

From the Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

**THERAPIST-GUIDED
INTERNET TREATMENT FOR
ALCOHOL USE DISORDERS**

Christopher Sundström



**Karolinska
Institutet**

Stockholm 2017

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet.

Printed by Universitetservice AB

© Christopher Sundström, 2017

ISBN 978-91-7676-878-5

Therapist-guided Internet Treatment for Alcohol Use Disorders

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Christopher Sundström

Principal Supervisor:

Associate Professor Anne H Berman
Karolinska Institutet
Department of Clinical Neuroscience

Co-supervisors:

Associate Professor Viktor Kaldö
Karolinska Institutet
Department of Clinical Neuroscience

Professor Paul Wallace
University College London
Research Department of Primary Care
and Population Health

Opponent:

Professor Heleen Riper
Vrije University
Department of Clinical Psychology

Examination Board:

Professor Maria Tillfors
Karlstads Universitet
Department of Social and Psychological Studies

Professor Anders Håkansson
Lund University
Department of Clinical Sciences

Associate Professor Pia Enebrink
Karolinska Institutet
Department of Clinical Neuroscience

In loving memory of my mother and father
who invited me to this great mingle party

ABSTRACT

Background: Alcohol Use Disorders (AUD) are among the most common psychiatric disorders but the vast majority never receive treatment. Internet interventions have the potential to reach some of those who currently do not seek or receive treatment. Such interventions for alcohol problems of varying forms have been shown to be effective, generally rendering small effect sizes, and some studies suggest that adding therapist guidance to these interventions can augment their effects.

Aims: The general aim of this thesis was to develop and evaluate therapist-guided internet-based treatment for AUD. Specifically, we aimed to investigate the added effect of therapist guidance to a previously evaluated internet treatment (study I), test feasibility and preliminary effects of a newly developed high-intensity internet treatment (study II), evaluate effects of high- as compared to low-intensity internet treatment and a wait-list control group (study III) and investigate predictors of adherence and low-risk drinking in the internet treatments in study III (study IV).

Methods: In Study I, we conducted a randomized controlled trial (RCT) where all groups received access to the same internet treatment, with one group receiving therapist guidance via messages, one group receiving therapist guidance via messages or chat (choice) and one group not receiving any therapist guidance (n=80). In Study II, a newly developed high-intensity therapist-guided internet treatment was tested in a pilot study among participants to investigate feasibility and preliminary effects (n=13). Study III was a second RCT where the high-intensity internet treatment from study II was tested against a low-intensity internet treatment and a wait list control group (n=166). In Study IV, we used data from study III to investigate predictors of 1) treatment adherence and 2) low-risk drinking at post-treatment and three-month follow-up.

Results: The results from study I showed that the groups that received therapist guidance reduced their number of standard drinks to a significantly higher degree than the group receiving no guidance. Study II showed that the newly developed high-intensity treatment was feasible and acceptable, and was associated with a significant reduction in number of standard drinks among participants. Study III showed that the high-intensity group reduced the number of standard drinks and heavy drinking days significantly more than the wait-list control-group, and reduced their number of heavy drinking days significantly more than the low-intensity group at post-treatment but not at three-month follow-up. Study IV showed that participants' rating of treatment credibility was predictive of treatment adherence, and that

pre-treatment abstinence, male gender and two personality variables (a high degree of alexithymia and a low degree of antagonism) were predictive of low-risk drinking.

Conclusion: The results in this thesis, provide support for the feasibility and efficacy of internet treatment for AUD, and offer interesting findings on predictors of outcome that should be investigated further. Overall, participants were satisfied with the treatments, and few negative effects were reported.

LIST OF SCIENTIFIC PAPERS

- I. **Sundström C**, Gajecki M, Johansson M, Blankers M, Sinadinovic K, Stenlund-Gens E, Berman AH. *Guided and Unguided Internet-Based Treatment for Problematic Alcohol Use - A Randomized Controlled Pilot Trial*. PLOS ONE. 2016;11(7)
 - II. **Sundström C**, Kraepelien M, Eék N, Fahlke C, Kaldo V, Berman AH. *High-intensity therapist-guided internet-based cognitive behavior therapy for alcohol use disorder: a pilot study*. BMC psychiatry. 2017;17(1):197
 - III. **Sundström C**, Eék N, Kraepelien M, Fahlke C, Gajecki M, Jakobson M, Beckman M, Kaldo V, Berman AH. *High- versus low-intensity internet treatment for alcohol use disorders: a randomized controlled trial*. Manuscript
 - IV. **Sundström C**, Eék N, Kraepelien M, Fahlke C, Kaldo V, Berman AH. *What predicts treatment adherence and what predicts low-risk drinking? An exploratory study of internet treatment for alcohol use disorders*. Manuscript
- Appendix **Sundström C**, Blankers M, Khadjesari Z. *Computer-Based Interventions for Problematic Alcohol Use: a Review of Systematic Reviews*. International journal of behavioral medicine. 2016. Epub 2016/10/21

