Predictors of Alcohol Treatment Outcome

Prognostic factors in Cognitive Behavioral Therapy for Problem Drinking including Targeted Use of Naltrexone

Salla Vuoristo-Myllys

Institute of Behavioural Sciences
University of Helsinki, Finland

and

Institute of Clinical Medicine
University of Helsinki, Finland

and

National Institute for Health and Welfare, Finland

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Supervisors:

Professor Hannu Alho, PhD
Institute of Clinical Medicine
Department of Medicine
University of Helsinki, Finland

Hely Kalska, PhD
Institute of Behavioural Sciences
University of Helsinki, Finland

Professor Emeritus Juhani Julkunen, PhD
Institute of Behavioural Sciences
University of Helsinki, Finland

Reviewers:

Professor Kalervo Kiianmaa, PhD
National Institute of Health and Welfare

Docent Kalle Jokelainen, PhD
Helsinki University Central Hospital

Opponent:

Docent Klaus Ranta, PhD, MD, MA (Psych)
University of Turku

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ABSTRACT

Randomized controlled trials and systematic reviews form a basis for evidence-based treatments of alcohol use disorders. However, generalizing the research findings of randomized controlled trials to clinical practice is sometimes difficult. Little is known about how many such treatments work in real-life treatment settings or to whom the results apply.

The aim of this study was to investigate how one of the evidence-based treatments for alcohol dependence, cognitive behavioral therapy (CBT) combined with targeted (used as needed) naltrexone, works in a real-life treatment setting with a heterogeneous patient sample. The study specifically investigated which factors were prognostic of treatment dropout, treatment outcomes, and patient adherence to naltrexone. The study also investigated whether CBT combined with medication (naltrexone/acamprosate/ disulfiram) can improve patient well-being and quality of life, in addition to reducing alcohol consumption.

The participants in studies I–III comprised of problem drinkers who attended an outpatient treatment program that combined CBT and naltrexone. The participants in study IV were treatment-seeking heavy drinkers who participated in a randomized controlled trial in which they received medication and CBT. In studies I–III, we evaluated the sociodemographic factors, alcohol-related factors and depressive symptoms of participants at treatment entry. We evaluated the change in alcohol consumption and symptoms of alcohol craving, as well as the patients' adherence to naltrexone use during the 20 weeks of treatment. In study IV, we evaluated the change in the quality of life, depression, and smoking habits of participants during the treatment (52 weeks) and follow-up (119 weeks).

In studies I–III, factors related to dropping out included a younger age, lower problem severity, lower adherence to naltrexone, and starting the treatment with abstinence. The alcohol-related outcomes were poorer for those with no previous treatment history and higher pretreatment alcohol consumption. Patients who drank more alcohol before and during the treatment had lower adherence to naltrexone. Poor naltrexone adherence was also associated with unemployment and a strong craving for alcohol. Study IV showed that in addition to significantly reducing drinking, combining

medication and CBT can improve the quality of life, depression, and smoking habits of those patients who commit to treatment. Participants who used disulfiram were the most successful in quitting smoking.

An important finding regarding routine treatment settings was the variability in how problem drinkers benefited from CBT and naltrexone. Those with lower problem severity may benefit from shorter interventions. However, those with the most severe alcohol problems may require more intensive and longer treatment, as well as the use of medications other than naltrexone. Non-adherence to medication is a barrier to the effectiveness of naltrexone in a real-life treatment setting, and those with a high craving for alcohol may need specific interventions to enhance medication use. For those who commit to treatment, CBT combined with medication may improve general well-being and quality of life, in addition to reduced drinking. The treatment may also help patients quit smoking, especially those who use disulfiram during treatment.

TIIVISTELMÄ

Alkoholiriippuvuuden näyttöön perustuvat hoitosuositukset luodaan yleensä satunnaistettujen ja kontrolloitujen tutkimusten sekä systemaattisten kirjallisuuskatsausten tuottaman tiedon perusteella. Satunnaistettujen ja kontrolloitujen tutkimusten yleistettävyys käytännön hoitotyöhön on kuitenkin joskus haasteellista. Tiedetäänkin melko vähän siitä, miten nämä hoidot toimivat luonnollisessa hoitoympäristössä ja kenelle ne erityisesti sopivat.

Tämän tutkimuksen tarkoituksena oli selvittää, kuinka yksi näyttöön perustuvista hoitomuodoista, kognitiivinen käyttäytymisterapia (KKT) yhdistettynä kohdennettuun (vain tarvittaessa käytettävään) naltreksoni–lääkitykseen toimii luonnollisessa hoitoympäristössä ja heterogeenisessa potilasaineistossa. Tutkimuksessa pyrittiin erityisesti selvittämään, mitkä tekijät ennustavat potilaiden sitoutumista hoitoon, hoidon tuloksellisuutta ja lääkkeen käytön tunnollisuutta. Lisäksi selvitettiin sitä, voiko KKT yhdistettynä lääkitykseen (naltreksoni, akamprosaatti tai disulfiraami) lisätä heidän hyvinvointiaan ja parantaa elämänlaatua vähentyneen alkoholin kulutuksen lisäksi.

Osallistujat tutkimuksissa I-III olivat hoitoon hakeutuvia ongelmajuojia, jotka osallistuivat KKT:sta ja naltreksoni-lääkityksestä rakentuvaan hoito-ohjelmaan. Tutkimuksessa IV tutkittavat osallistuivat satunnaistettuun ja kontrolloituun tutkimukseen, joka koostui lääkityksestä (naltreksoni, akamprosaatti tai disulfiraami) yhdistettynä terapiaan. Tutkimuksissa I-III osallistujien sosiodemografiset tekijät, alkoholin käyttöön liittyvät tekijät ja masennusoireet arvioitiin hoidon alussa. Muutosta juomismäärässä ja juomishimossa arvioitiin 20 viikon hoidon aikana. Tutkimuksessa IV arvioitiin muutosta osallistujien elämänlaadussa, masennusoireissa ja tupakoinnissa hoidon aikana (52 viikkoa) ja seurantakäynnillä (119 viikkoa).

Tutkimuksissa I-III hoidon keskeyttämiseen olivat yhteydessä nuorempi ikä, vähäisempi alkoholiongelma, heikompi sitoutuminen naltreksonin käyttöön ja hoidon aloittaminen täysraittiudella. Hoidon tulos oli heikompi niillä, joilla ei ollut aikaisempaa hoitohistoriaa ja joiden alkoholinkäyttömäärä oli ennen hoitoa korkeampi. Henkilöt, jotka joivat eniten hoidon aikana, sitoutuivat heikoimmin naltreksonin käyttöön. Heikompaa sitoutumista lääkityksen käyttöön ennustivat myös työttömyys ja suurempi juomishimo. Tutkimus IV osoitti, että KKT yhdistettynä lääkitykseen voi parantaa

potilaiden elämänlaatua ja masennusoireita vähentyneen juomisen lisäksi niillä, jotka sitoutuvat hoitoonsa. Hoito voi myös auttaa lopettamaan tupakoinnin, erityisesti niillä, jotka käyttävät disulfiraamia.

Tärkeänä havaintona käytännön hoitotyön kannalta voidaan pitää sitä, että luonnollisessa hoitoympäristössä potilaiden kyky hyötyä KKT & naltreksoni-hoidosta on vaihtelevaa. Henkilöille, joilla alkoholiongelma on lievempi, saattaa riittää lyhyempi hoitointerventio. Sen sijaan vaikeimmin alkoholiongelmaiset saattavat tarvita intensiivisempää ja pidempää hoitoa kuin tässä hoitomallissa ja hyötyä enemmän muista lääkityksistä. Heikko sitoutuminen lääkityksen käyttöön on yksi suurimpia esteitä naltreksonin tuloksellisuudelle luonnollisessa hoitoympäristössä ja henkilöt, joilla on korkea juomishimo, saattavat tarvita erityistä tukea lääkityksen käyttöön sitoutumiseen. Henkilöillä, jotka sitoutuvat hoitoonsa, KKT ja lääkitys saattaa vähentyneen juomisen lisäksi lisätä yleistä hyvinvointia ja parantaa elämänlaatua. Hoito voi auttaa myös lopettamaan tupakoinnin, erityisesti niillä, jotka käyttävät hoidon aikana disulfiraamia.

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Tuusula, February 8, 2014

Salla Vuoristo-Myllys

> "In a community..
> there is a gulf
> which has been much
> underestimated."
> **A.L. Cochrane (1972)**

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following publications:

I   **Vuoristo-Myllys, S.**, Lahti, J., Alho, H., & Julkunen, J. (2013) Predictors of dropout in an outpatient treatment for problem drinkers including cognitive behavioral therapy and opioid antagonist naltrexone. *Journal of Studies on Alcohol and Drugs*, 74, 894–901.

II   **Vuoristo-Myllys, S.**, Lipsanen, J., Lahti, J., Kalska, H., & Alho, H. (2014) Outcome predictors for problem drinkers treated with combined cognitive behavioral therapy and naltrexone. *The American Journal of Drug and Alcohol Abuse*. Advance online publication. doi:10.3109/00952990.2013.853074

III   **Vuoristo-Myllys, S.**, Laaksonen, E., Lahti, J., Lipsanen, J., Alho, H., & Kalska, H. (2013) Predictors of self-reported adherence to naltrexone medication in an outpatient treatment for problem drinking. *Journal of Addiction Research & Therapy,* 4, 2.

IV   Laaksonen, E., **Vuoristo-Myllys, S.,** Koski-Jännes, A., & Alho, H. (2013) Combining medical treatment and CBT in treating alcohol-dependent patients: effects on life quality and general well-being. *Alcohol and Alcoholism*, 48, 687–693.

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ABBREVIATIONS

ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
AUDIT	Alcohol Use Disorder Identification Test
BIC	Schwarz's (Bayesian) information criteria
BDI	Beck Depression Inventory
CBT	Cognitive behavioral therapy
DEPS	Depression scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EQ-5D	European Quality of Life Questionnaire
GABA-A	Gamma-aminobutyric acid
ICD-10	International Classification of Diseases
IBS SPSS	Statistical software
KQL	Quality of life scale
MINI	The Mini International Neuropsychiatric Interview
NMDA	N-methyl-D-aspartate
OCDS	Obsessive Compulsive Drinking Scale
QL	Quality of life
SAS	Statistical software
SADD	Severity of Alcohol Dependence Data
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

Alcohol use disorders are among the most important mental disorders, affecting an estimated 3.9% of the adult population in Finland (Pirkola et al., 2005). Globally, 4.6% of the burden of disease and injury has been reported to be attributable to alcohol (Whiteford et al., 2013). Alcohol use disorders are associated with remarkably high mortality, including younger age groups and those in treatment (Roerecke & Rehm, 2013). Therefore, the existing evidence-based strategies for reducing excessive drinking should be widely implemented in primary care, occupational health care, and specialized clinics that receive patients with problem drinking.

However, disseminating evidence-based practices, which are usually based on research findings from randomized controlled trials, into routine clinical settings is often challenging (Lamb et al., 1998; Marinelli-Casey et al., 2002; McGovern et al., 2004). Although randomized controlled trials have long been considered as the golden standard in trials of alcohol dependence treatments, the generalizability of their findings in routine alcohol treatment settings is often poor (Rothwell, 2005). Specifically, the strict inclusion and exclusion criteria used in the selection of study subjects and the process of randomization may alter treatment settings and patient samples in a way that differs from usual treatments. According to Rothwell (2005), the concern among clinicians about the external validity of randomized controlled trials has led to the underuse of treatments that are effective. Studies based on routinely collected data and non-randomized study samples have been suggested as an important adjunct to randomized controlled trials (Moyer & Finney, 2002; Rothwell, 2005). However, these studies are still scarce.

An important aspect in the dissemination of evidence-based treatments into routine clinical settings is to consider to whom the results of randomized controlled trials apply (Rothwell, 2005). The treatments demonstrated in randomized controlled trials cannot be expected to be effective in all patients and in all settings. It has been suggested that the results of randomized controlled trials should be reported in a way that allows clinicians to judge which patient groups the results can reasonably be applied to (Rothwell, 2005). More generally, predicting outcomes in various alcohol treatments

also provides an opportunity to improve treatments by identifying specific patient groups achieving poorer outcomes, identifying areas to target in treatment, and improving the accuracy of prognosis (Adamson et al., 2009). Clinical prognostic judgments can be aided by determining empirically established relationships using prospective data (Breslin et al., 1997).

1.1. Treatment of alcohol use disorders and problem drinking

Alcohol use disorders consist of alcohol dependence and alcohol abuse (Frances, 1994). The diagnostic criteria for each of these disorders are described in Table 1. *Hazardous drinking* is considered as a level of consumption or a pattern of drinking that is likely to result in adverse health effects (Alho et al., 2011). In Finland, hazardous drinking level for men has been defined as drinking more than 24 alcohol units (12 grams of pure alcohol) per week, 4 units per day, or more than 7 alcohol units on one occasion, and for women as drinking more than 16 alcohol units per week, 2 units per day, or more than 5 alcohol units on one occasion (Alho et al., 2011).

Although alcohol treatments typically take in patients with alcohol dependence, alcohol abuse, or hazardous drinking levels, individuals sometime seek treatment for perceived problematic alcohol use before their symptoms are severe enough to fulfill these diagnostic criteria. The term *problem drinking* is used to refer to a man whose alcohol consumption exceeds 14 standard drinks per week or who consumes 4 drinks per drinking day, or to a woman who consumes more than 7 standard drinks per week or 3 drinks per drinking day. These alcohol consumption levels have been suggested to increase the risks for alcohol-related problems by the National Institute of Alcohol Abuse and Alcoholism (2005).

Active screening and early detection are important in the treatment of problem drinking. After diagnosing the alcohol problem, a good working alliance between the patient and the clinician, and the use of proper psychosocial treatments form the cornerstone for the treatment (Alho et al., 2011). The use of pharmacotherapy with appropriate psychosocial treatments has been suggested to improve treatment outcomes (Alho & Aalto, 2013; Mann, 2004) by approximately 15–25% (Alho et al., 2011).

Table 1. DSM IV diagnostic criteria for alcohol dependence and alcohol abuse

Alcohol dependence	
A maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12-month period:	
A	Marked tolerance—the need for markedly increased amounts of alcohol to achieve intoxication; or a markedly diminished effect with continued use of the same amount of alcohol
B	Characteristic withdrawal symptoms for alcohol; or drinking to relieve or avoid withdrawal symptoms
C	Drinking larger amounts or over a longer period than was intended
D	Persistent desire or one or more unsuccessful efforts to cut down or control drinking
E	A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of drinking
F	Important social, occupational, or recreational activities given up or reduced because of drinking
G	Continued drinking despite knowledge of having a persistent or recurring social, psychological, or physical problem that is caused or exacerbated by drinking
Alcohol abuse	
A maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by at least one of the following occurring at any time in the same 12-month period:	
A	Recurrent use of alcohol resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household)
B	Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol use)
C	Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct)
D	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about the consequences of intoxication)

Source: Diagnostic and Statistical Manual of Mental Disorders IV (Frances, 1994)
Note: the new DSM 5 diagnostic criteria are not included because they differ from the DSM IV criteria and they were not used in this study.

1.1.1 Brief interventions

Brief interventions are short-term counseling sessions that are aimed at addressing problems associated with hazardous and harmful drinking (Moyer & Finney, 2004). They are generally implemented by professionals who have not specialized in alcohol treatment, and are carried out in places such as primary health care facilities or different medical units (Moyer & Finney, 2004). They usually aim at reducing alcohol consumption to nonhazardous levels and eliminating binge drinking (Moyer & Finney, 2004).

