenhangen met relief- en reward-drinken voor het effect van acamposaat en naltrexon op craving en/of fysiologische cue-reactiviteit. Bovendien waren er geen gevalideerde vragenlijsten beschikbaar die (a) reward- en relief-drinkers konden onderscheiden en (b) een sterke relatie tussen craving en fysiologische cue-reactiviteit konden aantonen.

Het hoofddoel van dit proefschrift was dan ook het vergroten van de effectiviteit van de behandeling van alcoholisten met naltrexon of acamprosaat door het opsporen van patiëntkenmerken die het effect van naltrexon en acamprosaat op cue-geïnduceerde craving en fysiologische cue-reactiviteit beïnvloeden. Voordat de hoofdstudie van start kon gaan, moesten echter eerst nog een aantal meetinstrumenten ontwikkeld worden om op betrouwbare en valide wijze drinkmotieven en craving te meten bij patiënten met een diagnose alcoholafhankelijkheid.

Het proefschrift probeert een antwoord te geven op de volgende onderzoeksvragen:

1. Kunnen reward- en relief-drinkers van elkaar onderscheiden worden op basis van hun drink-motieven?
2. Wat is de relatie tussen cue-geïnduceerde craving en fysiologische cue-reactiviteit?
3. Verschillen naltrexon en acamprosaat in de mate waarin zij cue-geïnduceerde craving en fysiologische cue-reactiviteit verminderen?
Samenvatting

Samenvatting van de bevindingen

Hoofdstuk 2 bestaat uit een literatuuroverzicht naar patiëntkenmerken die het effect van acamprosaat, naltrexon en serotonerge medicijnen op craving en terugval bij alcoholisten kunnen beïnvloeden. Er werd geconcludeerd dat studies die fenotypische variabelen voor toewijzing hebben gebruikt inconsistent en vrij teleurstellende resultaten hebben geboekt. Daarentegen bleken genetische matchingsvariabelen veelbelovend (bijvoorbeeld het $\mu$-opioid polymorfisme dat het effect van naltrexon op terugval voorspelt). Er werden geen studies gevonden die gekeken hebben naar de voorspellende waarde van endofenotypische matchingsvariabelen. Er werd geconcludeerd dat fenotypische matchingsvariabelen mogelijk te ver verwijderd zijn van de pathogenetische processen die ten grondslag liggen aan de stoornis in het gebruik van alcohol, en dat de aandacht in het matchingsonderzoek zou moeten verschuiven naar indicatoren die dichter bij het biopsychologische proces staan, dat wil zeggen genetische en endofenotypische variabelen.

Hoofdstuk 3 rapporteerde over de ontwikkeling en validatie van een vragenlijst die relief- en reward-drinkers op fenotypisch niveau van elkaar zou moeten onderscheiden: de Amsterdam Motieven om te Drinken Schaal (AMDS). De AMDS bleek betrouwbaar relief- en reward-motiveven om te drinken te meten, maar de schalen correleerden erg hoog ($r=0.84$). Alleen op subschaalniveau werden enkele wat lagere correlaties gevonden. Het leek er daarom op dat de meeste alcoholisten die in behandeling zijn zowel relief- als reward-motieven om te drinken hebben. In de discussie werd nog wel gesteld dat het van belang zou kunnen zijn toch nog te zoeken naar geschikte grenswaarden om beide groepen te onderscheiden.

In hoofdstuk 4 werden de resultaten gerapporteerd van een studie naar de ontwikkeling en validering van een nieuwe craving-vragenlijst (Jellinek Alcohol Craving Questionnaire; JACQ) met als doel cue-geïnduceerde craving beter te kunnen koppelen aan fysiologische cue-reactiviteit. De JACQ bleek betrouwbaar één dimensie te kunnen meten met daarbinnen vier aspecten van craving: (a) emotionele drang/verlangen, (b) lichamelijke sensaties, (c) verleiding om te drinken, (d) ongecontroleerde gedachten. De periode waarover de patiënt bevraagd werd bleek van groot belang te zijn voor de antwoorden die werden gegeven. Ondanks de aanwezigheid van een speciale subschaal voor lichamelijke sensaties, werden er slechts beperkte correlaties gevonden tussen cue-geïnduceerde zelfgerapporteerde craving en fysiologische indicatoren van cue-reactiviteit zoals een verhoogde hartslag en verhoogde zweetsecretie na cue-exposure. De conclusie was dat het gebrek aan een duidelijk verband tussen craving en fysiologische cue-reactiviteit niet toegeschreven kon worden aan verschillen in inhoud.
van de meting, maar dat de lage correlaties het resultaat waren van individuele verschillen tussen alcoholisten ten aanzien van hun bewustzijn en/of de wijze van rapportage van fysiologische verschijnselen volgend op alcoholgerelateerde stimuli. Verder onderzoek zou zich moeten richten op de kenmerken van deze individuele verschillen. Bovendien werd aanbevolen om meer onderzoek te verrijken naar verschillen in voorspellende waarde tussen zelfgerapporteerde craving en fysiologische cue-reactiviteit ten aanzien van de kans op terugval.