CONTENTS

1. INTRODUCTION	1
1.1 ALCOHOL AND GLOBAL HEALTH	1
1.2 ALCOHOL POLICY	2
1.3 THE TWO WORLDS OF ALCOHOL PROBLEMS	3
1.4 TREATMENT ALTERNATIVES	6
1.4.1 <i>Mutual-help approaches: Alcoholics Anonymous</i>	7
1.4.2 <i>Formal treatment: Relapse prevention and Community Reinforcement Approach</i>	7
1.4.3 <i>Secondary prevention: Brief intervention and Motivational Interviewing</i>	8
1.4.4 <i>Pharmacological treatment</i>	8
1.4.5 <i>General findings about treatment effects in alcohol treatment</i>	9
1.4.6 <i>What predicts treatment effect in alcohol treatment?</i>	10
1.5 INTERNET TREATMENT	11
1.5.1 <i>Internet interventions - Clinical and public health approaches</i>	11
1.5.2 <i>Advantages of internet interventions</i>	11
1.5.3 <i>Using the Internet to help people with alcohol problems</i>	12
1.5.4 <i>The issue of therapist guidance</i>	13
1.5.5 <i>What predicts outcomes in alcohol internet interventions</i>	14
1.6 RESEARCH QUESTIONS	15
2. THE EMPIRICAL STUDIES	17
2.1 THE TREATMENT PROGRAMS	17
2.1.1 <i>eChange (studies I and III)</i>	17
2.1.2 <i>ePlus (studies II, III and IV)</i>	18
2.2 MEASURES	21
2.3 THE STUDIES	21
2.3.1 <i>Study I</i>	21
2.3.2 <i>Study II</i>	23
2.3.3 <i>Study III</i>	24
2.3.4 <i>Study IV</i>	25
2.4 ETHICAL CONSIDERATIONS	26
3. GENERAL DISCUSSION	29
3.1 PRIMARY FINDINGS	29
3.1.1 <i>Differences between guided and unguided internet treatment in studies I- III</i>	29
3.1.2 <i>Differences between the unguided groups in studies I and III</i>	30
3.1.3 <i>Is internet treatment for AUD acceptable and feasible?</i>	31
3.1.4 <i>Are there negative effects of internet treatment for AUD?</i>	31
3.1.5 <i>Which individuals benefit most from internet treatment for AUD?</i>	32
3.2 STRENGTHS AND LIMITATIONS	33
3.3 FUTURE DIRECTIONS	34
4. CONCLUSIONS	37
5. ACKNOWLEDGEMENTS	39
6. REFERENCES	43

LIST OF ABBREVIATIONS

AUD	Alcohol Use Disorder
CBT	Cognitive Behavior Therapy
BI	Brief intervention
TSF	Twelve-step facilitation
RP	Relapse prevention
CRAFT	Community Reinforcement Family Therapy
WHO	World Health Organization
DSM	Diagnostic Statistical Manual
AA	Alcoholics Anonymous
eSBI	Electronic screening and brief intervention
TLFB	Time Line Follow Back
HDD	Heavy drinking days
RCT	Randomized controlled trial