Well-designed brief intervention strategies have been found to effectively alter the course of harmful alcohol use (Bien et al., 1993; Maisto et al., 2001; Moyer et al., 2002). However, there is contrary evidence concerning whom brief intervention is effective for. A meta-analysis by Wilk et al. (1997) revealed that heavy drinkers who received brief intervention were twice as likely to moderate their drinking 6–12 months after the intervention compared to heavy drinkers who received no intervention. In contrast, a study by Saitz and co-workers (2007) demonstrated that brief intervention was insufficient for medical inpatients. Similarly, a review by Moyer and co-workers (2002) found that brief interventions were only effective for persons with less severe alcohol problems. Brief intervention may thus best be seen as an appropriate form of initial treatment (Moyer & Finney, 2004), but patients who do not respond to it should be referred to more intensive and extensive forms of treatment, as suggested by a 'stepped care' approach (Sobell & Sobell, 2000).

1.1.2 Psychosocial interventions

The most typical form of psychosocial treatment for problem drinking is 'treatment as usual', a supportive therapeutic relationship that combines elements from different therapeutic orientations (Alho et al., 2011). Specific treatments for alcohol problems that are based on research evidence include motivational enhancement therapy or motivational interviewing, coping-skills therapy, cognitive behavioral intervention or cognitive behavioral therapy (CBT), cue-exposure interventions, the contingency management approach, behavioral couple therapy, and Alcoholics Anonymous or 12-step approaches (Emmelkamp & Vedel, 2012). Of these, there is perhaps most consistent evidence for the effectiveness of motivational enhancement therapy or motivational interviewing (Vasilaki et al., 2006), and for coping-skills therapy or CBT (Magill & Ray, 2009).

Motivational interviewing has two important phases: building a patient's motivation and strengthening the commitment to change (Miller & Rollnick, 1991). Motivational enhancement therapy is a treatment that uses the techniques of motivational interviewing (Miller, 1994). According to the theory presented by Miller (1983), motivation can been conceptualized as a state of readiness for change and, as such, it may fluctuate over time or from one situation to another. A lack of motivation or

resistance to change is seen as something that can be influenced to change in a particular direction (Miller, 1994). The main focus in motivational interviewing is to facilitate behavioral change by helping patients to resolve their ambivalent thoughts about the change (Miller, 1994).

In CBT for problem drinking, the main goals are to help the patient to identify high-risk situations for alcohol use and to develop coping strategies for these situations (Marlatt & Gordon, 1985). Coping skills are actions (cognitions or behaviors) that are encouraged to be taken in the face of challenges, such as preserving abstinence (Marlatt & Gordon, 1985). CBT approaches may also use self-monitoring exercises, skills training and cue exposure, as well as exercises to enhance motivation, increase self-efficacy and decrease positive alcohol-related outcome expectancies (Marlatt & Witkiewitz, 2002).

Cue-exposure interventions are treatments in which an addicted person is exposed to a variety of drug-related stimuli while self-report craving and physiological responses are monitored (Carter & Tiffany, 1999). Cue reactivity interventions appear to be effective for patients with a moderate severity of alcohol dependence (Loeber et al., 2006). Contingency management is a procedure in which a target behavior (such as abstinence) is frequently monitored and positive, tangible reinforcers are provided when the target behavior occurs, and removed if the target behavior does not occur (Petry et al., 2001). Contingency management has been reported to be efficacious in treating alcohol-dependent patients (Petry et al., 2000). There is also evidence that behavioral marital therapy, a treatment that involves one's spouse in the treatment, is effective for treating alcohol use disorders (Miller & Wilbourne, 2002)

There is somewhat contrary evidence for the effectiveness of Alcoholics Anonymous or 12-step facilitation. Although a large clinical trial that compared the effectiveness of CBT, motivational enhancement therapy, and 12-step facilitation found that all three had similar efficacy (Project MATCH Research Group, 1998a), a more recent review by Ferri et al. (2006) concluded that there is insufficient scientific evidence to support the effectiveness of 12-step facilitation or Alcoholics Anonymous. However, it was found that the 12-step approaches can help patients to accept treatment and keep them retained in treatment more than alternative treatments (Ferri et al., 2006).

1.1.3 Pharmacotherapy of alcohol use disorders

In the European Union, the pharmacological treatment of alcohol dependence includes four currently approved medications: disulfiram, acamprosate, and the opioid antagonists naltrexone and nalmefene. Disulfiram, an aldehyde dehydrogenase blocker, is the most traditional medication, and is used to aid abstinence. Disulfiram blocks the enzyme aldehyde dehydrogenase, which leads to an accumulation of acetaldehyde following the intake of alcohol (Heilig & Egli, 2006). The increased acetaldehyde leads to flushing, nausea, dizziness, tachycardia, headache, and shortness of breath (Alho & Aalto, 2013; Heilig & Egli, 2006). It is thought that anticipation of these symptoms would help patients abstain from alcohol (Alho & Aalto, 2013; Heilig & Egli, 2006). A review by Berglund et al. (2003) concluded that although the overall efficacy of disulfiram is lacking, it is seems to be effective when given under supervision. Similarly, a study by Laaksonen et al. (2008a) comparing the effects of three pharmacotherapies, disulfiram, naltrexone, and acamprosate in combination with CBT, in alcohol-dependent patients demonstrated that supervised disulfiram was more effective in reducing alcohol consumption than naltrexone or acamprosate.

Another proven pharmacological treatment for alcohol dependence is the functional glutamate antagonist acamprosate, which is only available in Finland under a special license. Acamprosate blocks dependence-induced drinking (Rimondini et al., 2002). It is known to facilitate GABA-A neurotransmission and to modulate neuronal responses to the stimulation of both NMDA-type glutamate receptors and certain classes of metabotropic glutamate receptors (Fogel et al., 2013). Acamprosate has been found effective in supporting abstinence (Carmen et al., 2004; Mann et al., 2004).

The main effects of the opioid antagonist naltrexone is related to reducing alcohol "liking" and alcohol craving (Rösner et al., 2010). It appears to work best when used as part of treatments that aim towards moderate alcohol use rather than abstinence (Alho & Aalto, 2013). Alcohol affects the opioid receptor system of the brain, which mediates the euphoric and pleasurable effects of alcohol, and the function of opioid antagonists is to block these receptors (Rösner et al., 2010). Indeed, naltrexone has been proven to reduce the "high" in drinking (Volpicelli et al., 1995). The use of opioid antagonists has been found to be an effective strategy in the treatment of alcohol dependence (Carmen

et al., 2004; Mann et al., 2012; Rösner et al., 2010; Srisurapanont & Jarusuraisin, 2005), although the effect sizes reported in many trials have been relatively small.

It has been suggested (Sinclair, 2001) that the effect of naltrexone is highly dependent on the manner in which it is used. Although most randomized controlled trials have included daily treatment with naltrexone, an alternative approach is to only use it in situations where the patient anticipates a high risk of starting to drink alcohol. A targeted approach or as-needed use of naltrexone has been explored in a few trials. A study by Heinälä et al. (2001) showed that targeted medication, taken only when cravings occur, during a 20-week period following on from a 12-week daily naltrexone treatment regimen combined with coping skills therapy was effective in maintaining the reduction in heavy drinking. Subsequent trials by Kranzler and coworkers (Kranzler et al., 2003; Kranzler et al., 2009) have found that targeted administration of naltrexone in addition to coping skills therapy reduces drinking more than placebo.

Another opioid antagonist, nalmefene, has also been demonstrated to reduce the total amount of alcohol consumed and number of heavy drinking days in patients with alcohol dependence when used on an as-needed (targeted) basis (Gual et al., 2013). Nalmefene is an opioid receptor modulator with antagonist activity at the μ and δ receptors, and it also has partial agonist activity at the κ receptor. The half-life of nalmefene is considerably longer than that of naltrexone (Bart et al., 2005). A recent narrative review by Niciu and Arias (2013) concludes that targeted or as-needed treatment with both opioid antagonists is an efficacious harm-reduction strategy for problem drinking and alcohol dependence.

Future directions in the pharmacological treatment of alcohol dependence include aiming to form more homogeneous subgroups, such as biologically defined endophenotypes, who benefit from certain medications (Mann & Hermann, 2010). To date, it has been demonstrated that patients with a high craving for alcohol (Monterosso et al., 2001), those with a younger age of alcoholism onset (Tidey et al., 2008), and those with a positive family history of alcoholism (Monterosso et al., 2001) may have a better response to naltrexone. However, in a study by Capone and co-workers (2010), the moderating effect of a positive family history of alcoholism was not found. naltrexone has also been reported to most benefit individuals with the G allele of A118G polymorphism of *OPRM1* (Chamorro et al., 2012). However, in a large

population study, no correlation was found between ORM1 and alcohol dependence or alcohol consumption (Rouvinen-Lagerström et al., 2013).

1.1.4 Detoxification

Among patients who consume excessive amounts of alcohol, abstinence is likely to cause alcohol withdrawal symptoms. These range from minor symptoms, such as insomnia and tremulousness, to more severe symptoms, including withdrawal seizures and delirium tremens (Bayard et al., 2004). Important aspects in treating withdrawal symptoms include reducing patients' unspecific symptoms and subjective suffering, but most importantly, preventing seizures, delirium tremens, and death (Bayard et al., 2004). Benzodiazepines are evidence-based medications for ameliorating withdrawal symptoms and reduce the risks associated with them (Alho et al., 2011).

1.1.5 Combined pharmacotherapies and behavioral interventions

The large Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study in the US and Canada sought to address questions about the benefits of combining behavioral and pharmacological interventions (naltrexone and acamprosate) in alcohol-dependent patients (Anton et al., 2006). It was found that patients who received medical management with naltrexone, cognitive behavioral intervention, or both fared better in drinking outcomes (percent of days abstinent from alcohol and time to the first heavy drinking day), whereas acamprosate showed no evidence for efficacy with or without cognitive intervention (Anton et al., 2006). It was concluded that naltrexone with medical management could be delivered in health care settings for patients who might not otherwise receive treatment (Anton et al., 2006).

However, as presented in Table 2, in many randomized controlled trials, naltrexone has been shown to be especially efficacious when combined with coping skills therapy or CBT, where one of the therapeutic goals is to address issues related to alcohol craving (Marlatt & Gordon, 1985). It has been suggested that CBT and naltrexone reinforce their active ingredients (Anton et al., 1999), although a meta-analysis by Agosti and co-workers (2012) revealed that CBT did not offer benefits beyond those derived from the use of only study medications. Nalmefene, a newer opioid antagonist, has been proven to be effective when used in combination with adherence-enhancing

intervention (BRENDA) (Mann et al., 2012), and in a study by Karhuvaara and co-workers (2007), even with minimal psychosocial support.

Table 2. Studies comparing naltrexone in combination with different psychosocial treatments or CBT

Clinical trial	Psychosocial treatment	Effect
Kranzler et al. (2009)	Coping skills therapy	+
Oslin et al. (2008)	CBT	+
	BRENDA	--
	Limited therapy	--
Hernandez-Avila et al. (2006)	Coping skills therapy	+
Anton et al. (2005)	CBT	+
	MET	--
Balldin et al. (2003)	CBT	+
	Supportive	--
Kranzler et al. (2003)	Coping skills therapy	
Monti et al. (2001)	CBT	+
Morris et al. (2001)	CBT	+
Heinälä et al. (2001)	Coping skills therapy	+
	Supportive	--
Krystal et al. (2001)	Supportive	--
Chick et al. (2000)	Multiple	--
Knox & Donovan (1999)	Supportive	--
Volpicelli et al. (1997)	CBT	+
Oslin et al. (1997)	CBT	+
O'Malley et al. (1992)	Coping skills therapy	+
	Supportive	+

+ = Reduction in alcohol-related measures
-- = Lower reduction in alcohol-related measures than in the comparison group or reduction non-significant

1.1.6 Treatment-specific factors vs nonspecific factors

One controversial issue regarding selection of the best possible care for patients with alcohol problems is the criteria associated with treatment selection. Some trials have investigated the hypothesis that matching alcoholic patients to treatments based on their particular characteristics can improve treatment outcomes. One of these, Project MATCH (Project MATCH Research Group, 1998a), was a large study conducted in the US that investigated the effect of matching different alcohol treatments (CBT, motivational enhancement therapy, and 12-step facilitation) according to patient characteristics. The project failed to show any differences between these three treatments, and improvement among patients was similar across the three treatment forms (Project MATCH Research Group, 1998a). A similar comparative study, the United Kingdom Alcohol Treatment Trial (UKATT, 2005a) compared the effectiveness of motivational enhancement therapy as well as social behavior and network therapy

(Copello et al., 2002). Similarly to MATCH, patients appeared to display similar improvement in both treatments (UKATT, 2005[a]).

While matching patients to different treatments according to their heterogeneity seems to add little benefit to treatment outcomes, it has been suggested that nonspecific factors rather than specific factors in treatments account for a considerable amount of the treatment outcome (Connors et al., 1997; Schneider et al., 2004; Wampold, 2001). Above all, these nonspecific factors appear to include a good therapeutic alliance between the clinician and the patient (Connors et al., 1997; Meier et al., 2005), therapist qualities (Najavits et al., 2000), and patients' expectations and attributions in relation to treatment (Kadden & Litt, 2011; Messer & Wampold, 2002).

1.2 Evidence-based practice in the treatment of alcohol problems

Evidence-based practice is an interdisciplinary approach to clinical practice that originated in medicine as evidence-based medicine (Hjørland, 2011). The basic principles of evidence-based practice are that: a) decisions in clinical practice should be based on the best available *evidence*; b) evidence should be understood as research-based knowledge; c) the documentation, collection, and interpretation of this evidence should be done in a systematic and controllable way; d) the results of this collection and interpretation of evidence should be published as *a systematic review*, which synthesizes knowledge from multiple primary studies; and e) explicit norms should be made for investigations that are most relevant (Hjørland, 2011). Norms that value different types of research methods are organized in a hierarchical order (Carter, 2010).

In accordance with evidence-based practice, clinicians are encouraged to use empirically supported treatments with their patients. One of the most important criteria for empirically supported treatments is to have demonstrated the efficacy of the treatment over a placebo or comparison treatment in at least two independent randomized clinical trials (Magill & Longabaugh, 2013). However, one of the main problems of randomized controlled trials is that the role of nonspecific factors has often been ignored and it has been argued that specificity in randomized controlled trials cannot and should not be inferred only via the nature of the experimental contrast (Magill & Longabaugh, 2013).

1.2.1 Efficacy and effectiveness trials

Alcohol treatment outcome studies are usually implemented as either efficacy trials or effectiveness trials. According to the American Psychological Association's Task Force on Promotion and Dissemination of Psychological Procedures (American Psychological Association, 1993), treatment *efficacy* must be demonstrated in controlled research in which it is reasonable to conclude that the benefits observed are due to the effects of the treatment and not to chance or confounding factors, such as the passage of time, the effects of psychological assessment, or the presence of different types of clients in the various treatment conditions (see also Campbell et al., 1963). The efficacy of a treatment is usually demonstrated in a randomized controlled tiral, a trial in which participants are randomly assigned to the treatment under investigation, or to one or more comparison conditions. Treatments are usually performed using treatment manuals for which therapists have received similar and adequate training. The clinical utility of the treatment is usually demonstrated in *effectiveness* studies, in which the intervention is tested in a real-life practice setting (American Psychological Association, 1993). It involves specific evaluation of the generalizability of the intervention (e.g. treatment settings or patient characteristics) and feasibility of the treatment (e.g. availability of trained therapists, patient acceptance of the intervention) (Abrahamson, 2001).

Efficacy and effectiveness studies emphasize different aspects of validity, i.e. the degree to which an investigation measures what it intends to measure. The *internal validity* of a trial refers to the degree to which the trial can attribute changes in a dependent variable as being caused by independent variable(s) while simultaneously ruling out alternative explanations (Campbell et al., 1963). In efficacy studies, internal validity is of particular importance. Potential threats to the internal validity of a research trial are presented in Table 3.