In hoofdstuk 5 werd het verschil in effect van acamprosaat en naltrexon op cue-geïnduceerde craving en fysiologische cue-reactiviteit beschreven. Het onderzoek betrof een dubbel-blinde, gerandomiseerde en placebo-gecontroleerde studie. In overeenstemming met de hypothesen resulteerde het gebruik van naltrexon in een grotere vermindering van craving dan het gebruik van acamprosaat, terwijl het gebruik van acamprosaat zorgde voor een grotere daling van de hertslag na cue-exposure dan het gebruik van naltrexon. Er werden geen aanwijzingen gevonden voor een effect van medicatie op veranderingen in cue-geïnduceerde cortisol productie. De bevindingen vormden een ondersteuning voor de stelling dat het effect van naltrexon, tenminste gedeeltelijk, verloopt via de reductie van cue-geïnduceerde craving, terwijl het effect van acamprosaat, tenminste gedeeltelijk, verloopt via reductie van fysiologische cue-reactiviteit.

Tenslotte werden in hoofdstuk 6 de resultaten gerapporteerd van een studie naar matchingsindicatoren van relief- en reward-drinken voor de behandeling met acamprosaat en naltrexon. Op fenotypisch niveau werden er geen voorspellers van het effect van acamprosaat of naltrexon gevonden die samenhangen met relief- en reward-drinken. Er werd op endofenotypisch niveau echter wel een significant matchingleffect gevonden voor de reductie van fysiologische cue-reactiviteit (huidgeleiding), terwijl er ook op genotypisch niveau significante matchingsresultaten werden gevonden (polymorfismen van het DRD2, GABRA6 en GABRB2 gen). Een trend in de verwachte richting werd gevonden voor een polymorfisme van het gen dat codeert voor de µ-opioid receptor (OPRM1); een bevinding die goed aansluit bij de studie van Oslin e.a. (2003) waarin terugval de belangrijkste uitkomstvariabele was. Er werd geconcludeerd dat de matchingshypothesen van Verheul e.a. (1999) slechts zeer ten dele bevestigd zijn. De aanbeveling was om de endofenotypische en genetische bevindingen verder te onderzoeken in grotere steekproeven.

Klinische implicaties

Naast een beter begrip van de werkingsmechanismen van naltrexon en acamprosaat, hebben de bevindingen in dit proefschrift ook belangrijke implicaties voor de dagelijkse klinische praktijk. Hoewel serotonerge medicamenten nog een ex-
perimenteel karakter hebben bij terugvalpreventie, hebben naltrexon en acamprosaat consistent laten zien dat ze effectief zijn voor een deel van de patiënten en daarom worden deze medicamenten beschouwd als de beste en veiligste farmacologische opties die momenteel beschikbaar zijn voor terugvalpreventie (hoofdstuk 2). Hoewel er nog geen bewezen effectieve fenotypische matchingsindicatoren zijn voor naltrexon of voor acamprosaat, wordt in veel gevallen aanbevolen om naltrexon voor te schrijven aan patiënten met de fenotypische kenmerken ‘hoge craving bij aanvang’ en ‘actief drinkgedrag’ (zie literatuuroverzicht in hoofdstuk 2). Een andere voorspeller voor naltrexon is mogelijk familiair alcoholisme, hoewel dit niet bevestigd wordt in onze studie (zie literatuuroverzicht in hoofdstuk 2 en de matching studie in hoofdstuk 6). Opgemerkt moet wel worden dat naltrexon over het algemeen niet leidt tot totale abstinentie (o.a. Garbutt e.a., 2005). Wanneer totale abstinente het behandeldoel is, is acamprosaat mogelijk de beste behandeloptie die op dit moment beschikbaar is. Verder moet opgemerkt worden dat het effect van naltrexon alleen lijkt te bestaan zolang de medicatie voortgezet wordt (Mann, 2004). Bovendien zijn er enkele aanwijzingen dat het effect van acamprosaat zelfs maanden na beëindiging van de behandeling blijft voortbestaan (Mann, 2004). Het lijkt er daarom op dat de keuze tussen acamprosaat en naltrexon op dit moment het beste gebaseerd kan worden op het beoogde behandeldoel, de bijwerkingen en contra-indicaties, en tenslotte op enige voorlopige patiëntkenmerken zoals het niveau van craving bij aanvang en het actuele drinkgedrag.