1. BACKGROUND

1.1 ALCOHOL AND GLOBAL HEALTH

With a mean world consumption of around 9.2 liters per capita, alcohol is unarguably the most widely used psychoactive substance in the world [1]. High national consumption levels are primarily found in Western Europe, Russia and non-Muslim parts of the former Soviet Union, while other parts of the world, for example India and most countries in the Middle East, have lower consumption levels, often due to high abstention rates in the general population [2]. In Sweden, the average alcohol per capita consumption is slightly lower than the European average (9.2 vs 10.9 litres of pure alcohol), while prevalence of alcohol use disorders (AUD) is somewhat higher (8.9% vs 7.5%) [1]. Alcohol has a significant impact on both burden of disease and death all around the world. The Global Burden of Disease 2010 project concluded that alcohol is the third leading risk factor for global disease burden, after high blood pressure and tobacco smoking [3], and according to the latest report from the World Health Organization (WHO), harmful use of alcohol accounts for 5.9% of all deaths worldwide, or about 3.3 million annual deaths [1]. Alcohol is causally linked to more than 200 diseases, most often with a direct dose-response relationship, i.e., the higher average volume consumed, the higher the likelihood of developing a disease. Among diseases linked to average volume of alcohol consumption are coronary heart disease, breast cancer and liver cirrhosis [4]. Although previous research suggested that moderate alcohol consumption might protect against some diseases, cardiovascular disease in particular [5], this claim has been called into question in recent years [6].

Not only the average volume of alcohol consumption but also an individual's drinking pattern – how much alcohol is consumed on each separate occasion – is relevant when assessing alcohol-related harm. Around 24 % of the world population over 15 years of age have had a heavy drinking episode, i.e. consumed more than 60 grams of alcohol (the equivalent of four standard drinks in Sweden), at least once during the last month [1]. Heavy drinking episodes are explicitly linked to certain categories of alcohol-related harm such as injuries, traffic accidents, homicide, suicide and injuries [2], of which injuries account for the largest portion of alcohol-attributable burden. Further, individuals with an AUD i.e. those with impaired control over their alcohol use and who continue drinking despite negative consequences, are estimated to account for half of all alcohol-related harm [7]. For these individuals, chronic social problems often develop negatively affecting work capacity and relations to family and significant others.

In sum, alcohol's ability to cause harm works through three mechanisms: 1) The toxic effects of alcohol on organs and tissue (leading to somatic disease); 2) intoxication with impairment of physical coordination, consciousness, cognition, perception, affect and behavior (leading to accidents/injuries and acute social problems); and 3) dependence, whereby the drinker's self-control over his or her drinking behavior is impaired (leading to chronic social problems)[8].

1.2 ALCOHOL POLICY

Alcohol policy can be defined as any purposeful effort or authoritative decision on the part of governments to minimize or prevent alcohol-related consequences [8]. Policy strategies that currently are used to prevent or reduce alcohol-related harm fall into seven key areas:

- 1) pricing and taxation (for example customs tariffs and excise duties)*
- 2) regulating physical availability of alcohol (for example government monopolies or use of licensing)*
- 3) modifying the drinking context (for example training bar staff in 'responsible beverage service')*
- 4) drink-driving countermeasures (for example license suspension or revocation)*
- 5) restrictions on marketing (for example compulsory warning texts in advertisements)*
- 6) education and persuasion strategies (for example school prevention programs)*
- 7) treatment and early intervention services[8]*

Although the evidence is unequivocal that alcohol is detrimental to public health and that several of the policy strategies mentioned above are effective in reducing alcohol consumption, alcohol has historically been a low priority in public health policy when compared to the resources given to preventive work on communicable diseases or non-communicable diseases such as cancer and cardiovascular disease [9]. However, recent initiatives to establish international policy frameworks, such as *The WHO Global Strategy to Reduce the Harmful Use of Alcohol*, are expected to lead to an increased global public health focus on alcohol in the future. An increasing number of member states implement national alcohol policies and introduce legislation on policy measures to reduce the prevalence of drunk-driving, limit the physical availability of alcohol and implement restrictions on current alcohol marketing [1].

1.3 THE TWO WORLDS OF ALCOHOL PROBLEMS

Two fundamentally different paradigms, the clinical perspective and the public health perspective, divide the research field targeting prevention and treatment of alcohol-related problems. This divide has been referred to as ‘the two worlds of alcohol problems’ [10].

The clinical perspective

The clinical perspective on alcohol problems primarily focuses on studying people in alcohol treatment and on dissecting the individual problem drinker’s behavior in relation to alcohol; i.e. the ‘alcoholic’. The classical description of the ‘alcoholic’ was originally developed by the U.S. physician E.M. Jellinek in the 1950’s [11], and broadly denotes someone who is unable to drink ‘normally’; i.e., in the same way as ordinary people. People who drink heavily but who do not suffer many consequences are believed to be in a prodromal phase. Behind Jellinek’s description lay primarily interviews and experiences with patients visiting clinical settings, as well as individuals encountered in self-help groups such as Alcoholics Anonymous. Alcohol dependence is seen as a chronically relapsing disorder with something of a core entity separating them from other drinkers. While this distinction is tightly connected with the AA tradition in its search for a core entity, modern neurobiological research has also adopted this perspective, conceptualizing addiction as a brain disease and/or as a result of genetic predispositions [12, 13].