Table 3. Potential threats to the internal validity of a research trial

1.	Selection of the study participants: the effects may reflect pre-existing differences between experimental and control conditions
2.	History: the effect may be caused by some event occurring at the same time as the intervention
3.	Maturation: the effect may reflect a continuation of pre-existing trends or normal change processes
4.	Instrumentation: the effect may be caused by a change in the method of measuring the outcome
5.	Testing: the pretest measurement may cause a change in the posttest measure
6.	Regression to the mean: Where an intervention is implemented on units with unusually high scores, a natural fluctuation will cause a decrease in these scores on the posttest, which may mistakenly be interpreted as an effect of the intervention. The opposite (an increase) happens when interventions are applied to units with unusually low scores.
7.	Differential attrition: the effect is caused by differential loss of units (e.g. study participants) from experimental compared to control conditions
8.	Causal order: it is unclear whether the intervention preceded the outcome

Source: Shadish et al. (2002)

The *external validity* of a trial refers to the extent that the results of the trial can be generalized to other populations and settings (Campbell et al., 1963). External validity is of particular importance in effectiveness studies. Issues that potentially affect external validity are presented in Table 4.

Table 4. Potential threats to the external validity of a research trial

1.	Setting of the trial: e.g. healthcare system; country; recruitment from primary, secondary or tertiary care; selection of participating centers; selection of participating clinicians
2.	Selection of participants: e.g. methods of pre-randomization diagnosis and investigation; eligibility criteria; exclusion criteria; placebo run-in period; treatment run-in period; enrichment strategies; ratio of randomized patients to eligible non-randomized patients in participating centers
3.	Characteristics of randomized participants: baseline clinical characteristics; racial group; uniformity of underlying pathology; stage in the natural history of their disease; severity of their disease; comorbidity; absolute risks of a poor outcome in the control group
4.	Differences between the trial protocol and routine practice: trial intervention; timing of treatment; appropriateness/relevance of control intervention; adequacy of non-trial treatment (both intended and actual); prohibition of certain non-trial treatments; therapeutic or diagnostic advances since trial was done
5.	Outcome measures and follow-up: clinical relevance of surrogate outcomes; clinical relevance, validity, and reproducibility of complex scales; effect of intervention on most relevant components of composite outcomes; who measured outcome; use of patient-centered outcomes; frequency of follow-up; adequacy of the length of follow-up
6.	Adverse effects of treatment: completeness of reporting of relevant adverse effects; rates of discontinuation of treatment; selection of trial centers and/or clinicians on the basis of skill or experience; exclusion of patients at risk of complications; exclusion of patients who experienced adverse effects during a run-in period; intensity of trial safety procedures

Source: Rothwell (2005)

1.2.2 External validity of randomized controlled alcohol trials

Randomized controlled trials have been the golden standard in alcohol treatment research for the past few decades. However, concerns about the external validity of alcohol treatment trials have included the process of randomization and selection of study samples. Namely, participants who agree to be randomized to treatment may differ from those who do not (Rothwell, 2005). Another important threat to external validity is the use of exclusion criteria and inclusion criteria in the selection of study samples. For instance, it has been shown that African-Americans, low-income individuals, and individuals who have more severe substance abuse or psychiatric problems are disproportionately excluded from alcohol treatment trials in comparison to real-world samples seen in clinical practice (Humphreys & Weisner, 2000). The exclusion of individuals with psychiatric disorders or other substance use problems may be particularly problematic from the point of view of external validity, because alcohol use disorders are highly correlated with both of these in the general population (Hasin et al., 2007).

In many trials that have examined the efficacy of CBT and naltrexone, it has been customary to exclude patients with major psychiatric or medical comorbidities (Anton et al., 2005; Heinälä et al., 2001; Hernandez-Avila et al., 2006; Kranzler et al., 2009). In addition, in many studies, only patients who fulfill the criteria for alcohol dependence (Heinälä et al., 2001; Killeen et al., 2004; Krystal et al., 2001; Mann, 2013) or those with high-risk alcohol consumption levels (Heinälä et al., 2001; Hernandez-Avila et al., 2006; Kranzler et al., 2009) have been included in the study sample.

Despite their limitations, randomized controlled trials are still the most reliable way to determine whether a cause–effect relation exists between a treatment and outcome and for assessing the cost-effectiveness of a treatment (Sibbald & Roland, 1998). However, more research is needed to test how evidence-based alcohol treatments work in real-life treatment settings using heterogeneous patient samples, including patients who have different comorbidities. As Moyer and Finney (2002) suggest, instead of debating the superiority of one versus the other, randomized and non-randomized research trials should be considered as complementary forms of treatment evaluation in alcohol treatment trials.

1.3 Predictors of treatment outcome

The prediction of treatment outcomes is a challenging task for a clinician who works with alcohol-dependent patients. The clinical prediction of human behavior may be inferior to formal and statistical methods (Grove et al., 2000), which has been explained by Grove and co-workers (2000) as due to "clinicians tendency to ignore base rates, assign non-optimal weights to cues, failure to take into account regression toward the mean, and failure to properly assess covariation." They also point out that clinicians often do not receive sufficient feedback on the accuracy of their judgments, which they could use to modify their possible judgment bias. Therefore, it is important to examine which patient- and treatment-related variables can be used to make a more accurate prognostication of treatment (Kraemer et al., 2001).

Another issue related to the importance of effective treatment planning is the cost-effectiveness of treating alcohol problems. Although there is evidence for effectiveness of brief interventions (Bien et al., 1993; Maisto et al., 2001; Moyer et al., 2002), it is clear that a portion of problem drinkers do not change their alcohol use in response them (Moyer et al., 2002; Saitz et al., 2007) and may need more intensive and longer treatments. Improved prognostication allows a clinician to improve treatment planning with respect to the intervention type, duration, and intensity (Kadden & Skerker, 1999).

Different predictors of alcohol treatment outcomes can be related to: a) patient-related factors, such as socio-demographic and internal factors (e.g. motivation for treatment, motivation for change, and alcohol-related self-efficacy); b) clinical factors, such as the comorbidity of other symptoms or disorders and the severity of the alcohol problem; and c) the treatment setting, such as the modality of the treatment (outpatient vs. inpatient treatment), length and intensity of the treatment, therapist qualities, and therapeutic alliance. Factors related to treatment outcomes can also be divided into predictors, mediators, and moderators. A *predictor* variable of a treatment's effectiveness is here referred to as a variable that is known to predict the value of the treatment outcome. A *mediator* of a treatment's effectiveness is a variable that intervenes temporally between the initiation of treatment and the alcohol-related outcome variable (Longabaugh, 2007). A *moderator* is a variable that identifies subgroups of patients within the population who have different effect sizes (Kraemer et al., 2002).

1.3.1 Treatment dropout and predictive factors

One of the most pervasive phenomena in treating alcohol problems is the frequency with which patients drop out of treatment. In a comprehensive review by Baekeland and Lundwall (1975), it was reported that 52–75% of alcoholism outpatients drop out before the fourth session. In more recent studies, reported dropout rates from alcohol treatment services have been within the range of 23–60% (Mammo & Weinbaum, 1993; McCaul et al., 2001; Wickizer et al., 1994). In a large, retrospective analysis of the discharge statuses of 48 299 patients entering alcohol treatment services in Scotland, it was found that more than half of entries to alcohol misuse services resulted in an unplanned discharge (Newham et al., 2010).

Dropping out of treatment is often seen as a sign of noncompliance, resistance, or a failure of treatment, and there is indeed evidence that time spent in treatment correlates with a positive post-treatment outcome (Gottheil et al., 1992; Moos & Moos, 2003a; Welte et al., 1981). However, it is important to note that dropping out may not always occur for negative reasons. Patients may report significant levels of satisfaction and problem improvement despite attending fewer appointments than originally intended (Pulford et al., 2006; Scamardo et al., 2004). Pulford and co-workers (2006) have argued that instead of interpreting dropout as a failure of treatment, it can be understood as a failure of treatment fit, meaning that a patient leaves in response to the treatment not being optimally suited to his or her presenting problem.

Sociodemographic predictors of dropout from treatments for substance misuse have included a younger age (Brorson et al., 2013; Elbreder et al., 2011; Mammo & Weinbaum, 1993; McKellar et al., 2006; Wickizer et al., 1994) and lower educational level (King & Canada, 2004; Mammo & Weinbaum, 1993; Wickizer et al., 1994). The results have been mixed in terms of gender, with some studies showing poorer treatment participation among women (King & Canada, 2004; Mammo & Weinbaum, 1993; McCaul et al., 2001; Wickizer et al., 1994) and others finding no differences between genders (Elbreder et al., 2011; Veach et al., 2000; Wickizer et al., 1994). Other patient-related predictors of dropout include cognitive deficits (Brorson et al., 2013), personality disorders (Brorson et al., 2013), and lower levels of psychological distress tolerance (Daughters et al., 2005). Better treatment retention has been reported among those with higher depressive syndromes at treatment entry (MacMurray et al., 1987).

Studies that have investigated substance-related factors related to dropout have demonstrated that dropping out is more common for those with a lower severity of alcohol dependence (Elbreder et al., 2011; McKellar et al., 2006), a shorter history of substance misuse (Wickizer et al., 1994), and a high craving for alcohol at the time of treatment entry (Soyka et al., 2003). Treatment-related factors predictive of treatment retention have included the use of disulfiram during treatment (Elbreder et al., 2010) and receiving a rapid initial response and individual attention in treatment (Stark, 1992), which have both been reported to relate to better treatment retention. A weak therapeutic alliance has been reported to increase the risk of dropout (Brorson et al., 2013), whereas a strong therapeutic alliance seems to be related to better treatment retention (Meier et al., 2005)

1.3.2 Patient characteristics and clinical factors as predictors of outcomes

A systematic review by Adamson and co-workers (2009) examined 63 published papers describing the findings from 51 unique treatment outcome studies collating 31 baseline predictors of alcohol use disorder treatment outcomes. The most consistent predictors overall were dependence severity, psychopathology ratings, alcohol-related self-efficacy, motivation, and the treatment goal. The two predictor variables that accounted for the greatest variance when controlling for broader methodological variables were baseline alcohol consumption and dependence severity. Predictably, negative outcomes were related to more severe alcohol dependence, higher psychopathology ratings, and higher alcohol consumption. In contrast, high alcohol-related self-efficacy, high motivation, and having a treatment goal of abstinence were related to better outcomes.

In another review by McKay and Weiss (2001), which examined 12 studies, the most consistent baseline predictors of the outcome were the pretreatment level of substance use and psychiatric severity. Lower problem severity predicted better outcomes, but the nature of the relationship and psychiatric severity varied. Motivation and coping skills were also related to the outcome. Gibbs and Flanagan (1977) identified lower psychopathology, higher Wechsler arithmetic scores, a steady work history, being married/cohabiting, employment, a higher status occupation, a history of fewer arrests, a history of Alcoholics Anonymous contact, and a higher social class as "somewhat stable" predictors of a better outcome.

In contrast to stable variables, some predictor variables may be considered more malleable and may therefore be identified as important targets for manipulation during the treatment process (Adamson et al., 2009). For example, patients' alcohol-related self-efficacy, employment status, or amount of social support may be factors that change during the course of treatment and lead to positive treatment outcomes. The amount of drinking during treatment is obviously likely to be related to the post-treatment outcome. Indeed, it has been demonstrated that higher alcohol consumption during treatment is related to higher alcohol consumption in the post-treatment period (Breslin et al., 1997).

1.3.3 Treatment characteristics as predictors of treatment outcomes

Treatment characteristics that predict or mediate treatment outcomes may be related to active ingredients of the treatment, the nonspecific factors in the treatment, or modality of the treatment. While the support for the influence of active ingredients of different treatments on treatment outcomes has been weak (Longabaugh et al., 2005; Magill & Longabaugh, 2013; Meier et al., 2005; Project MATCH Research Group, 1998a), there is consistent support for the effect of the therapeutic alliance on treatment outcomes (Najavits & Weiss, 1994; Project MATCH Research Group, 1998b). *Therapeutic alliance* can be defined as the collaborative relationship between the clinician and the patient, including an affective bond between the patient, and the therapist and the patient's and therapist's ability to agree on treatment goals and tasks (Martin et al., 2000).

According to a review by Najavits and Weiss (1994), the primary therapist characteristic associated with higher effectiveness of treatment outcomes is the possession of strong interpersonal skills. These skills include empathy, supportiveness, warmth, and understanding (Lafferty et al., 1989; Najavits & Weiss, 1994). However, according to a review by Meier and co-workers (2005), the therapeutic alliance appears to influence early improvements during treatment, but is an inconsistent predictor of post-treatment outcomes in different substance use treatments. Meier and co-workers (2005) concluded that too little is known about what determines the quality of the relationship between substance abusers and clinicians. Patients' perceptions of different characteristics of the treatment and their active participation in the therapeutic process

are also likely to influence the treatment outcomes. Indeed, it has been demonstrated that patients' involvement in therapy and perception of treatment efficacy are related to positive outcomes (Long et al., 2000).

One potential contributor to treatment outcomes is related to the modality of the treatment. Although there is no consistent support for the use of inpatient care over outpatient care (Mattick & Jarvis, 1994), it has been suggested that certain types of patients may benefit more from placement in one treatment setting over another (Finney et al., 1996; Rychtarik et al., 2000). Rychatarik and co-workers (2000) suggested that particularly patients who are low in cognitive functioning and those with more severe alcohol problems may benefit more from inpatient care. There is also some evidence that the length of stay may be related to treatment outcomes (Gottheil et al., 1992; Moos & Moos, 2003b).

1.3.4 External factors as predictors of treatment outcomes

External factors, such as life events outside the treatment, may have a strong influence on treatment outcomes (Longabaugh, 2007). Another factor that may have an influence is social support. Beattie and Longabaugh (1999) found that alcohol-specific and general social support were important in maintaining abstinence in the short term (3 months) after the treatment, but alcohol-specific support was most important 15 months post-treatment. Similarly, Billings and Moos (1983) who compared recovering and relapsed alcoholics after treatment, found that recovering alcoholics made effective use of coping strategies and social support, and successfully avoided environmental stressors compared to those who relapsed. There is also evidence that participation in Alcoholics Anonymous during or after outpatient treatment may be related to better treatment outcomes (Morgenstern et al., 1997; Ouimette et al., 1998).

1.3.5 Medication adherence

Despite the relatively strong evidence supporting the use of pharmacotherapy as part of alcohol treatment, medication adherence is particularly low in the alcohol-dependent population (Pettinati, 2006a). This is problematic, because the effect of naltrexone, for instance, has been demonstrated to be associated with medication adherence (Baros et al., 2007; Chick et al., 2000). Indeed, the modest effect sizes for naltrexone reported in

systematic reviews and meta-analyses may at least partly be attributable to variability in naltrexone adherence rates (Swift et al., 2011).

In trials with daily use of naltrexone, the reported medication adherence rates have ranged from 40% to 88% (Carmen et al., 2004; Namkoong et al., 1999). The non-adherence rate for disulfiram is known to be as low as 80% (Fuller et al., 1986). Similarly, a meta-analysis by Carmen and co-workers (2004) reported an average adherence rate of only 53% to acamprosate in treatments lasting from 3 to 24 months. In studies exploring the targeted use of naltrexone, the reported adherence rates have generally been more consistent, around 86–87% (Hernandez-Avila et al., 2006; Kranzler et al., 2003; Kranzler et al., 2009). However, in real-life treatment settings, medication adherence is likely to be much lower than in clinical trials, in which medication use is usually monitored intensively and where the participants usually receive their study medication at no cost. Indeed, studies based on retrospective analyses of prescription claims databases by Kranzler and co-workers (2008) and Hermos and co-workers (2004) have reported that only 14–22% of patients who had an initial prescription for naltrexone persisted in picking up the medication after 6 months.