Onze bevindingen vormen geen ondersteuning voor de hypothese dat de kenmerken van relief- en reward-motieven op fenotypisch niveau gebruikt kunnen worden voor de keuze van acamprosaat of naltrexon bij het voorkomen van terugval. Daarentegen lijken het endofenotypische kenmerk ‘hoge fysiologische cue-reactiviteit bij aanvang’ (hoofdstuk 6) en bepaalde genetische polymorfismen (hoofdstuk 6; Oslin e.a., 2003) veelbelovend. Echter, voordat deze bevindingen geïmplementeerd kunnen worden, is er meer onderzoek nodig om onze hoopvolle resultaten te bevestigen. Er is ook meer onderzoek nodig naar de praktische en financiële aspecten van de zogenaamde farmacogenetica. Op dit moment zou het bepalen van endofenotypen en genotypen mogelijk logistieke problemen kunnen geven en zou dit tijdintensiever en duurder zijn dan het bepalen van fenotypen. Echter, de ontwikkeling van efficiëntere, minder dure technologieën gaat snel. Het is daarom te verwachten dat effectievere, efficiëntere en kosteneffectievere behandelingen aangeboden kunnen worden wanneer genetische en endofenotypische informatie zal worden gebruikt voor toekomstige strategieën bij het toewijzen van patiënten aan behandelingen. Een laatste suggestie voor de klinische praktijk is om de combinatie van acamprosaat met naltrexon te overwegen (Kiefer et al., 2003; Mason, 2005; Feeney et al., 2006) of de combinatie
van acamprosaat met disulfiram (Besson et al., 1998). Hoewel rekening gehouden dient te worden met een grotere kans op bijwerkingen en een groter aantal te slikken pillen, is een combinatie van deze medicijnen een goede optie zolang nog onvoldoende voorspellende patiëntkenmerken beschikbaar zijn voor de klinische praktijk.

**Conclusies**

Het is herhaaldelijk aan de orde gekomen dat de bevindingen in de huidige studie slechts in zeer beperkte mate de oorspronkelijke matchingshypothesen, die gebaseerd zijn op het drie-paden model van craving naar alcohol (Verheul e.a., 1999), hebben bevestigd. De vraag die daarom opkomt is daarom wat deze bevindingen betekenen voor de validiteit van het originele model en voor de noodzaak van daaruit voortvloeiende aanpassingen van de oorspronkelijke matchingshypothesen.