A key element in all clinical work involves diagnosing individuals, which in psychiatric contexts often is done with the *Diagnostic and Statistical Manual* (DSM). The DSM version prior to the current DSM-5 (DSM-IV), made a distinction between alcohol abuse and alcohol dependence, where abuse primarily indicated a use causing harm to self or others, and dependence primarily indicated withdrawal symptoms and repeated failures in quitting. With the DSM-5, this distinction has disappeared. Alcohol Use Disorder (AUD) is now, instead, defined as a dimensional diagnosis with 11 criteria (see figure 2), where 2-3 criteria indicate a mild AUD, 4-5 criteria indicate a moderate AUD and 6-11 criteria indicate a severe AUD [14]. See Figure 1.

- 1) Using alcohol in larger amounts or for longer than you meant to
- 2) Wanting to cut down or stop using alcohol but not managing to
- 3) Spending a lot of time getting, using, or recovering from use of alcohol
- 4) Cravings and urges to use the alcohol
- 5) Not managing to do what you should at work, home or school, because of alcohol use
- 6) Continuing to use alcohol, even when it causes problems in relationships
- 7) Giving up important social, occupational or recreational activities because of alcohol use
- 8) Using alcohol again and again, even when it puts you in danger
- 9) Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the alcohol
- 10) Needing more alcohol to get the effect you want (tolerance)
- 11) Development of withdrawal symptoms, which can be relieved by using more alcohol.

Figure 1. DSM-5 criteria for alcohol use disorders [14]

The term addiction is a broadly applied term considered to be synonymous with dependence, i.e. a severe form of attachment to a substance or behavior. There have been many attempts to define addiction. Below are four examples, presented in a condensed form.

Edwards (1976)[15]

- Addiction is a syndrome of disorders
- “Primary symptoms” of the syndrome and “secondary damage” are separated

West & Brown (2013)[16]

- Addiction is a motivational dysfunction that can be explained by PRIME theory (Plans, Responses, Impulses, Motives, Evaluations): a hierarchical representation of the motivational system as a template for human behavior
- Addiction arises out of a failure of balancing input, leading the system down maladaptive paths in which an unhealthy priority is given to certain behaviors

Bühringer et al (2008)[17]

- Addiction is an imbalance between an automatic “impulsive” system and a higher order “reflective” system

- Impaired cognitive control is a vulnerability factor or proximal risk factor for the onset of addiction and an important moderator in cessation processes

Volkow et al. (2009)[18]

- Addiction is a brain disease
- Prefrontal and striatal deregulation lead to loss of control and compulsive drug intake when the person takes the substance or is exposed to conditioned cues

The public health perspective

The public health perspective on alcohol problems took form during the 1970's, and was in essence a reaction to the then prevailing clinical perspective, according to which individuals in treatment were the main target of research. Instead of focusing on the individual in alcohol treatment; i.e., "the alcoholic", the public health perspective considers the general population as its prime focus, emphasizing that alcohol-related problems are found not only among the heavy drinkers in clinics, but among *the entire drinking population*, although admittedly in various degrees [10]. Several concepts have been central to the emergence of the public health perspective on alcohol problems. One such concept is the 'total consumption model', originally developed by the French sociologist Ledermann and subsequently developed by Skog [19]. This model states that the total alcohol consumption in a society is positively related to alcohol-related problems as a whole, i.e. the higher average alcohol consumption in a society, the greater the number of individuals with alcohol-related problems will be. Accordingly, to prevent alcohol-related problems, instruments that reduce the *total* consumption in a society provide the greatest benefit, in particular policies affecting price and availability of alcohol [8]. Another important development was that of sophisticated survey research, which was important in developing an understanding of the distribution of alcohol consumption in the general population, and in developing tools to estimate the number of problem drinkers in the general population not receiving treatment, i.e. "the treatment gap" [10]. Survey research has had and continues to have a major impact on the WHO yearly reports on global alcohol consumption [20]. A third influential concept in the consolidation of the public health perspective was the 'prevention paradox' theory which states that a large number of people at small risk give rise to more disease and higher cost to society than a small number of people at high risk and accordingly, it may often be more effective to produce small changes in the population than to focus on the smaller group at high risk [21]. Although this epidemiological theory originally was applied to a public health approach in reducing high blood pressure, it was soon incorporated into the public health approach to alcohol problems.