Certain factors that may affect adherence with naltrexone have been reported in the literature. Although naltrexone in generally well tolerated, it may cause unpleasant side effects for some patients, such as nausea and vomiting (Streeton & Whelan, 2001). Unpleasant side effects are suggested as one reason for non-compliance (Rohsenow et al., 2000; Volpicelli et al., 1997). Other predictors of poor adherence have been suggested to include a lack of belief in the utility of naltrexone in managing alcohol use (Rohsenow 2000), younger age (Baros et al., 2007; Gueorguieva et al., 2013), greater drinking severity (Gueorguieva et al., 2013), dissatisfaction with medicine (Gueorguieva et al., 2013), and a lack of benefit (Gueorguieva et al., 2013).

Alcohol-dependent patients who use any alcoholism medications have been reported to have fewer detoxification admissions, alcoholism-related inpatient care and alcoholism-related emergency department visits in the 6 months following medication initiation in comparison to patients who have not received alcoholism medication (Mark et al., 2010). Therefore, in addition to promoting the use of pharmacotherapy as an adjunct to psychosocial treatment in substance abuse clinics and general practices, it is important to understand the factors that may lead to low adherence. Identifying and

tackling the factors associated with poor adherence may lead to improved treatment planning and enhanced effectiveness.

1.4 The effect of alcohol treatments on depression, quality of life and smoking

Depressive symptoms and depressive disorders are common among patients with alcohol-related disorders (Driessen et al., 2001; Hasin et al., 2007; O'Donnell et al., 2006), and the co-occurrence of depression may be an important determinant of treatment seeking (Lynskey, 1998). Comorbid depressive symptoms are also associated with an increased risk of relapse after treatment (Burns et al., 2005; Curran et al., 2000; Driessen et al., 2001). Therefore, it is important to treat depression along with alcohol use. While antidepressants used with psychosocial treatments alleviate depressive symptoms, they appear to have relatively little impact on reducing alcohol drinking (Pettinati, 2004). However, there is evidence that combined pharmacotherapy that addresses both depression and alcohol use may lead to improved outcomes in both of these (Pettinati et al., 2010).

Alcohol dependence also appears to be associated with a markedly decreased quality of life (QL) (Foster et al., 1999). However, achieving and maintaining a marked reduction in drinking, even without complete abstinence, has been found to be associated with significant increases in QL (Donovan et al., 2005; Foster et al., 1999; Frischknecht et al., 2013). As LoCastro and co-workers (2009) suggest, when evaluating alcohol treatment effectiveness, it is important to include secondary nondrinking outcomes, such as QL, in clinical alcohol-treatment trials.

In addition to an increased risk of depression, as many as 80% of alcohol-dependent individuals smoke cigarettes (Miller & Gold, 1998). Alcohol-dependent smokers also experience more depression, sleep disturbances and symptoms of craving for nicotine (Hertling et al., 2005). Accordingly, it may be important to take into account the issue of smoking when planning treatment and assessing treatment outcomes.

2 AIMS OF THE STUDY

Despite the large number of randomized controlled studies on cognitive behavioral therapy and naltrexone, studies that have investigated CBT and targeted naltrexone in a real-life treatment setting appear to be lacking. Little is also known about which patient-related factors are associated with treatment outcomes.

The aim of this study was to investigate how the combination of CBT and targeted (used as needed) use of naltrexone works in a community outpatient treatment setting consisting of a heterogeneous sample of patients. The study also investigated whether the combination of medication (acamprosate, disulfiram or naltrexone) can improve patients' general well-being, quality of life and smoking habits, in addition to reducing alcohol use. The specific aims of the study were as follows:

1. To determine the pretreatment and treatment-related factors that are related to treatment dropout;

2. To determine the pretreatment and treatment-related factors that are related to treatment outcomes evaluated as the change in alcohol consumption and symptoms of alcohol craving in patients during treatment;

3. To determine the pretreatment predictors of patient adherence to the targeted use of naltrexone in situations of drinking alcohol;

4. To investigate using a randomized study protocol how the combination of medication (acamprosate, disulfiram or naltrexone) and CBT can affect patients' symptoms of depression, quality of life, sleeping, and smoking habits, in addition to reducing alcohol consumption.

3 METHODS

3.1 Selection of the participants

3.1.1 Participants in studies I–III

The participants in studies I-III were 476 problem drinkers aged 20–70 years who contacted a private Finnish outpatient clinic providing CBT combined with naltrexone for the treatment of problem drinking between November 1998 and November 2001. The following exclusion criteria were used: the use of opiates or opiate-based painkillers, severe untreated somatic problems, serious dysfunction of the liver (ASAT and ALAT >200), risk of suicide, breastfeeding women, or women who were pregnant or planning pregnancy. Those (n = 98) who decided not to enroll in the treatment program after the initial interview were excluded from the study. Due to missing data in all variables other than age and gender, six patients were excluded from the samples. No other exclusion criteria were applied.

The final study sample in study I consisted of 372 participants. The baseline characteristics of the sample are described in Table 5. The study samples were smaller in studies II–III because, due to practical reasons, no drinking diaries were collected at the clinic after June 2002. In study II, after applying the above selection criteria, the final study sample consisted of 315 participants. In study III, the final study sample consisted of 299 participants, because 16 participants were excluded for not committing to the reporting of their naltrexone use during the treatment. Due to minimal exclusion criteria, the patient samples included those with comorbid psychiatric and/or medical disorders (54.4% in study I, 51.8% in study II, and 52.4% in study III). All participants signed a written informed consent form. Ethical permission for the study was granted by the Ethics Committee of the Hospital District of Helsinki and the Province of Uusimaa.

Table 5. Baseline patient characteristics in study I (n = 372)

	n	$\%$	$M\ (SD)$
Age	366		46.0 (8.6)
Gender	372		
Female		34.9%	
Marital status	356		
Not cohabiting		29%	
Education	295		
High/higher intermediate		40.0%	
Lower intermediate		24.8%	
Basic or none		35.2%	
Employment	363		
Employed		70.0%	
Unemployed		18.7%	
Retired or other		11.3%	
Alcohol consumption pattern	342		
Regular drinking		85.1%	
Episodic heavy drinking		14.9%	
Alcohol consumption pattern (regular drinkers)	285		
Low-risk drinking		15.1%	
High-risk drinking		84.9%	
Problematic drinking in years	352		10.5 (7.7)
DSM IV Alcohol dependence symptoms	296		6.6 (2.0)
DSM IV Alcohol dependence diagnosis	296		
No		4.0%	
OCDS	328		17.5 (5.8)
BDI	300		8.0 (5.8)
A first-degree relative with alcoholism	372		
No		44.9%	
Psychiatric/medical disorders	307		
No		45.6%	
Previous treatment history	313		
No		53.4%	

M = mean; SD = standard deviation
Low risk: ≤24 standard drinks for men and ≤18 standard drinks for women
High risk: ≥24 standard drinks for men and ≥18 standard drinks for women
DSM IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Frances, 1994)
OCDS = Obsessive Compulsive Drinking Scale (Anton et al., 1995; Anton et al., 1996)
BDI = short version of the Beck Depression Inventory (Beck & Beck, 1972)
Note: due to missing data, n varies between 285 and 372.

3.1.2 Participants in study IV

The participants in study IV were 243 men and women aged 25–65 years who were voluntarily seeking outpatient treatment for alcohol problems at three outpatient treatment centers for alcohol problems (A clinics) and three occupational health-care units in cities in southern Finland between 2000 and 2005. For inclusion, the patients had to meet the ICD-10 criteria for alcohol dependence (WHO, 2010). Detoxification was not required and at least one month had to have elapsed since the last date of the previous treatment. The exclusion criteria in the study were: clinically significant symptoms of alcohol withdrawal; significant recently diagnosed psychiatric disease (psychosis or suicidal tendency that appeared during the initial interview); a current psychiatric disease demanding special treatment or medication, including drug dependence other than alcohol or nicotine dependence determined by the DSM-IV (Frances, 1994); current use of any opioids with the 4 weeks before screening; a significant brain, thyroid or kidney disease; an uncompensated heart disease; a clinically significant liver disease (cirrhosis, alcohol hepatitis, or alanine transaminase (ALAT) <200); or pregnancy, nursing, or women who refused to use a reliable birth control method.

The study protocol, written information for subjects, and consent form were approved by the Ethical Committee of Helsinki and Uusimaa Hospital District, the Turku Health Care Organization Ethical Committee, and the Finnish National Medical agency. The study was conducted according to the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, guidelines for Good Clinical Practice, and the 1964 Helsinki Declaration. All subjects had to be able to read and understand the patient information sheet and sign the informed consent. All participants were free to finish the study medication whenever they wanted, and were not paid or reimbursed for their participation.

3.2 Measures

3.2.1 Pretreatment alcohol use

In the protocol of studies I–III, the data on the participants' characteristics and backgrounds were obtained from the initial structured screening interview with a physician at the clinic. A structured clinical interview, MINI (Sheehan et al., 1997), was used at the treatment entry interview to assess the total number of DSM-IV (Frances, 1994) alcohol dependence symptoms for each patient and for categorizing whether they had alcohol dependence or not. The participants were also asked to evaluate the age at which their alcohol drinking became problematic. Based on this information, the length of their problematic drinking was calculated in years. The participants were interviewed in order to obtain their medical and psychiatric history, including the use of any medications and concerning their family history of alcoholism.

A daily drinking and naltrexone use diary was introduced to the participants of studies I–III at treatment entry, and they were taught how to calculate their alcohol consumption in standard units (12 g of pure alcohol) for the preceding month. An average amount of weekly consumption of alcohol (measured as the number of standard 12 g drinks) was calculated for regular drinkers. Accordingly, the patients were categorized into regular drinkers (consuming alcohol weekly) and episodic heavy drinkers (those whose primary problem was occasional, not weekly heavy drinking). Regular drinkers were further categorized into those with higher-risk alcohol consumption level (weekly alcohol consumption of ≥ 24 standard drinks for men and $\geq$ 18 standard drinks for women) and lower-risk alcohol consumption level (weekly consumption of <24 standard drinks for men and <18 standard drinks for women). This categorization was the same as used in studies by Kranzler and coworkers (Kranzler et al., 2003; Kranzler et al., 2009) examining the efficacy of targeted naltrexone and CBT for treating problem drinking. Episodic heavy drinkers (n = 51) were not categorized according to their weekly consumption group, since they were typically unable to describe the amounts of alcohol consumed during their heavy drinking episodes, which often lasted for a period of several days. In study I, patients were also categorized into those who started the treatment with abstinence (for the first 2 weeks) and those who started the treatment with drinking.

In study IV, the severity of the alcohol problem was measured with the Alcohol Use Disorder Identification Test, AUDIT, and the Severity of Alcohol Dependence Data, SADD (Babor et al., 2001; Davidson & Raistrick, 1986; Saunders et al., 1993) during the study period (52 weeks) and follow-up periods (up to 1.5 years). Smoking habits were examined with simple 'yes or no' questions at weeks 0, 12, 26, and 52.

3.2.2 Alcohol craving

In studies I–III, a Finnish translation of the Obsessive Compulsive Drinking Scale, OCDS (Anton et al., 1995; Anton et al., 1996), was used to measure the craving for alcohol at treatment entry. The OCDS has been suggested as a useful instrument in evaluating therapeutic approaches such as CBT (Anton et al., 1996). In addition to calculating the total score for the OCDS, the three factors ascertained by Roberts et al. (1999) were calculated for the purpose of studies I and III. The subscales are interpreted as "resistance/control impairment," "obsession," and "interference," and they have been found to distinguish between subjects who remained abstinent, exhibited "slip" drinking, or relapsed to heavy drinking during the 12 weeks of active treatment (Roberts et al., 1999). In addition to the OCDS, a 10 cm Visual Analogue Scale (VAS) was used to measure the intensity of the craving during each therapy session. In the VAS, patients were asked to imagine themselves in a situation where they typically drank alcohol and evaluate how strong their desire to consume alcohol was at that moment, on a scale ranging from "no desire" to "if alcohol were available, I could not resist the urge to drink." Although scales such as the Visual Analogue Scale have been criticized for relying exclusively on the patient's interpretation of craving, significant correlations have been found between the VAS and the OCDS (Anton et al., 1996).

3.2.3 Alcohol use, smoking, and medication use during treatment

The participants of studies I–III were instructed to keep a daily record of their intake of alcohol (reported in standard units) and report their as-needed use of naltrexone in drinking diaries during the course of the treatment. Compliance measurements based on daily diaries have been shown to provide information similar to data obtained using electronic medication-use monitoring (Feinn et al., 2003). During each therapy session,

drinking diaries were thoroughly monitored and their information was copied and filed at the clinic. If the patient forgot his/her drinking diary, it was filled in retrospectively.

In study IV, changes in alcohol-related symptoms were monitored with AUDIT (Babor et al., 2001; Saunders et al., 1993) and SADD (Davidson & Raistrick, 1986) during the study period (52 weeks) and follow-up periods (up to 1.5 years). Alcohol consumption and the use of study medication during the 52 study weeks were also assessed using a retrospective drinking diary (Poikolainen & Kärkkäinen, 1983). Smoking habits were examined at weeks 0, 12, 26, and 52 by asking the patients whether they smoked or not.

3.2.4 Quality of life and depressive symptoms

For studies II–III, patients' depressive symptoms were evaluated at baseline with a short version of the Beck Depression Inventory (Beck & Beck, 1972). In study IV, depression was evaluated with the regular version of the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Depression Scale (DEPS) (Salokangas et al., 1995) during treatment weeks 0, 6, 26, 52, and 119.

The quality of life of participants was evaluated with the Visual Analogue Scale (VAS) (Scott & Huskisson, 1976), Koskenvuo Quality of Life Scale (Koskenvuo & Kaprio, 1979), and the modified (Muhonen et al., 2008) European Quality of Life (EQ-5D) instrument (The EuroQol Group, 1990). The modified version includes a dimension for sleep and excludes mobility. The sleep dimension was included because sleep is often disturbed in cases of alcohol dependence and significantly affects quality of life. The EQ-5D test covers patients' anxiety, sleeping, pain, mood, and self-care issues. This test was completed during weeks 0, 12, 52, and 119.

3.3 Study procedures and treatments

3.3.1 Study procedure and treatment program in studies I–III

The treatment procedure in studies I–III followed a standardized procedure and comprised the targeted use of naltrexone and eight semi-structured CBT sessions that were conducted according to a treatment manual (Sinclair & Jakobson, 1996), for which the clinicians had received similar training at the clinic. Four sessions were conducted

with a physician (the first, second, fifth, and eighth) and four with a psychologist (the third, fourth, sixth, and seventh). The time spent with the physician and the psychologist was standardized and was 50–60 minutes per session. The treatment program included homework for recognizing triggers for drinking, for developing coping skills, and for assessing motivational factors associated with alcohol use. The outline of the treatment program in studies I–III is presented in Table 6. The projected interval between each of the first 4 sessions was 1 week and between the last sessions 2–4 weeks. Thus, the projected length of treatment was 18–20 weeks. However, for practical reasons, further follow-up sessions were possible beyond the eighth session when agreed upon between the clinic and the patient. Most patients set a goal of becoming moderate drinkers rather than totally abstinent.