Met betrekking tot de typologie voor relief (verlichting)- en reward (beloning)- drinken, laat dit proefschrift zien (hoofdstuk 3) dat we niet in staat zijn om reward- en relief-drinkers van elkaar te onderscheiden op fenotypisch niveau. Dit komt overeen met andere studies die laten zien dat de meeste niet-verslaafde sociale drinkers zowel reward- als relief-motieven beschrijven voor hun alcoholconsumptie (Cooper e.a., 1995) en met studies die laten zien dat dit ook geldt voor de meeste alcoholafhankelijke patiënten (Kiefer e.a., 2003). Anderen hebben gevonden dat relief-motieven na verloop van tijd zelfs prominenter werden dan reward-motieven in een groep aan alcohol verslaafde patiënten (Farber e.a., 1980; Carey en Carey, 1995). Deze bevindingen ondersteunen de validiteit van het drie-paden model niet, aangezien dit model uitgaat van een fenotypische typologie die gebaseerd is op twee of drie verschillende typen drink-motieven in aan alcohol verslaafde patiënten, terwijl er vanuit deze fenotypische categorieën teruggeduceerd wordt naar een meer neurobiologisch niveau. Een andere bevinding die problematisch is voor het drie-paden model wordt beschreven in het vierde hoofdstuk van dit proefschrift: cue-geïnduceerde craving en fysiologische cue-reactiviteit correleerden niet hoog. Deze bevinding is in overeenstemming met eerdere onderzoeken die gemiddelde correlaties van ongeveer \( r=0.40 \) laten zien (zie voor een overzicht: Tiffany, 1990), terwijl het drie-paden model veronderstelt dat er een sterke conceptuele overlap is en daarom een hoge correlatie verwacht moet worden op basis van dit model. Verder kon een recente studie van Heinz e.a. (2003) het drie-paden model slechts gedeeltelijk bevestigen, aangezien geconditioneerde onthoudingsverschijnselen niet alleen in negatieve maar ook in positieve situaties met drinken correleerden. Om deze redenen moeten er ernstige vraagtekens gezet worden bij de juistheid van het model.
Genotypen en endofenotypen blijken veel nauwer gerelateerd aan de originele neurobiologische mechanismen van alcoholisme (hoofdstuk 2) en hebben mogelijk om deze reden een betere potentie voor matching dan fenotypen (hoofdstuk 6). Gottesman en Gould (2003) hebben een literatuuroverzicht uitgevoerd t.a.v. het gebruik van endofenotypen in neuropsychiatrisch onderzoek, inclusief een korte beschrijving van enkele mogelijkheden binnen het schizofrenieonderzoek. Het artikel beschrijft o.a. het dynamische zich ontwikkelende samenspel tussen genetische- en omgevings-factoren die optellen tot kwetsbaarheid voor het ontwikkelen van schizofrenie (zie ook Figuur 1, te vinden aan het eind van de Engelstalige samenvatting). Aangezien verschillende genen mogelijk gerelateerd zijn aan één endofenotype, verschillende interacterende endofenotypen mogelijk gerelateerd zijn aan één fenotype, en veel genen en kandidaat endofenotypen nog ontdekt moeten worden, laat het voorbeeld voor schizofrenie ook de complexiteit zien van de ontwikkeling van een chronische psychiatrische stoornis. Een ander recent overzicht presenteert een strategie die geconstrueerd was om de fenotypische definitie van een andere chronische psychiatrische stoornis (bipolaire stoornis) te verbeteren, namelijk via het ophelderen van kandidaat endofenotypen (Hasler e.a., in druk). Gebaseerd op deze literatuuroverzichten en de bevindingen in dit proefschrift, is het een nuttige en noodzakelijke stap om processen in de ontwikkeling van alcoholgerelateerde stoornissen op dezelfde multidimensionele manier te beschrijven en niet als een één-dimensioneel model met twee of drie parallelle paden die uitgaan van het fenotype. Wij adviseren daarom een model voor verslaving te ontwerpen dat gebaseerd is op het model voor schizofrenie van Gottesman en Gould (2003; zie ook Van Nimwegen e.a., 2005), een model dat zich ontwikkelt van genotypen en endofenotypen die te maken hebben met terugval, naar drinkgedrag en/of alcoholisme. Figuur 2 (te vinden aan het eind van de Engelstalige samenvatting) laat een voorlopige versie zien van dit niet-definitieve en niet-uitputtende heuristische model voor de ontwikkeling van alcoholgerelateerde stoornissen, dat mogelijk nuttig zal blijken te zijn voor het verder modelleren en het genereren van hypothesen. Het model laat de dynamische ontwikkeling zien van het genotype, via het endofenotype, naar het eindstadium: het pathologische fenotype alcoholisme. De genen onder aan de figuur zijn allen bestudeerd in relatie tot alcoholafhankelijkheid. De genen die bestudeerd zijn in dit proefschrift ten aanzien van hun potentie als matchingsvariabele voor een behandeling met acamprosaat of naltrexon, zijn allemaal al eerder in verband gebracht met de kans op de ontwikkeling van alcoholafhankelijkheid (o.a. Connor e.a., 2002; Wernicke e.a., 2003; Bart e.a., 2005; Town e.a., 1999; Sander e.a., 1999; Loh en Ball, 2000). Andere genen die ook in verband zijn gebracht met alcoholafhankelijkheid zijn bijvoorbeeld de volgende genen: Cannabinoid receptor 1 (CNR1), Monoamine oxidase A (MAOA), Catechol-O-methyl trans-
ferase (COMT), de Serotonin receptor 1B en 2A (HTR1B, HTR2A) en de Serotonin transporter (SERT) (zie voor een overzicht: Kreek e.a., 2005). Deze genen zijn niet bestudeerd in dit proefschrift omdat we speciaal zochten naar genetische indicatoren voor matching met acamprosaat en naltrexon, twee medicamenten die zich primair richten op respectievelijk het glutamaat/GABA systeem en het opiaat/dopamine systeem.