Table 1. Differences in research focus between the clinical and public health perspective

The clinical perspective	The public health perspective
People in alcohol treatment	People in the general population reporting alcohol problems

Differences between the clinical and public health perspective

From a public health perspective, the clinical perspective creates an arbitrary dichotomy between disordered and non-disordered alcohol consumption. Not only is this dichotomy considered false, it may also be damaging, as it often leads to ignorance of effective public health approaches. Public health researchers have questioned commonly recurring claims that dependence is best understood as a ‘chronically relapsing disorder’ caused by brain dysfunctions and genetic predispositions [12, 13], and instead point to the fact that, according to survey data, the majority of people who meet criteria for alcohol dependence 1) do not seek treatment, 2) resolve their alcohol dependence with time and 3) do not relapse repeatedly. Also, the clinical perspective runs the risk of creating a ‘self-fulfilling prophecy’ among patients, when they are told that they have a chronic disorder from which they cannot be cured [22]. From a clinical perspective, on the other hand, the public health perspective ignores important experiences of some of those who cannot control their use, and also ignores the large body of research implicating brain dysfunctions and genetic predispositions in the development of substance use disorder [13].

1.4 TREATMENT ALTERNATIVES

During the past 70 years, the range and number of services for people with alcohol problems has increased dramatically [8]. After World War II, many countries invested in establishing permanent treatment services as a public health response to the major negative consequences of alcohol on society, which ultimately led to an established service system. Treatment for AUD was placed in specialized addiction services within health care, both in-patient (usually restricted to detoxification) and out-patient, in social welfare agencies and, to a less degree, in primary care [8].

There is an abundance of different psychosocial approaches that have been developed specifically for people with alcohol problems [23, 24]. The evidence on alcohol treatment can be divided into three categories: mutual-help approaches, formal treatment and secondary prevention [8]. Below, the most common and evidence-based alternatives within each category are presented.

1.4.1 Mutual-help approaches: Alcoholics Anonymous

Alcoholic Anonymous (AA) is the most well-known mutual-help organization in the world. Developed in the United States during the 1930's, AA is an international organization composed of recovering alcoholics who offer each other emotional support through weekly anonymous meetings [25]. It considers total abstinence the primary goal of treatment. AA assumes substance dependence to be a spiritual disease, and the foundation for recovery is the 12 'steps' that any participant is encouraged to go through in order to reconcile with one's past [26]. Importantly, the AA movement believes alcohol dependence to be a chronically relapsing disorder, and therefore encourages participants to keep coming to meetings indefinitely, also after having achieved abstinence. As AA is not really a treatment per se, a standardized version of AA, Twelve Step Facilitation (TSF), is often used when scientifically evaluating its effectiveness. A Cochrane review published in 2006 states that evidence for the effectiveness of AA and TSF is inconclusive, that selection bias is a common problem in their evaluation, and that more controlled efficacy studies are needed [27].

1.4.2 Formal treatment: Relapse prevention and Community Reinforcement Approach

Several treatment forms based on cognitive behavior therapy (CBT) have been developed. In relapse prevention (RP), the primary focus of treatment lies on 1) identifying the needs currently being met by drinking alcohol, and 2) developing coping skills that provide alternative ways of meeting those needs [28]. By doing this, the risk of relapsing to drinking as a way of meeting these needs decreases. From a CBT perspective, AUD is a maladaptive way of coping with problems that has developed as a set of learned behaviors acquired through experience. Thus, if alcohol on repeated occasions has had reinforcing effects, it may become the preferred way of achieving those effects [29]. RP was developed during the 1970's and was highly controversial when it first came, since, at the time, even mentioning relapse in treatment was considered as giving patients implicit permission to start drinking again. RP is a treatment method developed to be used in alcohol treatment but the principles have been applied on a wide range of problem behaviors such as gambling, eating disorders and sexually risky behaviors [28]. Community Reinforcement Approach Family Therapy (CRAFT) is another form of CBT treatment that focuses on changing the environment surrounding the drinker to make it more reinforcing of sober behavior, often by including and engaging family members and significant others [30]. There is evidence that CRAFT is effective, particularly among treatment resistant individuals [31].