Table 6. Outline of the treatment program in studies I–III

Treatment session	Therapy provider	Content of the session
One	Physician	Initial interview and assessment Information about the treatment Treatment contract Introducing the drinking diary
Two	Physician	Psychoeducation about naltrexone Laboratory tests
Three	Psychologist	Discussion about drinking habits and triggers Constructing a profile of high-risk and low-risk drinking situations
Four	Psychologist	Teaching the patient to recognize high-risk situations for drinking and avoiding these Discussion about coping skills and self-regulation skills Discussion about pleasurable activities to replace alcohol use
Five	Physician	Monitoring the use of naltrexone and discussion about coping skills
Six	Psychologist	Monitoring the use of coping skills
Seven	Psychologist	Monitoring the use of coping skills Discussion about motivational factors related to drinking and setting long-term goals (Having a spouse at the therapy session, discussion about social support)
Eight	Physician	Evaluating the change in alcohol use and health Laboratory tests if necessary Discussion about the possible need for continued treatment

(Sinclair & Jakobson, 1996)

3.3.2 Study procedure and treatment program in study IV

In study IV, participants were randomized 1:1:1 (81 patients/medical group) to receive disulfiram, naltrexone, or acamprosate. Doses were 50 mg of naltrexone once a day, 666 mg of acamprosate three times a day (1998 mg/day, or if the patient's weight was <60 kg, 1333 mg/day), or 100–200 mg of disulfiram once a day, or twice a week. The study comprised a 12-week period with continuous medication, followed by targeted medication (as needed) for up to 52 weeks, and an additional 67-week follow-up period, amounting to 119 weeks (2.5 years). The patients were instructed to use medication until week 52, after which it could be either stopped or continued until week 119. However, after week 52, the medication was no longer free of charge. The patients visited the same physician during weeks 0, 2, 6, 12, 26, and 52. After the end of the follow-up period, the participants also had the choice to visit a doctor (week 119).

At their first visit in study IV, patients received a booklet entitled *Winning at Last: Defeating the Drinking Problem* (Laaksonen et al., 2008b) that they were instructed to follow during the study. The booklet was based on the principles of CBT and contained motivational components based on self-assessment and goal-setting, as well as relapse prevention, life-style change, and problem-solving components. The treatment program in study IV is outlined in Table 7. The components and related homework assignments were discussed at each of the four initial visits with the doctor (during the first 12 weeks).

Table 7. Outline of the treatment program (sessions 1–4) and follow-up sessions in study IV

Treatment session	Therapy provider	Content of the session
One (week 0)	Physician	Initial interview and assessment Introduction of the treatment program and the booklet Measuring openness to change Random assignments to medication groups (by an independent person) Laboratory tests and other measures
Two (week 2)	Physician	Identification of high-risk situations Safe situations and previous successes Coping with dangerous situations and self-regulation To reduce or give up? Long-term goals Measures
Three (week 6)	Physician	Improving the use of leisure time Social support for change Problem solving without alcohol Laboratory tests and other measures
Four (week 12)	Physician	Reviewing the program Giving up daily use of medication and continuing with targeted medication Preventing relapse Assessment of the current situation Plans for the future Measures
Five (week 26)	Physician	General discussion on the change
Six (week 52)	Physician	General discussion on the change Laboratory tests and other measures
Seven (week 119)	Physician	Voluntary follow-up session Measures

Source: Laaksonen and co-workers (2008b)

3.4 Statistical analyses

3.4.1 Study I

In study I, a multiple imputation method by chained equations (Rubin, 2004) was used to fill in the missing items in all pretreatment variables with missing data in order to improve the efficiency of data utilization. Treatment entry factors (the number of DSM IV alcohol dependence symptoms, the duration of problematic drinking measured in years, the total score of the OCDS, and the OCDS factors) predictive of dropout were investigated with analyses of covariance, considering the number of attended treatment sessions as the dependent variable in all analyses. First, the predominant effects of all

predictors were independently explored in the analyses, and then computed adjusting for sociodemographic variables.

The relationships between dropout and treatment-related factors (change in alcohol consumption and symptoms of craving) were then tested with additional analyses adjusted for gender and age. In the first phase, the number of attended sessions was predicted by whether the patient began the treatment by either abstaining for two weeks or continuing to drink, and in the second phase they were predicted by the average alcohol consumption measured during the last week of the treatment (week 20) while covarying for pre-treatment consumption. The method of last observation carried forward was used to replace missing values of dropouts for week 20. In the third phase, they were predicted by the VAS score of the last therapy session while covarying for the VAS score measured at the beginning of treatment. Finally, in the fourth phase they were determined by the adherence to medication use, and in the fifth model, in order to control for the effectiveness of naltrexone, by the interaction between alcohol consumption in the last week of the treatment program and medication adherence. The statistical analyses in study I were performed using IBM SPSS 18.0 for Windows and the statistical software R (Version 2.11.1).

3.4.2 Study II

In study II, the changes in weekly alcohol consumption and the VAS scores were analyzed using group-based developmental trajectory modeling (Jones & Nagin, 2001; Jones & Nagin, 2007). One advantage of group-based trajectory modeling is that it is not necessary to have complete cases in repeated measurements and that it is possible to approximate complex data distributions. The trajectory model for daily alcohol consumption reported in the drinking diaries was analyzed using a zero-inflated Poisson model, and the trajectory groups for VAS scores were analyzed using the censored normal model. All of the trajectories were also constructed using only data with no missing values, and it was observed that the trajectories were very similar, even when using the incomplete data.

The relationship between alcohol and craving trajectories was analyzed with a χ^2-test. A medication adherence percentage was calculated based on the number of times patients took naltrexone while drinking divided by the number of measured drinking

time points in a diary. Patients were categorized into two groups: those who had good adherence (≥80%) to naltrexone in drinking situations and those who had poor adherence (<80%). The data on baseline factors were examined to detect any systematic patterns for missing values and missing cases.

Predictors of treatment outcomes were investigated with analyses of multinomial logistic regression using alcohol consumption and the VAS trajectories as dependent variables, while independent variables consisted of gender, age, drinking pattern, alcohol consumption risk level, adherence with medication, the total score of the OCDS, the number of DSM-IV alcohol dependence symptoms, the total score of the BDI, the number of years with problematic drinking, the presence of medical/psychiatric comorbidity, the presence of a strong family history of alcoholism, and a history of previous treatments. Second, the analyses were performed adjusting all of the models for age, gender, medication adherence, and the number of attended CBT sessions. Third, in order to examine the potential moderating effect of a family history of alcoholism and baseline craving on the association between naltrexone use and the treatment outcome, interaction analyses were performed by using interaction terms of these variables and medication adherence as independent variables, and the drinking and craving trajectories as dependent variables. The statistical analyses in study II were performed using IBM SPSS 18.0 for Windows and the PROC TRAJ procedure in SAS 9.2.

3.4.3 Study III

In study III, similar to the procedure used in study II, adherence to the use of naltrexone before situations of drinking was calculated as a percentage of the number of times a patient took naltrexone prior to drinking divided by the number of measured drinking time points in the patient diary. Patients were categorized into two groups: those who had good adherence (≥80%) to naltrexone in drinking situations and those who had poor adherence (<80%). A patient's compliance with reporting naltrexone use in the drinking diary during the treatment was calculated as a percentage of number of weeks with complete drinking diary data divided by the number of weeks the patient stayed in the treatment during the first 20 weeks of the treatment program, and the data were examined to detect any systematic patterns in missing values and missing cases.

Logistic regression analyses were used to determine first the unadjusted relationships between socio-demographic (age, gender, marital status, employment, and education), clinical (primary drinking pattern, pre-treatment alcohol consumption level, and comorbid disorders), and alcohol-related or psychiatric variables (DSM IV alcohol dependence symptoms, alcohol craving measured by the OCDS and the VAS, and depression measured by the BDI) at the treatment entry and medication adherence status. The analyses were also performed when adjusting all of the models for socio-demographic variables. Finally, DSM IV alcohol dependence symptoms, the OCDS, and the BDI were examined simultaneously by including them in a multivariate analysis adjusted for socio-demographic variables. All of the above analyses were also performed with linear regression models using log-transformed continuous medication adherence as a dependent variable.

3.4.4 Study IV

The average alcohol intake per week, BDI, DEPS, quality of life -tests, and smoking habits were analyzed using a per protocol analysis that included all the patients who completed the study. The groups' average weekly alcohol consumption rates were analyzed by analysis of variance for repeated measures to examine differences at each time point using PROC MIXED in statistical software SAS version 8.2. To control for individual differences at baseline, the baseline values of all variables were added to the model as covariates.

All *p*-values concerning treatment group comparisons were Bonferroni adjusted. Descriptive statistics were calculated for all variables. Categorical variables were listed in frequency tables by group (PROC FREQ in SAS), and the numerical variables were tabulated by group (PROC UNIVARIATE in SAS) (Medicalla). In addition, logistic regression models were fitted to the data to explore the effects of different medications on quitting smoking during treatment. In the models, smoking was considered as a binary (yes/no) response variable, and using medication (yes/no) as a fixed explanatory variable. The confounding effect of drinking was investigated by introducing alcohol consumption during the last 10 weeks to the models as an explanatory variable.

To control for selective dropout, patient attrition was analyzed by comparing the initial demographic, drinking, BDI, DEPS, and quality of life data of those who had

dropped out of the study with those who could be measured at weeks 12 and 52 using the Mann–Whitney U-test. In addition, differences in depression between medical groups were examined during weeks 26 and 52 using the Kruskal–Wallis test (PROC NPAR1WAY in SAS version 9.2). The missing results from patients who withdrew from the study were replaced by their initial BDI values. Finally, Fisher's test was used to analyze differences in keeping a drinking diary between those who dropped out and those who completed the study.

4 RESULTS

4.1 Study I: Predictors of dropout in an outpatient treatment for problem drinking including CBT and naltrexone

A total of 196 (53%) of the 372 patients dropped out prior to completion of the basic treatment program (8 sessions). Drinking diary data were available for 299 (80%) of the patients in the sample of study I. For the 20% of the patients who had no drinking diary data, a systematic pattern was observed in relation to the number of treatment sessions attended ($p < 0.001$). Those who did not commit to keeping the drinking diary were likely to drop out from the treatment earlier.

As Table 8 demonstrates, younger patients, those with lower resistance/control impairment and obsession over alcohol, and those who had fewer symptoms of alcohol dependence dropped out from the treatment program earlier. Those who had a high or higher intermediate education were more likely to drop out earlier than those who had lower intermediate education. Treatment-related predictors of dropout were starting the program by abstaining from alcohol (F(1,283) = 4.26, $p < 0.05$) and having lower adherence to naltrexone (F(1,304) = 53.09, $p < 0.001$). The number of attended sessions was not predicted by alcohol consumption, the patients' intensity of craving during the treatment, or the interaction between alcohol consumption and naltrexone adherence.

Table 8. Treatment entry predictors of dropout in a treatment program for problem drinking combining CBT and naltrexone

Predictor	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
DSM IV alcohol dependence symptoms	0.21 (0.00-0.41)*					
Problematic drinking in years		0.09 (-0.22-0.39)				
OCDS total score			0.05 (-0.02-0.13)			
OCDS "resistance/control impairment"				0.08 (0.00-0.149)*		
OCDS "obsession"					0.123 (0.03-0.21)*	
OCDS "interference"						0.07 (-0.06-0.2)
Age	0.04 (0.01-0.07)*	0.04 (0.00-0.07)*	0.04 (0.01-0.08)**	0.04 (0.01-0.07)*	0.04 (0.00-0.07)*	0.04 (0.01-0.08)**
Gender	-0.22 (-0.76-0.32)	-0.17 (-0.71-0.38)	-0.14 (-0.68-0.40)	-0.22 (-0.76-0.32)	-0.17 (-0.71-0.38)	-0.14 (-0.68-0.40)
Cohabiting/living alone	0.28 (-0.40-0.95)	0.26 (-0.40-0.92)	0.26 (-0.41-0.93)	0.28 (-0.40-0.95)	0.26 (-0.40-0.92)	0.26 (-0.41-0.93)
Employment						
Unemployed	-0.36 (-1.18-0.46)	-0.18 (-0.98-0.63)	-0.26 (-1.06-0.55)	-0.36 (-1.18-0.46)	-0.18 (-0.98-0.63)	-0.26 (-1.06-0.55)
Retired	-0.65 (-1.73-0.43)	-0.67 (-1.75-0.42)	-0.77 (-1.82-0.29)	-0.65 (-1.73-0.43)	-0.67 (-1.75-0.42)	-0.77 (-1.82-0.29)
Education						
Lower intermediate	0.67 (-0.04-1.38)	0.74 (0.01-1.47)*	0.73 (0.01-1.46)*	0.67 (-0.04-1.38)	0.74 (0.01-1.47)*	0.73 (0.01-1.46)*
Basic or none	-0.02 (-0.83-0.79)	-0.02 (-0.86-0.82)	-0.01 (-0.84-0.81)	-0.02 (-0.83-0.79)	-0.02 (-0.86-0.82)	-0.01 (-0.84-0.81)

a. Values reported are regression coefficients or main effects (95% confidence interval)
b. *p < 0.05, **p < 0.01
c. In categorical variables, "employed" and "high or higher intermediate" were used as reference groups
d. Gender was coded as male = 1, female = 0; cohabiting status was coded as cohabiting = 1, living alone = 0.
e. DSM IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Frances, 1994)
f. OCDS = Obsessive Compulsive Drinking Scale (Anton et al., 1995; Anton et al., 1996)

4.2 Study II: Predictors of outcome in an outpatient treatment for problem drinking including CBT and naltrexone

Using the Schwarz's information criteria (BIC) and the logarithm of Bayes factor ($-2\log(B_{10})$), five growth-curve classes were created for average weekly alcohol consumption and craving (Figures 1–2). Inter-correlations between different potential predictors of treatment outcomes are presented in Table 9.
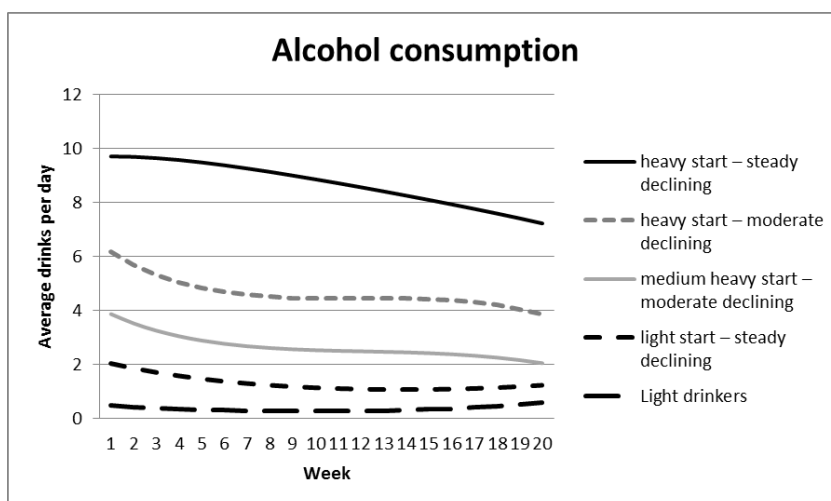

Figure 1. Trajectories of patients' alcohol consumption during CBT & naltrexone treatment
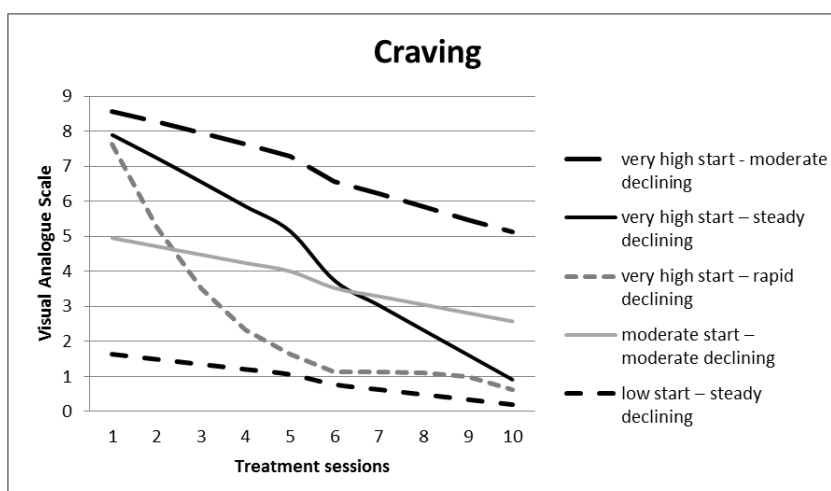
Figure 2. Trajectories of patients' cravings for alcohol during CBT & naltrexone treatment

Table 9. The intercorrelations between predictive variables in study II

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Gender												
2. Age	0.5											
3. Alcohol consumption pattern	-0.16**	0.04										
4. Alcohol consumption risk group	0.05	0.03	0.15*									
5. Problematic drinking in years	0.09*	0.10**	-0.19**	-0.02								
6. Naltrexone adherence	-0.00	0.05	-0.10*	-0.12*	-0.05							
7. OCDS total score	-0.03	-0.12**	0.02	0.16**	0.10*	-0.15**						
8. DSM IV alcohol dependence symptoms	0.09	-0.09*	-0.16**	0.14*	0.19**	-0.09	0.34**					
9. BDI total score	-0.20**	-0.07	0.05	0.00	0.05	-0.11*	0.44**	0.27**				
10. Psychiatric/medical disorders	-0.10	0.12*	-0.09	0.00	0.02	-0.05	0.03	-0.01	0.10			
11. Family history of alcoholism	-0.08	-0.11*	-0.04	-0.01	0.04	-0.01	0.08	0.10	0.06	-0.04		
12. Previous treatment history	0.02	0.05	-0.24**	-0.03	0.26**	-0.07	0.19**	0.22**	0.20**	0.21**	-0.06	
13. The number of CBT sessions	-0.01	0.10*	0.13*	-0.06	0.01	0.31**	0.04	0.07	0.02	-0.03	0.08	-0.12*

Gender was coded male= 1, female = 0.