De meeste neurotransmittersystemen in de hersenen zijn in verband gebracht met meerdere endofenotypen die een rol spelen bij de ontwikkeling van alcoholisme, en met slechts één. Dopamine is bijvoorbeeld in verband gebracht met een verstoord belonings- of motivatiesysteem, maar ook met conditionering, automatische processen (gewoonte vorming), en impliciete cognities (veranderingen in aandachtsprocessen (‘attentional bias’); Van den Brink en Van Ree, 2003; Van Ree e.a., 2000; De Vries en Shippenberg, 2002; Kreek e.a., 2002; Kosten e.a., 2002; Koob, 2003).

Een paar andere voorbeelden van endofenotypen, die mogelijk een rol spelen bij de ontwikkeling van alcoholisme en die mogelijk een verband hebben met een of meerdere receptorgenen, zijn: lage respons in reactie op alcohol (o.a. Schuckit e.a., 2004; Hinckers e.a., 2006; Schuckit en Smith, 2006), impliciete associaties (o.a. Stacy, 1997; Wiers e.a., 2002; Goldberg en Weinberger, 2004), onregelmatige stress reactiviteit (o.a. Kreek e.a., 2005; O’Malley e.a., 2002), respons disinhibitie (o.a. Jacob e.a., 2005; Hellemans e.a., 2005; Kamarajan e.a., 2005; Kreek e.a., 2005; Twitchell e.a., 2001), en (motivationele) sensitisatie (o.a. Robinson en Berridge, 1993; Heinz e.a., 2003). De weergegeven genen en endofenotypen in figuur 2 zijn niet definitief. Bovendien probeert het figuur niet volledig te zijn ten aanzien van de interacties tussen endofenotypen, en tussen genotypen en omgeving. In plaats daarvan probeert het een indruk te geven van de vele interacterende fenomenen die mogelijk een rol spelen bij de ontwikkeling van alcoholisme.

Een endofenotype kan zich ontwikkelen tot een of meer fenotypen die de kwetsbaarheid van een individu verhogen zoals stress sensitiviteit, behoefte aan beloning, risicogedrag, impulsiviteit, verwachtingen ten aanzien van alcohol, en zich tenslotte ontwikkelen tot een of meer symptomen van alcoholisme zoals tolerantie, ontwenningsverschijnselen, gebrek aan controle over gebruik, geconditioneerd verslavingsgedrag, en zelfgerapporteerde craving (niet weergegeven in de figuur) (zie ook Heinz e.a., 2003). De bovenkant van de figuur laat de gevoeligheid voor alcoholisme zien en de invloed van omgevingsfactoren (die schadelijk of beschermend kunnen zijn), cumulatief samenkomend aan de ‘reaction surface’ (het reactief oppervlak) (aangepast naar een model van Gottesman en Gould, 2003).

Met betrekking tot de matchingshypothesen van Verheul c.s. (1999), hebben we geen bewijs gevonden op fenotypisch niveau. Op het endofenotypisch niveau
worden de hypothesen slechts gedeeltelijk bevestigd: wél cue-reactiviteit van de huidige geleiding bij aanvang, maar cue-reactiviteit van de hartslag blijkt geen goede matching variabele te zijn. Op genetisch niveau vinden we significante resultaten voor een aantal geselecteerde (kandidaat) genen (drie van de zes onderzochte genen laten significante resultaten zien). Hoewel de selectie van de genen gebaseerd is op de matchingshypothesen, is de richting van de effecten niet altijd in overeenstemming met de hypothesen, bijvoorbeeld het DRD2 gen is in het voordeel van acamprosaat wanneer deze homozygoot is voor het A1-allel, maar in het voordeel van naltrexon wanneer deze homozygoot is voor het A2-allel. Blijkbaar hangt de effectiviteit van beide medicamenten samen met het DRD2 genotype en hangt deze af van het specifieke polymorfisme. Dit werpt de vraag op of acamprosaat enkel en alleen interacteert met het glutamaat en GABA systeem, en of naltrexon enkel en alleen interacteert met het dopaminergic en opioidergic systeem, zoals in de oorspronkelijke hypothesen gesteld werd (Verheul e.a., 1999).