1.4.3 Secondary prevention: Brief intervention and Motivational Interviewing

Brief interventions (BI) are a set of principles regarding interventions developed from the public health perspective on alcohol problems [32]. Nick Heather, one of its central figures, has described BI as an umbrella term encompassing *‘practices that aim to identify a real or potential alcohol problem and motivate an individual to do something about it’* [33]. BI is intended as secondary prevention, i.e. for people not actively seeking treatment for alcohol problems, but who may be in the process of developing such problems. The opportunistic approach of BI stems from the knowledge that people with alcohol problems rarely seek formal treatment [34]. The application of BI has quite naturally come to focus on delivery by physicians or nurses in primary care, a setting where many people seek treatment for somatic conditions associated with excessive alcohol consumption. The content of BI varies; usually current alcohol consumption is screened, after which some form of advice is offered on how to quit or cut down. Sometimes BI can contain a form of ‘condensed CBT’, for example tips on coping skills. Usually, controlled drinking rather than complete abstinence is promoted. However, the brevity of the intervention, usually one or a few sessions, is central to its concept [35]. The first trial of a BI was conducted in an emergency ward in the late 1950’s, and showed that simple advice from a doctor or nurse significantly increased the chance of patients in inpatient treatment seeking outpatient treatment after acquittal [36]. Despite the success of this early study, research on brief interventions did not take off until the 1980’s, when a series of studies were conducted sparking a research agenda that has moved from efficacy to pragmatic trials and large scale implementation programs [37-40]. There is evidence that BI can be as effective as more extended treatments, at least in some contexts [24, 41]. A large body of evidence supports the efficacy of BI in primary care [42], while evidence of its efficacy in other contexts is scarce [41]. A related tradition is that of motivational interviewing (MI), a brief counselling method that intends, by way of different techniques and principles, to evoke the individual’s commitment to changing a problematic behavior [43]. A standardized form of MI is Motivational Enhancement Therapy (MET), which has been found to be effective both in clinical and general populations [24].

1.4.4 Pharmacological treatment

There are currently three available evidence-based pharmacological treatments; The first drug to be used specifically for alcohol problems, disulfiram, is intended as a deterrent for the user from alcohol use, due to the adverse effects it produces in combination with alcohol such as nausea and dizziness. It has been shown to render small short-term effects, in particular when administered under supervision [44]. There are also two pharmacological “anti-craving”

drugs available, Acamprosate [45] and Naltrexone [46], which have been shown to render modest effect sizes [47, 48].

1.4.5 General findings about treatment effects in alcohol treatment

Although a range of different treatment options exists for people with AUD with different theoretical frameworks, rationales and levels of intensity, several large-scale trials have failed to find differential effects when comparing different psychological treatments as well as when comparing pharmacological and psychological treatments [49-52]. A meta-analysis, correcting for allegiance among researchers, has confirmed these findings among psychological treatments (see Figure 2) [53]. Importantly, more intensive clinical treatments, such as RP or TSF, are not necessarily more effective than less intensive treatments such as BI or MI [41]. Thus, intensity of the treatment does not seem to be related to outcome. Analogous to the infamous ‘dodo bird’ debate on psychotherapy and ‘common factors’ [54], these results have generated a scientific discussion about whether identifying the active ingredients of psychological treatment for alcohol problems is a more worthwhile endeavor than focusing on evaluating different treatment rationales [55-57].