Family history of alcoholism, psychiatric/medical disorders, and previous treatment history were coded as yes = 1, no = 0.

Naltrexone adherence was coded as good adherence (uses naltrexone in $\geq$80% of situations of drinking) = 1, poor adherence = 0.

OCDS = Obsessive Compulsive Drinking Scale (Anton et al., 1995; Anton et al., 1996)

DSM IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Frances, 1994)

BDI = short version of the Beck Depression Inventory (Beck & Beck, 1972)

$**p < 0.01$, $***p < 0.001$

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A statistically significant, negative linear trend was observed for the alcohol consumption trajectories "light start – steady declining" (Beta = -0.0287, $p < 0.001$) and "heavy start – steady declining" (Beta = -0.0177, $p < 0.001$). A statistically significant negative linear trend in cravings for alcohol was observed for all patient groups: "low start – steady declining" (Beta = -0.0287, $p < 0.001$), "moderate start – moderate declining" (Beta = -0.471, $p < 0.001$), "very high start – rapid declining" (Beta = -0.0452, $p < 0.05$), "very high start – steady declining" (Beta = -1.41, $p < 0.001$), and "very high start – moderate declining" (Beta = -0.730, $p < 0.001$).

As presented in Table 10, poorer adherence with naltrexone predicted belonging to trajectories with higher alcohol consumption compared to "light drinkers", which was used as a reference group in all analyses. The average (mean) medication adherence was 92% in the trajectory "light drinkers", 80% in the trajectory "light start – steady decline", 74% in the trajectory "medium heavy start – moderate decline", 71% in the trajectory heavy start – moderate decline" and 76% in the trajectory "heavy start – steady decline". Regular drinking patterns, higher-risk pretreatment alcohol consumption and having no history of previous treatments predicted belonging to trajectories "heavy start – moderate decline" and "medium heavy start – moderate decline", in which no negative linear trend was observed in alcohol consumption compared to the trajectory "light drinkers". High cravings measured by the OCDS predicted belonging to trajectories of "medium heavy" or "heavy start" alcohol use compared to "light drinkers". Lower depression predicted belonging to the trajectory "light start – steady decline" compared to the trajectory "light drinkers". In the fully adjusted models, all of the other associations remained significant, except the association between higher-risk pretreatment alcohol consumption and belonging to the trajectory "medium heavy start – moderate decline", which was attenuated to non-significant ($p = 0.10$), and the association between a higher OCDS score and belonging to the trajectory "medium heavy start – moderate decline", which was also attenuated to non-significant ($p = 0.08$).

The predictors of belonging to different craving trajectories are presented in Table 11. Those with lower-risk pretreatment alcohol consumption in comparison to those with higher-risk pretreatment alcohol consumption were more likely to belong to the VAS trajectory "very high start – rapid declining" compared to the trajectory "low start

– steady declining", which was used as the reference group in all analyses. None of those with lower-risk pretreatment alcohol consumption level belonged to the trajectory "very high start – moderate declining", which presented the highest symptoms of cravings. Those who had more severe alcohol dependence were more likely to belong to the VAS trajectories "very high start – moderate declining" and "very high start – steady declining" compared to the trajectory "low start – steady declining". In the fully adjusted models, all of the other associations remained statistically significant except the association between the previous treatment history and belonging to the trajectory "moderate start – moderate declining", which was statistically significant ($p = 0.03$) after the adjustments. Those without a previous treatment history were more likely to belong to the trajectory "moderate start – moderate declining" compared to the trajectory "low start – steady declining". In the final models testing the potential moderating effect of a family history of alcoholism and baseline craving on the association between naltrexone use and the treatment outcome, no statistically significant associations were found between the study variables.

Table 10. Predictors of belonging to different alcohol consumption trajectories during CBT & naltrexone treatment

Predictor	Adjusted OR (95% CI)			
	Group 2	Group 3	Group 4	Group 5
Gender	1.66 (0.79–3.5)	1.00 (0.48–2.08)	0.56 (0.24–1.27)	0.47 (0.13–1.64)
Age	1.01 (0.97–1.05)	1.00 (0.96–1.05)	0.96 (0.92–1.01)	1.00 (0.94–1.06)
Alcohol consumption pattern	0.64 (0.26–1.54)	0.29 (0.11–0.75)*	0.26 (0.11–0.75)*	1.00 (0.09–0.75)
Alcohol consumption risk level	0.83 (0.30–2.32)	0.41 (0.15–1.16)*	0.04 (0.01–0.34)**	0.20 (0.22–1.79)
Problematic drinking in years	1.01 (0.96–1.06)	0.97 (0.92–1.02)	1.00 (0.95–1.05)	1.05 (0.99–1.12)
Naltrexone adherence	4.08 (1.44–11.52)**	6.31 (2.28–17.42)***	10.67 (3.76–30.28)***	9.78 (2.72–35.19)***
OCDS total score	1.01 (0.94–1.08)	1.07 (1.03–1.2)**	1.11 (1.03–1.2)**	1.20 (1.08–1.33)***
DSM IV alcohol dependence symptoms	0.99 (0.82–1.21)	1.09 (0.90–1.32)	1.11 (0.91–1.37)	1.41 (0.99–2.01)
BDI total score	0.93 (0.97–0.99)*	0.98 (0.92–1.04)	0.94 (0.88–1.01)	1.00 (0.91–1.10)
Psychiatric/medical disorders	0.81 (0.37–1.80)	1.02 (0.48–2.20)	0.82 (0.36–1.87)	0.57 (0.17–1.88)
Family history of alcoholism	1.15 (0.56–2.38)	0.98 (0.48–1.98)	0.82 (0.38–1.74)	1.59 (0.55–4.57)
Previous treatment history	1.90 (0.84–4.30)	2.42 (1.10–5.35)*	2.78 (1.20–6.43)*	1.07 (0.34–3.44)

The reference group was "light drinkers"

OR = odds ratio; CI = confidence interval; Gender was coded as male = 1, female = 0.

Alcohol consumption pattern was coded as regular drinker = 1, episodic drinker = 0; Alcohol consumption risk level was coded as high risk = 1, low risk = 0.

Family history of alcoholism, psychiatric/medical disorders and previous treatment history were coded as yes = 1, no = 0.

Naltrexone adherence was coded as good adherence (uses naltrexone in ≥80% of situations of drinking) = 1, poor adherence = 0 (<80%).

OCDS = Obsessive Compulsive Drinking Scale (Anton et al., 1995; Anton et al., 1996)

DSM IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Frances, 1994)

BDI = short version of the Beck Depression Inventory (Beck & Beck, 1972)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; due to missing data, n varies in models between 254–315.

Table 11. Predictors of belonging to different craving trajectories during CBT & naltrexone treatment

Predictor	Adjusted OR (95% CI)			
	Group 2	Group 3	Group 4	Group 5
Gender	2.24 (0.93–5.43)	0.84 (0.44–1.59)	0.72 (0.39–1.35)	1.35 (0.43–4.26)
Age	1.00 (0.93–1.00)	0.96 (0.93–1.00)	1.00 (0.96–1.03)	0.98 (0.92–1.05)
Alcohol consumption pattern	2.02 (0.53–7.62)	2.21 (0.85–5.77)	1.84 (0.71–4.78)	2.61 (0.59–11.64)
Alcohol consumption risk level	4.06 (1.25–13.16)*	0.77 (0.27–2.16)	1.07 (0.43–2.66)	<0***
Problematic drinking in years	1.00 (0.93–1.05)	0.99 (0.95–1.03)	1.01 (0.97–1.05)	1.01 (0.94–1.09)
Naltrexone adherence	0.99 (0.40–2.45)	0.92 (0.49–1.72)	1.19 (0.65–2.16)	2.53 (0.76–8.43)
OCDS total score	1.02 (0.94–1.10)	1.02 (0.96–1.08)	0.95 (0.90–1.01)	1.08 (0.98–1.20)
DSM IV alcohol dependence symptoms	1.15 (0.91–1.45)	1.11 (0.94–1.32)	1.27 (1.07–1.51)**	1.53 (1.02–2.29)*
BDI total score	1.03 (0.95–1.12)	1.00 (0.95–1.06)	0.97 (0.92–1.03)	1.08 (0.98–1.19)
Family history of alcoholism	1.41 (0.59–3.40)	0.71 (0.39–1.31)	0.84 (0.47–1.51)	1.13 (0.36–3.52)
Psychiatric/medical disorders	1.39 (0.52–3.68)	1.36 (0.71–2.62)	1.19 (0.62–2.29)	0.90 (0.26–3.11)
Previous treatment history	1.45 (0.54–3.87)	1.89 (0.98–3.68)	1.44 (0.76–2.74)	0.42 (6.23)

The reference group was "low start – steady declining"

OR = odds ratio; CI = confidence interval; Gender was coded as male = 1, female = 0.

Alcohol consumption pattern was coded as regular drinker = 1, episodic drinker = 0; Alcohol consumption risk level was coded as high risk = 1, low risk = 0.

Family history of alcoholism, psychiatric/medical disorders and previous treatment history were coded as yes = 1, no = 0.

Naltrexone adherence was coded good adherence (uses naltrexone in ≥80% of situations of drinking) = 1, poor adherence = 0.

OCDS = Obsessive Compulsive Drinking Scale (Anton et al., 1995; Anton et al., 1996)

DSM IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Frances, 1994)

BDI = short version of the Beck Depression Inventory (Beck & Beck, 1972)

*p < 0.05, **p < 0.01, ***p < 0.001; due to missing data, n varies in models between 254–311.

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4.3 Study III: Predictors of medication adherence in an outpatient treatment for problem drinking including CBT and naltrexone

The average medication adherence in situations of alcohol use during the first four months of the treatment was 78% (SD = 21). Figure 3 illustrates the distribution of medication adherence among patients: 178 patients (59.5%) used naltrexone in 80% or more of the drinking situations and were categorized as having good adherence; 121 patients (40.5%) used naltrexone in less than 80% of the drinking situations and were categorized as having poor adherence. As expected, those patients who were less committed to keeping a drinking diary were more likely to belong to the group of lower medication adherence ($\chi^2(1) = 31.87, p < 0.001$).

Poor naltrexone adherence was associated with being unemployed (adjusted OR 0.43, 95% CI: 0.22–0.86, $p = 0.02$), having higher symptoms of alcohol craving measured by the total score of the OCDS (adjusted OR 0.94, 95% CI: 0.90–0.98, $p < 0.01$) and VAS (adjusted OR 0.86, 95% CI: 0.92–1.01 $p < 0.001$), the OCDS factor "resistance/control impairment", and with a higher number of alcohol dependence symptoms (adjusted OR 0.87, 95% CI: 0.73–1.02, $p = 0.04$). Adjusting the models for sociodemographic variables did not change the associations between these variables. In the linear regression models, all of the above results remained the same, except for the association between the DSM IV alcohol dependence symptoms ($b = 0.01$, $t_{(242)} = 1.25$, $p = 0.21$).   In the multivariate model assessing the relative contribution of the DSM IV alcohol dependence symptoms, the total score of the OCDS and the BDI on medication adherence, the total score of the OCDS remained statistically significant ($p < 0.05$) in the unadjusted model as well as in the model adjusted for socio-demographic variables, whereas the DSM IV alcohol dependence symptoms did not.
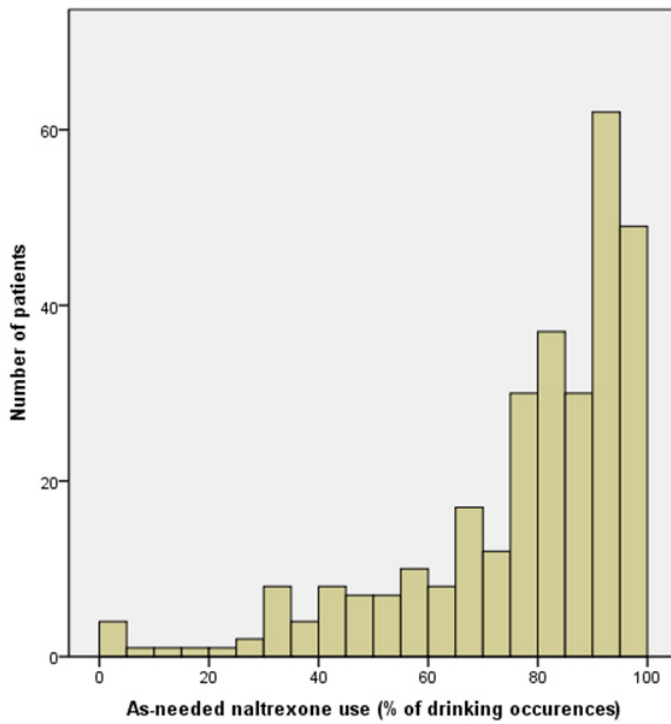
Figure 3. Adherence of patients to targeted (used as needed, i.e. only in drinking occurrences) medication use in a CBT and targeted naltrexone treatment

4.4 Study IV: Combining medical treatment and CBT in treating alcohol dependent patients: effects of treatment on quality of life and general well-being

By the end of the first 12-week study period, 25.1% of the patients in study IV had dropped out, and by the end of the study (52 weeks), the dropout rate was 51.8%. There were no significant differences in the completion of the study between the different medication groups. The socio-demographic background of participants was similar in all medication groups. Detailed information has been published previously by Laaksonen and co-workers (2008a). Dropping out from the treatment was associated with a younger age and lower persistence in keeping a drinking diary.