Het is bekend dat neurotransmittersystemen in de hersenen niet als geïsoleerde eilanden opereren, maar intensief met elkaar kunnen interacteren (o.a. Ronken e.a., 1993; Schoffelmeer e.a., 2000). Matchingshypothesen die specifieke medicatienen koppelen aan specifieke typen neurotransmitter systemen zijn mogelijk te eenvoudig. Daarom is de suggestie gedaan om niet alleen te focussen op de verschillende typen neurotransmitters, maar om vooral ook te kijken naar hun specifieke polymorfismen, en hun relatie met het werkingsmechanisme van acamprosaat en naltrexon op receptorniveau (bijvoorbeeld de bindingseigenschappen van een receptor) (Ray en Hutchison, 2004; Ritchie en Noble, 1996; Bond e.a., 1998).

Concluderend geeft dit proefschrift slechts beperkte steun aan het drie-paden model en de daaraan gerelateerde matchingshypothesen. We adviseren daarom een alternatief model te ontwerpen met daarin een verschuiving in aandacht van het fenotypische naar het genetische en endofenotypische niveau. Dit nieuwe model moet leiden tot nieuwe matchingshypothesen voor zowel huidige strategieën voor terugvalpreventie (bijvoorbeeld acamprosaat en naltrexon) als voor toekomstige strategieën ten behoeve van terugvalpreventie (bijvoorbeeld topiramaat, rimonabant). Dit betekent echter niet dat fenotypische indicatoren nooit meer onderzocht moeten worden. Sommige fenotypische indicatoren (bijv. craving niveau bij aanvang of drinkpatronen) hebben mogelijk nog steeds potentie voor matching (zie ook hoofdstuk 2). Aangezien onze studie geen klinische uitkomsten gebruikt heeft die direct gerelateerd zijn aan het drinken van alcohol (over het algemeen de meest belangrijke indicatoren van een succesvolle behandeling), is er in toekomstige studies ook meer aandacht nodig voor uitkomsten zoals terugval. Tenslotte zou ook rekening gehouden moeten worden met factoren die mogelijk endofenotypen en fenotypen met elkaar ver-
Samenvatting

binden, zoals bewustzijn en sociale wenselijkheid (zie ook hoofdstuk 4). Al met al openen de bevindingen in dit proefschrift een groot aantal nieuwe wegen om te komen tot een effectievere en met name ook efficiëntere vorm van behandeling van patiënten met een stoornis in het gebruik van alcohol.
### List of frequently used abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Δ peak</td>
<td>Delta peak</td>
</tr>
<tr>
<td>ACQ</td>
<td>Alcohol Craving Questionnaire</td>
</tr>
<tr>
<td>AEFQ</td>
<td>Alcohol Effects Questionnaire</td>
</tr>
<tr>
<td>AMDS</td>
<td>Amsterdam Motives for Drinking Questionnaire</td>
</tr>
<tr>
<td>ASI</td>
<td>Anxiety Sensitivity Index</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
</tr>
<tr>
<td>BAS</td>
<td>Behavioural Activation System</td>
</tr>
<tr>
<td>BIS</td>
<td>Behavioural Inhibition System</td>
</tr>
<tr>
<td>CE</td>
<td>Cue Exposure</td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>FH</td>
<td>Family History</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma Amino Butyric Acid</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HPA axis</td>
<td>Hypothalamic Pituitary Adrenal axis</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>HSP</td>
<td>High Sensitive Person</td>
</tr>
<tr>
<td>IDS</td>
<td>Inventory of Drinking Situations</td>
</tr>
<tr>
<td>JACQ</td>
<td>Jellinek Alcohol Craving Questionnaire</td>
</tr>
<tr>
<td>MACL</td>
<td>Mood Adjective Checklist</td>
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<tr>
<td>MDQ</td>
<td>Motives for Drinking Questionnaire</td>
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<tr>
<td>OCDS</td>
<td>Obsessive Compulsive Drinking Scale</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>RR</td>
<td>Respiration Rate</td>
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</tbody>
</table>
List of Abbreviations