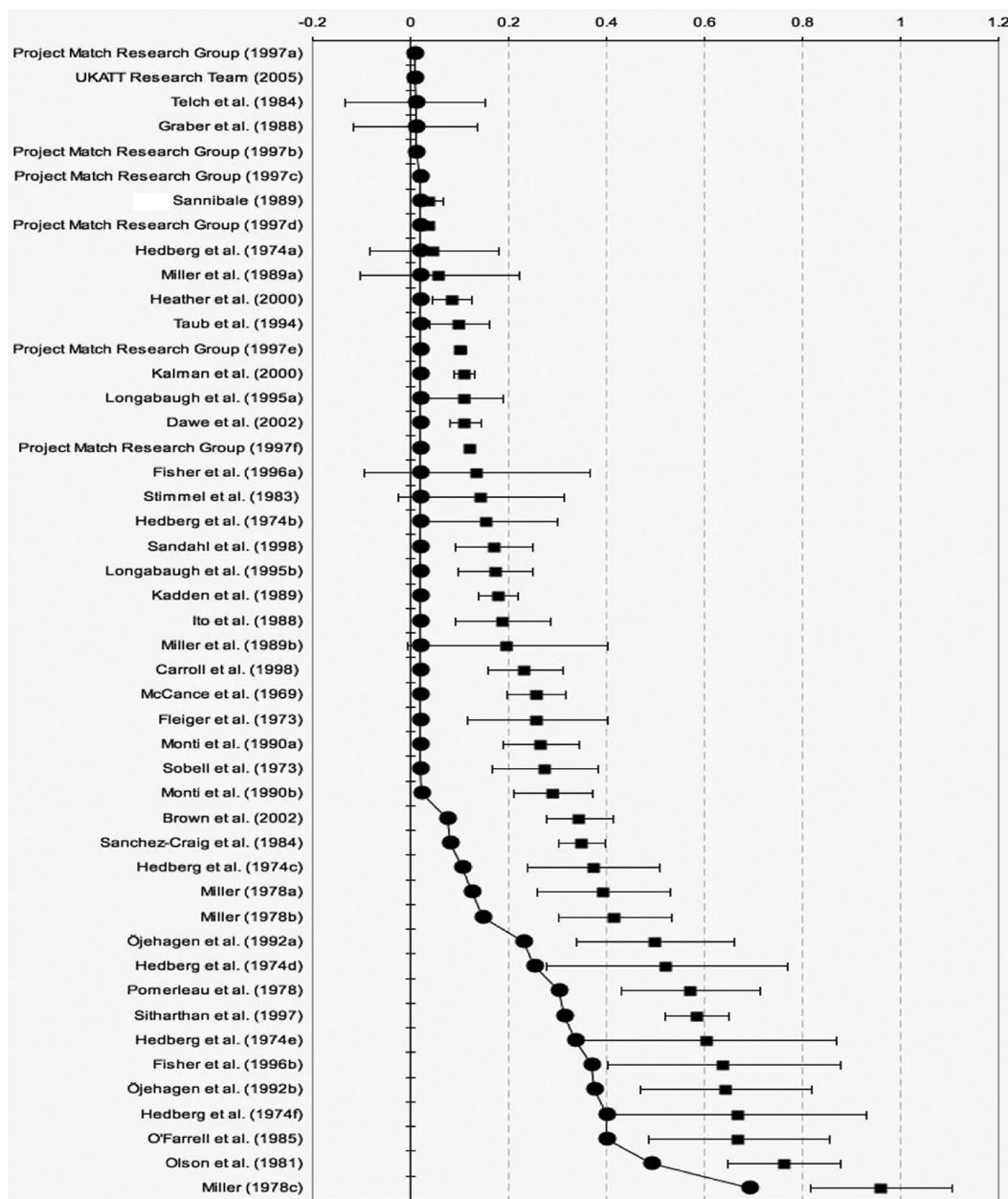


Figure 2. Comparisons of different alcohol treatments. Squares indicate actual differential effect size (Cohen's d), ovals indicate absolute value of each differential effect size corrected for allegiance. Wampold et al 2008. Reprinted with permission from American Psychological Association [53]

1.4.6 What predicts treatment effect in alcohol treatment?

Successfully identifying predictors of treatment outcome has proven to be a somewhat elusive quest. Predictors that are significant in one study are not always significant in subsequent studies, and sometimes the direction of prediction is reversed [58]. A literature review on predictors of alcohol treatment outcome was published in 1977. This review concluded that although there were no consistently significant predictors, two demographic factors (being employed and being married) and one treatment history factor (previous contact with Alcoholics Anonymous) were consistently found to be positive predictors in the majority of studies [59]. The only systematic review of predictors in alcohol treatment was published in 2009. This review suggested that a low degree of psychiatric comorbidity

and four alcohol-related factors (low degree of dependence severity, high alcohol-related self-efficacy, high motivation and having abstinence as a treatment goal) were the most consistent positive predictors [60].

1.5 INTERNET TREATMENT

1.5.1 Internet interventions – clinical and public health approaches

Internet interventions have by now been studied for over 20 years, and there is a large body of evidence supporting its relevance and effectiveness. There are two different traditions within the field of internet interventions [61], that largely echo the division of the “two worlds of alcohol problems” previously mentioned. First, there is a clinical tradition that sees internet interventions primarily as a development and extension of clinical alternatives aside regular face-to-face therapy [62, 63]. In these interventions (often referred to as ICBT), manuals are quite extensive akin to the bibliotherapy tradition within CBT, and there is often a therapist guiding the user through the intervention. Further, diagnostic assessments are largely a prerequisite, as clinical generalizations are essential [64]. Secondly, there is a public health tradition that sees internet interventions as an avenue for secondary prevention, with the potential to attract people in the general population who may not yet realize that they have a problem, or who for some reason are reluctant to seek help within the health care system. In this later tradition, the texts are briefer, diagnostic assessments are not relevant as the interventions are not intended to be used in clinic, and therapists are not involved in the delivery [61].