All three study groups showed a significant reduction in drinking from baseline to the end of the study. As was demonstrated in the earlier trial by Laaksonen and co-workers (2008a), treatment with disulfiram was more effective than acamprosate or naltrexone in reducing heavy drinking and average weekly alcohol consumption, and in increasing the time to the first drink, as well as the number of abstinent days (Figure 4). AUDIT and SADD scores indicated significant reductions during the study ($p < 0.0001$) in the severity of the alcohol problem and in alcohol dependence.
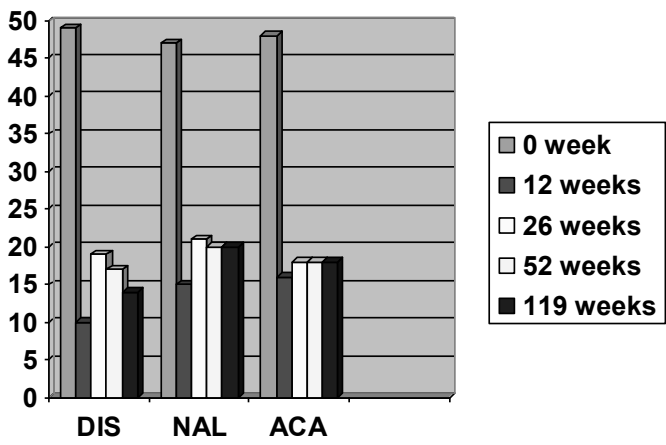

Figure 4. Number of drinks per week at baseline and on follow-up, 0–119 weeks. (Disulfiram, DIS; naltrexone, NAL; acamprosate, ACA).

The improvement in the QL scores was statistically significant for VAS ($F_{(3,215)} = 20.14$, $p < 0.001$), KQL ($F_{(3,220)} = 21.76$, $p < 0.001$) and EQ-5D dimensions of sleep (Wald $\chi^2 = 19.69$, df = 3, $p < 0.001$), the ability to act (Wald $\chi^2 = 25.38$, df = 3, $p < 0.001$, pain (Wald $\chi^2 = 8.64$, df = 3, $p < 0.05$), and mood (Wald $\chi^2 = 31.40$, df = 3, $p < 0.001$) over the whole study period (52 weeks and follow-up), with no differences between the groups. However, in subscales of self-care, there were no significant differences between medical groups or with time (Wald $\chi^2 = 2.98$, df = 3, p = 0.39). Both of the depression scales, BDI ($F_{(4,222)} = 44.18$, $p < 0.001$) and DEPS ($F_{(4,222)} = 38.92$, $p < 0.001$), also showed that depression scores decreased significantly during the whole study period when compared to the first visit. However, no significant differences were found between medical groups.

As is shown in Table 12, a significant reduction in the proportion of patients who reported smoking was seen in the disulfiram group during the first 26 weeks (from 55.7 to 35.1%), and again at 52 weeks (from 55.7 to 34.3%), compared with the naltrexone group ($p < 0.001$) and acamprosate group ($p < 0.02$). No such drop was seen in the naltrexone or acamprosate groups. The logistic regression model revealed that using disulfiram had a statistically significant effect on smoking at treatment week 52 ($p = 0.008$). At treatment week 52, naltrexone and acamprosate users were three times more likely to smoke compared with the disulfiram users (OR = 3.06). Including patients' alcohol consumption during the previous 10 weeks in the model did not have a confounding effect on the results.

Table 12. Percentage of smokers during treatment weeks 0–52.

Medication group	Smoking Yes/No	0 weeks		12 weeks		26 weeks		52 weeks	
		N	%	N	%	N	%	N	%
Acamprosate	Yes	42	51.9	30	53.6	21	50.0	22	53.7
	No	39	48.1	26	46.4	21	50.0	19	46.3
Disulfiram	Yes	44	55.7	25	47.2	13	35.1[a]	12	34.3[a]
	No	35	44.3	28	52.8	24	64.9	23	65.7
Naltrexone	Yes	58	72.5	40	69.0	25	59.5	29	69.0
	No	22	27.5	18	31.0	17	40.5	13	31.0
Total	Yes	144	60.0	95	56.9	59	48.8[b]	63	53.4[b]
	No	96	40.0	72	43.1	62	51.2	55	46.6

[a] Significantly more patients using disulfiram stopped smoking than patients using naltrexone (compared to disulfiram, $p < 0.001$) and acamprosate ($p = 0.015$).
[b] The reduction in smoking habits (total) was most prominent during weeks 26 and 52.

5 DISCUSSION

Randomized controlled trials form the basis for planning evidence-based treatment guidelines in alcohol treatment. Studies based on routinely collected data and non-randomized study samples have been suggested as an important adjunct to randomized controlled trials (Moyer & Finney, 2002; Rothwell, 2005), but such studies are scarce.

This study investigated how one evidence-based treatment for problem drinking, a combination of cognitive behavioral therapy and targeted naltrexone (Hernandez-Avila et al., 2006; Kranzler et al., 2009), works in a community outpatient treatment setting. Specifically, the purpose of the study was to identify predictors of treatment outcomes. The study aimed to contribute to what Rothwell (2005) argued was needed in the field of treatment intervention research: studies reporting determinants related to external validity, i.e. reporting to whom the results of evidence-based treatments apply. Another purpose of this study was to investigate how the combination of pharmacotherapy (naltrexone/acamprosate/disulfiram) and CBT can improve the well-being and quality of life of patients, in addition to reducing alcohol use.

This study demonstrated that although many randomized controlled trials (e.g. Anton et al., 2005; Heinälä et al., 2001; Hernandez-Avila et al., 2006; Kranzler et al., 2009; O'Malley et al., 1992; Oslin et al., 2008) have proven CBT and naltrexone to be an efficacious treatment for problem drinking, there may be variability in the effectiveness of this treatment in real-life treatment settings including heterogeneous patient samples. The study also identified several predictors of treatment dropout, treatment outcomes, and patient adherence to medication. Furthermore, this study revealed that in addition to a reduction in drinking, the combination of medication and CBT can improve general well-being and quality of life for those patients who commit to treatment. The treatment may also help patients to quit smoking, especially those who use disulfiram during treatment.

5.1 Predictors of treatment dropout

The study demonstrated that those with a less severe alcohol dependence, lower obsession with alcohol, and a better ability to resist and control their drinking were likely to drop out from the treatment. Those who started the treatment with abstinence instead of continuing to drink were also at a higher risk of dropout. The dropouts had lower adherence with naltrexone and reporting their alcohol use in drinking diaries.

The fact that patients with less severe alcohol dependence and a lower craving for alcohol had a higher risk of dropping out from the treatment is noteworthy, because dropping out is typically

perceived as a sign of noncompliance, resistance, or a failure of treatment (Pulford et al., 2006). However, as Pulford and co-workers (2006) pointed out, dropout can also be understood as a failure of treatment fit, meaning that the patient may leave because the treatment is not optimal to his or her presenting problem. Patients with better control over their drinking behavior may be more motivated and have better retention in brief interventions, which have proven effective for those with less severe problems (Moyer et al., 2002). One alternative explanation for higher risk of dropout of those with less severe alcohol problems may be that these patients are not yet concerned about their drinking behavior. Namely, the severity of the alcohol problem appears to increase feelings of distress about the problem and thereby influence decision making about treatment (Ryan et al., 1995). It should be noted that perceived control over alcohol use may also be a sign of over-confidence. Namely, the work of Burling and co-workers (1989) indicated that those with high alcohol-related self-efficacy were likely to drop out from treatment, despite not having successful outcomes on alcohol-related measures.

The study also observed that dropping out from the treatment was related to a younger age. The same finding has been reported in several previous studies (Brorson et al., 2013; Elbreder et al., 2011; Mammo & Weinbaum, 1993; McKellar et al., 2006; Wickizer et al., 1994). One explanation for possibly lower motivation for treatment among younger patients may be that they have experienced fewer adverse consequences related to alcohol use (McKellar et al., 2006). They may still be in a contemplation stage of change (see Norcross et al., 2011), balancing between the pros and cons of their drinking behavior.

The patients who chose abstinence at treatment entry were more likely to drop out from the treatment than those who continued to drink. Using naltrexone during abstinence has not been proposed to be useful (Sinclair, 2001). Therefore, a manualized treatment program based on targeted medication and a progressive reduction in drinking rather than abstinence may not be beneficial for patients who choose not to drink upon entry to treatment. Although it should be noted that most of the therapists would try to adjust the treatment program to the patients' situation, the changed structure of the program may lead to some degree of confusion in therapy, and thereby to less commitment to treatment on the patients' part.

5.2 Effectiveness of treatment and predictors of alcohol-related outcomes

Similarly to the systematic reviews by Adamson and co-workers (2009) and McKay and Weiss (2001), the pretreatment alcohol consumption level was a significant predictor of treatment outcomes in study II. A higher level of pretreatment drinking was associated with poorer drinking outcomes during the treatment, and a lower level of pretreatment drinking was associated with the most rapid reduction in craving for alcohol. Patients who drank more alcohol before and during the treatment had lower adherence to naltrexone. A lower reduction in alcohol consumption was also observed for those with no history of previous treatments.

The patients in the treatment program of studies I–III were generally encouraged to continue drinking progressively down to lower levels or to abstinence during the treatment, as suggested by Sinclair (2001). However, 23% of the patients started and continued the treatment with minimal alcohol consumption. A marked reduction in alcohol consumption was observed for a further 32% of the patients. For the remaining 45% of the patients, the effect of the treatment appears to have been modest compared to the results demonstrated in randomized controlled trials of targeted naltrexone and CBT (Kranzler et al., 2003; Kranzler et al., 2009). However, it should be noted that patients were encouraged to set their own treatment goals and many chose to reduce their drinking below the hazardous drinking levels suggested in the Finnish guidelines for problem drinking (Alho et al., 2011).

It is also noteworthy that the patients who started with most excessive drinking belonged to the group that had better outcomes. These may have represented a subgroup of patients who derived most benefit from naltrexone. Namely, naltrexone has been found to be especially beneficial for heavy or excessive drinking (Pettinati et al., 2006b). In accordance with the treatment goals of naltrexone (Rösner et al., 2010) and CBT (Marlatt & Gordon, 1985), a significant reduction in craving for alcohol was observed for all patients in study II. These results confirm the proposal by Tiffany and Conklin (2000) that patterns of alcohol use can operate independently of craving.

Study IV revealed a significant reduction in drinking in all three medication groups during the first 12 weeks of the treatment, and the results remained the same until the end of the treatment, at 119 weeks. One reason for the seemingly poorer treatment outcomes in study II compared to study IV is likely to be related to methodological differences. In study IV, only patients who completed the treatment were included in the analyses, whereas in study II those who dropped out were also included in the alcohol consumption trajectories. In study IV, those who continued with the treatment for as long as 52–119 weeks were likely to be the ones who most benefited from the

treatment. Namely, those receiving a rapid initial response and individual care are likely to remain in treatment (Stark, 1992), and there is evidence that the time spent in treatment correlates with a positive post-treatment outcome (Gottheil et al., 1992; Moos & Moos, 2003; Welte et al., 1981). Another reason for the differences in the outcomes of studies II and IV is likely to be associated with the different mediation adherence rates. Because study IV was a clinical randomized trial, patients received their study medication at no cost and their medication compliance was assessed with pill counts. The average naltrexone adherence rate was 82.5% (Laaksonen et al., 2008a) compared to the adherence rates of 71–74% that were observed in trajectories with the most modest alcohol consumption reduction in study II. Finally, in study IV, only those with a history of heavy drinking were invited for the trial, whereas in study II, those with lower pretreatment alcohol consumption levels were also included. Therefore, there was high variability in the baseline alcohol consumption levels in study II compared to study IV.

The reason why those without any history of previous treatment were most likely to have a modest reduction in alcohol consumption remains unclear. One possible reason for this finding may be that these patients may have experienced fewer adverse consequences related to their drinking behavior and consequently have a lower motivation to reduce their alcohol use. In a systematic review by Adamson and co-workers (2009), treatment history showed significant variability in the direction of association relative to treatment outcomes. In three of the reviewed studies, more treatment was related to better outcomes, whereas in five studies, better outcomes were associated with less treatment.

5.3 Adherence to naltrexone use

Study II revealed that the alcohol consumption level among patients during the treatment was inversely associated with adherence to targeted naltrexone. Baseline predictors of poor adherence with naltrexone included unemployment and a high craving for alcohol at treatment entry, particularly difficulty in resisting alcohol-related impulses and controlling drinking behavior.

As suggested above, one probable reason for the considerable variability in alcohol-related outcomes was likely to be the differences between patients in their adherence to naltrexone use. Although the overall adherence rate was 78%, adherence was much lower, 71–74%, in trajectories with the most modest reduction in alcohol consumption. This is in line with results reported by Gueorguieva and co-workers (2013), who observed that lower adherence was related to greater drinking severity during treatment. In contrast, those who continued to drink only moderately during treatment were most compliant in using the medication. Considering that the effect of

naltrexone is associated with medication adherence (Baros et al., 2007; Chick et al., 2000; Volpicelli et al., 1997), poor adherence with naltrexone is a notable obstacle to the effective pharmacological treatment of problem drinking in real-life treatment settings. Poor medication adherence among hazardous drinkers has been demonstrated previously (Cook et al., 2001).

Very little data are available to indicate the extent to which patients in real-life clinical practices adhere to using medications for alcohol dependence. In natural treatment settings, medication adherence is likely to be much lower than in clinical trials, in which medication use is usually intensively monitored and the participants receive their study medication at no cost. Therefore, the average naltrexone adherence rate of 78% during the 4 months of the treatment can be considered relatively high in the light of the results of Kranzler and co-workers (2008) and Hermos and co-workers (2004), who reported that only 14–22% of the patients who filled an initial prescription for naltrexone persisted in obtaining the medication after 6 months.

Possible reasons for the comparatively high overall medication adherence may be that the treatment program included psycho-education on the neurobiological effects of naltrexone, and the clinic and its staff were all specialized in this treatment model. Educational approaches have been found to be most effective when used in combination with behavioral and supportive services (Zygmunt et al., 2002). Also, as Pettinati (2006a) pointed out, a clinician's attitude concerning the effectiveness of a medication is critical, because it may be transferred to the patient. Another reason for the good overall medication adherence may be related to using naltrexone in a targeted manner instead of as a daily dose, since the prescribed dosage has proven to be inversely related to compliance (Claxton et al., 2001). In particular, patients who are not drinking on a daily basis may find it difficult to motivate themselves to use daily medication.

Reasons for the poor naltrexone adherence of those who were unemployed may include the cost of the medication and lower social support, which have both been shown to be associated with lower adherence to medication (Balkrishnan, 1998; DiMatteo, 2004). The association between high craving for alcohol at treatment entry and poorer naltrexone adherence may be somewhat less straightforward. The use of naltrexone is associated with decreased pleasurable effects of alcohol (Rösner et al., 2010), and some patients might have competing and contrary motivations in giving up these effects. However, different subtypes of patients may have different neurobiochemical mechanisms underlying their symptoms of craving (Addolorato et al., 2005), and reasons for not taking the tablet may vary accordingly. There is also evidence that patients with substance dependence have problems in the executive processes of working memory (Bechara & Martin, 2004), which may have caused patients struggling with high alcohol craving, in particular, to simply forget to take the pill. One reason for not taking the medication may be associated with alcohol-

related outcome expectancies. These include positive ones, such as social interaction, fun, and tension reduction (Monk & Heim, 2013), which a person may perceive as diminished when taking the medication.

5.4 Effects of alcohol treatments on quality of life, smoking habits, and depression

The results of study IV demonstrated that, in addition to a significant reduction in drinking, the combination of medication (naltrexone, acamprosate, or disulfiram) and CBT can improve sleeping, quality of life, and depression for those patients who commit to treatment. The dimensions of the quality of life that were improved during the treatment included mood, sleeping, the ability to act, and pain. The improvement was similar across medication groups. Moreover, although a reduction in smoking rates was observed in all medication groups by treatment weeks 26 and 52, those who used disulfiram were more successful in quitting smoking than those who used naltrexone or acamprosate.