SCA  Simultaneous Components Analysis
SCL  Skin Conductance Level
SCR  Skin Conductance Response
SPECT Single Photon Emission Computed Tomography
SSRI Selective Serotonin Reuptake Inhibitor
STAI Spielberger State-Trait Anxiety Inventory
VAS  Visual Analog Scale
HET VERLANGEN

door het prisma van verlangen
naar alle namen die ik noem
heeft de lichtval mij gevangen
binnen de bloeitijd van een bloem

Arie Visser
Uit: Voorlopig overzicht, gedichten 1965-1980
Dankwoord

Aan het einde gekomen zou ik graag iedereen willen bedanken die een bijdrage
heeft geleverd aan dit proefschrift. Allereerst wil ik alle deelnemers van het on-
derzoek bedanken voor hun deelname en alles wat zij mij geleerd hebben.

Natuurlijk was dit proefschrift niet tot stand gekomen zonder mijn promoto-
res en co-promotores: Wim van den Brink, Roel Verheul, Maarten Koeter en
Gerard Schippers. Gerard, wetenschapper en therapeut ineen: zonder jou was de
brug naar de praktijk nog verder geweest. Bedankt voor je feedback tijdens onze
overleggen. Maarten: je bent briljant. Dankzij jou ben ik statistiek leuk gaan vin-
den en ik denk met veel plezier terug aan onze eigenwijze discussies. Ik zal je mis-
zen. Roel: zonder jou was dit project er niet geweest. Bedankt voor je initiërende
energie. Herinner je ons werkbezoek in de VS nog? Wim: voor mij ben je de per-
fecte promotor geweest. Ik heb veel van je geleerd. Hoe je onderzoek moet doen,
maar ook hoe je met de mensen van je team moet omgaan. Je hebt me op de juis-
te momenten vrij gelaten of juist aangestuurd, precies wat ik nodig heb. Of het
nu ging om de details of de grote lijn, altijd kreeg ik snel goede feedback. Ik hoop
dat onze paden zich nog regelmatig zullen kruisen!

De leden van de promotiecommissie wil ik bedanken voor het lezen en beoor-
delen van mijn proefschrift: Ingmar Franken, Ton Schoffelmeer, Aart Schene,
Vincent Hendriks en Reinout Wiers. Ingmar: ook bedankt voor je hulp in de be-
ginfase van het onderzoek.

Alle collega’s van het AIAR bedank ik voor hun feedback en vriendschap. Sa-
men discussiëren, zingen, hardlopen, borrelen, of naar het theater, het is altijd ge-
zellig. Van de 4e verdieping wil ik bedanken: Hans, Sandra, Wil, Edith, Marja, Su-
zan, Masha, Peter, Udo, Maarten, Paul, Annemarie en Angela. Dankzij jullie
voelde ik me thuis. Lieve Sandra en Hans: zonder onze wandelingen tijdens de
lunch had ik het niet gered! Jullie nemen een speciaal plekje bij me in! Van de
‘good old times’ bedank ik Mieke, Laura, Riët, Femke, Marjolein, Andrea, Anneke,
Ewout, Chris, Marcel, Gijs, Mark, en Monique. Anneke: bedankt ook voor al je
tips in de laatste fase! Dank aan ‘neuroimagers’ Gerry, Kuan, Maartje en Michiel.
Dankwoord

Arne en Victor: bedankt voor de nuttige en gezellige bijeenkomsten over cortisol.


Ook collega’s van anderen instellingen en universiteiten hebben bijgedragen: zo wil ik Frank Brook (Kuno van Dijk Stichting), Ben van de Wetering (Boumanhuis), Michel Odufré (Parnassia), Sjaan Nederkoorn (Universiteit Maastricht), Jack van Honk (Universiteit Utrecht) bedanken voor hun hulp tijdens de pilot van het onderzoek. Special thanks to my French co-workers from l’Université de Picardie Jules Verne in Amiens: Mickaël Naassila, Hakim Houchi and Martine Daoust, thank you for sharing your genetic knowledge and data, for being patient and enthusiastic. Dear Raymond Anton, Dave Drobes, Peter Monti, Raymond Niaura, Ned Cooney, Mark Litt, Bruce Rounsaville, Hank Kranzler, and Clemens Kirschbaum: thanks to you I have learnt a lot about psychophysiology, I enjoyed my visit in your lab a lot. A special thanks to Irving Gottesman who inspired me with his scientific view.