These findings are important considering that the comorbidity of depressive symptoms in association with problematic alcohol use is associated with an increased risk of relapse after treatment (Curran et al., 2000; Driessen et al., 2001), and the presence of either alcohol use disorder or major depression doubles the risk of a second disorder (Boden & Fergusson, 2011). Although this study did not control for patients' antidepressant medication use, it is plausible that some of the patients received antidepressant medication while in treatment. Previous research has demonstrated that combined pharmacotherapies for alcohol dependence and depression can reduce the symptoms of both disorders (Pettinati et al., 2010). It has also been demonstrated that the treatment of alcohol use disorder results in a reduction in depressive symptoms (Brown & Schuckit, 1988), which may be one reason for the positive outcomes in depression observed in this study.

Improvement in patients' sleeping is also important, because it has been shown that sleep disturbances increase the risk of relapse (Roehrs & Roth, 2001). The observed improvement in other measures of QL, the ability to act and experience of pain, are also noteworthy, because QL among alcohol-dependent patients is known to be poor compared to general population norms (Foster et al., 1999).

This is to the best of our knowledge the first study to report an association between successful quitting of smoking and the use of disulfiram, in particular, during treatment. The finding was not only explained by the change in alcohol consumption, which was most reduced in the disulfiram group in an earlier study by Laaksonen and co-workers (2008a). One of the possible explanations

for the effect of disulfiram on reduced smoking may be related to the inhibition of dopamine beta-hydroxylase, which is associated with the use of disulfiram (Lippmann & Lloyd, 1969), and which may lead to reduced pleasure associated with smoking. Another explanation may be associated with the combined effect of disulfiram and tobacco smoke. The use of disulfiram and exposure to tobacco smoke are both associated with the accumulation of acetaldehyde in the body (Heilig & Egli, 2006; Salaspuro & Salaspuro, 2004), which may lead to more side effects in alcohol-dependent smokers using disulfiram than in those using naltrexone or acamprosate. The observed effects of the treatment on quitting smoking were observed during treatment weeks 26 and 52, suggesting that longer treatment may be needed to achieve these results. There is high comorbidity in nicotine and alcohol dependencies (Grant et al., 2004), and the smoking status among alcoholics appears to increase the odds of relapse (Baltieri, et al., 2009). Therefore, this result may have some important clinical implications.

5.5 Methodological considerations

5.5.1 Strengths of the study

The foremost strength of studies I–III was their high external validity and good generalizability of the findings to real-life treatment practice. Due to the minimal exclusion and inclusion criteria, the patient sample included those with psychiatric and medical disorders, which are typical in problem drinkers. The lack of a randomization procedure was likely to have improved the external validity of the results. Namely, it has been indicated that participants in randomized versus self-selected samples often differ at baseline (Moyer & Finney, 2002) and e.g. low-income individuals, and individuals who have more severe substance abuse or psychiatric problems are disproportionately excluded from alcohol treatment trials in comparison to real-world samples seen in clinical practice (Humphreys & Weisner, 2000). A methodological strength in study II included the use of trajectory analyses to describe the changes in alcohol consumption and craving, which has been proposed as a valid exploratory method for evaluating the efficacy of pharmacotherapy in alcohol trials (Chen et al., 2012). Finally, considering that dropout can impair the internal validity of any trial (Leichsenring, 2004), the thorough analysis of the dropouts in study I improved the internal validity in these studies.

Study IV also possessed good external validity compared to typical pharmacological randomized controlled trials, because the patients were voluntary treatment-seeking individuals who contacted outpatient addiction treatment centers and occupational health-care units, which are typical places to take in patients with alcohol problems. Patients who had a history of heavy drinking and accepted

the study protocol were recommended for screening, and despite using some exclusion and inclusion criteria (see Laaksonen et al. 2008a for further details), only 20 patients out of 277 screened patients did not meet these criteria and were excluded from the study. The methodological strengths of study IV included the fairly large sample size and the long study duration and follow-up period for those who completed the treatment, lasting 2.5 years in total.

5.5.2 Limitations of the study

A major limitation in studies I–III was the large amount of missing data resulting from the data having been gathered in a community setting. However, in study I we used the procedure of multiple imputations by chained equations (Rubin, 2004), which has been shown to perform favorably in situations of missing data (Bryant et al., 1997). When analyzing the drinking diaries in study II, we used group-based trajectory modeling, where it is not necessary to have complete cases in repeated measurements, and it is possible to approximate complex data distributions. The use of trajectory analysis has been found to yield consistent results in the event of data missing at random (Chen et al., 2012). In studies II–III, the baseline data were examined to detect any systematic patterns for missing values. Another limitation in studies I–II was that patients' alcohol consumption was only estimated for one month preceding entrance to the treatment program, which may not accurately reflect typical alcohol use during a longer interval.

Further limitations in studies I–II include the lack of more objective measures, such as liver enzyme values, to evaluate the treatment outcome, the lack of follow-up data on patients' alcohol use or symptoms of craving in the post-treatment period, and the lack of biochemical measures at different points of the treatment. In study III, the lack of more sophisticated measures for monitoring patients' medication adherence can be considered a limitation. However, it should be noted that the assessment methods in studies I–III, such as the use of drinking diaries, were typical of those used in real-life alcohol treatment settings, and despite their methodological shortcomings, they possess good external validity. Compliance measurements based on daily diaries have also been reported to provide information similar to that obtained using electronic medication-use monitoring (Feinn et al., 2003). One limitation in studies I–III was that although it was plausible that some of the patients in the studies were likely to continue their attendance at the clinic after the 20th week of treatment, no data were available for their treatment outcomes after week 20.

In study IV, limitations included not assessing the patients' possible antidepressant medication use during the treatment and not diagnosing patients using psychiatric criteria. It also remains unclear whether the improved QL and depression were associated with patients' reduction in alcohol use and craving. Limitations also included only assessing the patients' smoking behavior

with a simple yes/no question and not by using a validated instrument. A further limitation of study IV was the use of per protocol analyses, which only included patients who completed the treatment in the analyses. The problem with a per protocol analysis is that it only includes 'ideal patients' in the analyses, which may lead to bias (Boutis & Willan, 2011).

One limitation in all four studies was the lack of assessment of potential mediators of the treatments. In studies I–II, due to the lack of comparison group(s) and because the role of specific active elements of CBT was not examined, the identified predictors of treatment outcomes cannot be ascertained to be specific to CBT and naltrexone alone. In all four studies, the role of mediators remained unclear. In addition to the active ingredients of the treatment, these include the data source, behavior of the therapist, therapist–patient or doctor–patient interactions and relationships, and the behavior of the patient (Longabaugh, 2007). Patients' motivation for treatment and motivation for change are likely to have influenced the outcomes in all studies. It has not been typical to examine these factors in randomized controlled trials or effectiveness studies, although, as suggested by Magill and Longabaugh (2013), clinical research should move towards understanding these proven active treatment ingredients and the mechanisms by which a patient changes.

5.6 Clinical implications of the findings

An important finding of this study in respect to routine treatment settings was the variability in how problem drinkers benefited from CBT and naltrexone. The findings suggest that the patients' age, ability to control alcohol use, pretreatment alcohol consumption level, and treatment goals should be used as a basis for planning more effective alcohol treatments. The findings also suggest that targeted naltrexone may not be the best choice of medication for everyone. Instead, patients who drink heavily in the pretreatment period may benefit more from supervised disulfiram, or starting the treatment with daily naltrexone as used in study IV and, for instance, in a study by Heinälä and co-workers (2001). Nalmefene, a newer opioid antagonist that has a considerably longer half-life than naltrexone (Bart et al., 2005), may show more promising results even for heavy drinkers when used in an as-needed manner (Gual et al., 2013; Niciu & Arias, 2013).

The observed inverse relationship between patients' medication adherence and the level of alcohol consumption in study II confirms the concern raised by Pettinati (2006a), among others, related to poor medication adherence among the alcohol-dependent population. Pettinati (2006a) suggests that if non-adherence is identified as a problem in treatment, "the clinician should address the issue with the patient in order to uncover the rationale behind it in an empathetical and non-judgmental way." Accordingly, patients with non-adherence should be offered additional support

for enhancing their adherence to medication use, or be provided with alternative medications. As was found in a study by Gueorguieva and co-workers (2013), those who exhibited early problems with adherence to one treatment modality received better outcomes when offered an alternative behavioral or pharmacological treatment.

It may be important that clinicians acknowledge patients' high craving for alcohol as one potential reason for not taking the medication. In addition, the cost of medication may be an important obstacle for medication adherence and should be discussed with the patient. The findings also support the use of the pretreatment alcohol consumption level as an important determinant when planning treatments for problem drinking. As Rychtarik and co-workers (2000) and Klein and co-workers (2002) suggest, improved outcomes may be achieved by matching the degree of alcohol involvement or problem severity to the level of care. Observing patients' alcohol consumption during treatment is important. Namely, drinking higher amounts while receiving treatment seems to be related to higher drinking in the post-treatment period (Breslin et al., 1997). If the goal of treatment is to reduce drinking to progressively lower levels, the length of treatment should be adjusted according to the level of progress. Alternatively, although the support for the use of inpatient care over outpatient care is inconsistent (Mattick & Jarvis, 1994), patients with the most severe alcohol problems may benefit more from inpatient treatment, as suggested by Rychtarik and co-workers. (2000), or longer treatment, which has been found to improve the outcomes of those with more severe alcohol problems (Gottheil et al., 1992; Moos & Moos, 2003).

A behavioral intervention, BRENDA (Starosta et al., 2006), has been developed for alcohol-dependent patients to improve adherence to alcoholism medication. It has 6 components, consisting of a biopsychosocial evaluation of the patient's situation, a report of the findings from the patient evaluation, the use of empathy, addressing the patient's needs, providing direct advice and assessing the patient's reaction to the given advice, and adjusting the treatment plan accordingly (Starosta et al., 2006). Contingency management has also been shown to improve adherence to naltrexone (Preston et al., 1999). Osterberg and Baschke (2005) noted the possibilities that come with new technology, such as cell phones, personal digital assistants and pillboxes with paging systems in helping patients to meet the goals of medication adherence.

It has been suggested that it is important to discuss patients' drinking goals when they enter treatment and use this information as a basis for negotiation (Adamson et al., 2010). Clinicians should be also prepared "to identify and support goal change as an unexceptional part of the treatment process that need not jeopardize good outcome" (Adamson et al., 2010). Medications should then be targeted on the basis of the goal of the treatment (Alho & Aalto, 2013).

Klein and co-workers (2002) emphasized the importance of taking into account patients' demographic factors when planning treatment. The findings of this study suggest that younger patients may need special attention in order to enhance their retention in treatment. Although motivation for changing a problematic behavior is not necessarily synonymous with motivation for participating in treatment (DiClemente et al., 1999), with younger patients it may be particularly important to discuss motivational factors related to their drinking behavior.

One factor in improved treatment planning is to take account of the stage of change in the patient at treatment entry. A meta-analysis of 39 studies by Norcross and co-workers (2011), including several alcohol trials, reported clinically significant effect sizes for the association between the patients' stage of change and psychotherapy outcomes. It was also suggested that clinicians should treat all patients as though they are in action, and when planning the treatment always take account of the patients' current stage of change.

Our findings demonstrated that those who chose abstinence were more likely to drop out of treatment than those who continued to drink. One of the reasons for this may have been the use of a manualized study protocol. Patients who have good control over their drinking behavior at an early phase of treatment may already have effective coping skills for controlling their alcohol use, and may find irrelevant or unnecessary tasks in therapy frustrating. Although treatment manuals are important in randomized controlled trials, in real-life treatment settings they may be less appropriate (Addis et al., 2006). At least a rigid use of a therapy manual may miss the amount of variance attributed to patient variables and nonspecific factors of therapy (Addis et al., 2006), which have been proven to account for a considerable amount of the treatment outcome (Connors et al., 1997; Schneider et al., 2004; Wampold, 2001). However, it should also be noted that a clear structure and well-defined interventions appear to have favorable effects on the treatment of alcohol dependence (Berglund et al., 2003). Therefore, therapy manuals may be best used in a flexible way, taking into account the patients' individual situation.

The positive effects of a combination of medical treatment and CBT for general well-being and smoking habits may have important clinical implications. They indicate that the alcohol-dependent patients who smoke may benefit from the use of disulfiram in helping them to quit smoking, in addition to reduced alcohol use. Another important implication of these findings may be related to the length of the alcohol use treatments. Considering that the positive result for smoking was observed in the 26th week of the treatment, a longer treatment period may be needed to achieve this result. However, longer treatment does not mean that the treatment should be intensive. As Moos and Moos (2003) reported, the continuity and duration of treatment may be more important for achieving good outcomes than its intensity.

5.7 Conclusions and suggestions for future research

In conclusion, the results demonstrate that there is relatively large variability in how problem drinkers benefit from CBT and naltrexone in real-life treatment settings. The results of randomized controlled alcohol trials may not be directly generalized to routine clinical practice, and more research is needed on testing the evidence-based alcohol treatments using data of heterogeneous patient samples with typical comorbidities.

According to the results, younger patients and those with lower alcohol dependence may lack motivation or not need long CBT and targeted naltrexone treatment, and they may be at a higher risk of prematurely dropping out from the treatment. Having good control over alcohol use and being able to abstain from drinking in the early phase of the treatment may also indicate a higher risk of dropout. Patients with less severe alcohol dependence and better control over drinking may benefit from less intensive or shorter treatments or need motivational interventions (e.g. Roche et al., 1995) in order to enhance their treatment retention.

In contrast, this study showed that patients who have no previous treatment history and those with a high pretreatment consumption level and higher level of drinking during the treatment may be at risk of having poorer outcomes. These patients may need longer or more intensive care in order to reduce their drinking, or alternative medications to the targeted use of naltrexone. The results also demonstrate that poor medication adherence is a considerable obstacle to the effective treatment of alcohol problems in a real-life treatment setting. Excessive drinking during the treatment may be associated with poor adherence to naltrexone, and heavy drinkers may therefore need specific interventions to enhance medication adherence.

One finding of this study was that unemployed patients with a possible lack of financial resources and low social support may have difficulty in adhering to medication. A high craving for alcohol may also lead to poor medication adherence. It may be important to pay attention to these factors when evaluating the patient's willingness to use medication.

Finally, the study indicated that for those who commit to treatment, the combination of medication and CBT can improve smoking habits, sleeping, quality of life, and depression, alongside a reduction in drinking. Specifically, the use of disulfiram during treatment may help patients to quit smoking, in addition to reducing their alcohol use.

The results of this study confirm earlier proposals (Breslin et al., 1997; Sobell & Sobell, 2000) that treatments should be better adjusted to the patients' individual needs, both at treatment entry and during the course of the treatment, using the best possible clinical judgment and the present knowledge base. Randomized controlled trials indicate that the treatment of alcohol use disorders is

cost-effective (UKATT, 2005b; Zarkin et al., 2008). However, as O'Brien and McLellan (1996) pointed out, the expectation of a cure after treatment is unrealistic, and the treatment of addictions should be compared to that of other chronic disorders.

It is clear that the current system of care for alcohol problems often does not respond to the diversity of patients, such as the nature and severity of the problem, the resources of the patient, treatment preferences, goals, motivations, behavior change pathways, and patient–treatment interactions. Future research should include naturalistic studies on these factors. Moreover, although a more individualized approach in the pharmacological treatment of the alcohol-dependent population is well on its way (Mann & Hermann, 2010b), more research is needed not only on who benefits from which medication, but also on the factors related to medication adherence in alcohol-dependent patients. As Longabaugh (2007) noted, behavior change is a complex process, and research needs to reflect this complexity.

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