Wie dacht dat ik dit onderzoek alleen heb gedaan, komt bedrogen uit. Ik wil alle stagiaires en onderzoeksmedewerkers van harte bedanken voor hun toewijding en enthousiasme. Lieve Lonneke, Marielle, Femke, Sigrid, Dorine, Gjalt, Weena, Kai, Maja, Simone en Premal: dankzij jullie hebben veel deelnemers meegegaard en was er leven in het lab! Jullie hebben allemaal je eigen kwaliteiten en ik denk met veel plezier terug aan onze samenwerking en de etentjes bij de Kamelen. Gloria, Huub en natuurlijk onze ‘buddy’ Ron, bedankt voor je inzet bij het buddy project. Lieve Ron: ik heb genoten van jouw werklust, enthousiasme en harde lach; en wat een resultaat!

Dank aan Bep de Lange, die met haar goede zorgen, lief geplaaeg en altijd ter- rechte kritiek (ik ben inderdaad een ongeduldig vogeltje) onmisbaar was.

Gelukkig waren er ook mensen om me heen die niets met verslavingsonder-

Mijn paranymph wil ik bedanken voor het paranymph zijn, maar vooral omdat het gewoon twee fantastische mensen zijn. Lieve Siets en Nanno: sinds 1993 zijn we ‘onafscheidelijk’ en dat wil ik graag zo houden. Ik vind het mooi te zien hoe jullie blijven groeien en dat onze band alleen maar hechter wordt. Ik kan niet meer zonder jullie!

Dankzij mijn familie hield ik vertrouwen in mezelf en het onderzoek. Zij hebben mij geleerd uitdagingen aan te gaan, maar ook mijn grenzen te bewaken. Lieve Ien en Wim: bedankt voor jullie liefde en dat jullie er voor me zijn! Lieve Kevin, onze lunches hebben me erdoor gesleept. Ik ben gek op je inzicht en gevoelsleven, en kan me geen betere broer wensen! Ook wil ik mijn ‘andere familie’ bedanken: Ot, Guus, Karin en Astrid: bij jullie op de Bosplaat voel ik me helemaal thuis, Ronald en ik boffen maar met jullie. En natuurlijk alle ooms en tantes, nichtjes en neven van de Ooteman en Gosens kant: bedankt!

Lieve Ronald, alles waarvoor ik jou wil bedanken fluister ik het liefste in je oor als we straks in de zon lopen. Er is zoveel moois dat jij in je hebt en kan geven. Ik realiseer me iedere dag weer dat ik ongelofelijk bof met je. Bij jou kan ik ontspannen, lachen, mezelf zijn. Ik kan niet wachten met jou aan onze toekomst te beginnen. Je bent m’n liefie!

Wendy
List of publications


gebroken uit het licht der dagen
en het verlangen van de nacht
wij weten niet maar blijven vragen

Arie Visser
Uit: Licht en Vuur, gedichten, 1996;
in memoriam Cedric Vonk (1947-1980).
About the author

Wendy Ooteman was born on February 11, 1975. In 1999, she obtained a master's degree in medical biology from the University of Utrecht in the Netherlands. Her master's thesis, conducted at the University of Iowa, United States of America, focused on structural magnetic resonance imaging of the thalamus in schizophrenic patients. After completing her master's degree, she took on a position as a PhD student at the Amsterdam Institute for Addiction Research, University of Amsterdam (posting to the Jellinek addiction treatment center). From 2000 to 2005, she conducted the research presented in this thesis. In collaboration with Groupe de Recherche sur l’Alcool et les Pharmacodépendances (GRAP) (Université de Picardie Jules Verne, France) and her supervisors, she has also written a paper on the association of genetic polymorphisms with alcohol dependence. Currently, she is planning to obtain a postdoctoral position, where she will continue her research in the field of addiction.
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