1.5.2 Advantages of internet interventions

Anonymity is often heralded as a central argument for internet interventions, but one can distinguish between different forms of anonymity; it can mean complete anonymity, in the sense that the user registers no personal information or minimal such information to get access to the intervention. This form of anonymity is more commonly stressed in the public health tradition. It can also refer to physical anonymity, in the sense that the user does not have to visit a local clinic to access the intervention, and risk being seen there by other members of the community. Other commonly mentioned advantages of Internet interventions are that they are accessible anytime and that they are geographically boundless. Using the Internet may also increase access to evidence based treatment for a larger number of people, and also be cost effective in terms of less therapist time [65]. Table 2 summarizes commonly mentioned advantages of internet interventions.

Table 2. Commonly mentioned advantages of internet interventions

<p>For the user</p> <ul style="list-style-type: none">• Complete anonymity - “being invisible”, not having to register or give out your name• Physical anonymity - not having to physically visit a treatment center and risk being seen by others in the community <p>For health care</p> <ul style="list-style-type: none">• Cost-effectiveness - being able to help more patients at a low cost• Accessibility - overcoming geographical boundaries for people who live in remote areas• Evidence-based treatment – consistent treatment delivery, avoiding ‘therapist drift’

1.5.3 Using the Internet to help people with alcohol problems

Because it is well-known that the vast majority of people with alcohol problems never seek treatment [34], there has been great enthusiasm among public health researchers about the possibilities of Internet interventions for alcohol problems [66]. It has been proposed that the Internet could be an attractive alternative for the large group of problem drinkers in the general population who are reluctant to seek treatment, mainly due to the anonymity provided on the Internet which may circumvent the stigma often reported as the major obstacle to seeking help in clinical settings [67]. The anonymity aspect seems to be more frequently stressed in the alcohol internet interventions literature [65], while accessibility and cost-effectiveness is more commonly referred to in the depression and anxiety internet interventions literature [62].

Most internet interventions for alcohol problems fall into one of two categories: *electronic Screening and Brief Interventions* (eSBIs) or CBT programs.

eSBIs

eSBI, the most common Internet intervention for alcohol problems [65], is a form of electronically delivered BI typically taking no more than 10-15 minutes to complete. These interventions are based on the same theoretical framework as BI [68], and consist of asking participants a short series of questions about their drinking and then providing them automatic personalized and normative feedback based on the answers given. Often, the participant is informed about their individual risk of developing alcohol-related problems and how their alcohol consumption compares to norm groups. Participants are then given some standard tips about how to reduce their alcohol consumption. As with BI, eSBIs are primarily considered secondary prevention i.e intended for those who are in the process of developing problems, and controlled drinking rather than abstinence is usually considered the goal. The

vast majority of studies on eSBIs have targeted college students, a group known for having high levels of binge drinking. In the US, two out of five college students are heavy drinkers, defined as having had 5 or more drinks during the last two weeks [69]. Systematic reviews on eSBIs used in college drinking populations have suggested that these interventions can render small reductions in both frequency and quantity of alcohol consumption [70-72]. However, the evidence here is mixed. Other reviews have found no significant differences between intervention and control groups among college students [73]. eSBIs have also been studied in the general public, with participants being recruited online or via ads in the media [74]. A systematic review of effects of eSBIs in the general public, where studies on college students were excluded, showed that effect sizes were in the small-to-moderate range [75].

Cognitive behavioral therapy programs

Aside from eSBIs, a number of CBT programs for alcohol problems have been developed and tested. These interventions are usually intended to be used for several consecutive weeks, and typically consist of 6-8 modules covering the main pillars of relapse prevention [76]; identifying risk situations, teaching coping skills and dealing with relapses. Examples of such interventions are DownYourDrink, developed and tested in the UK [77], MinderDrinken, developed and tested in Holland [77, 78] and Alkoholhjälpen developed and tested in Sweden [79]. No systematic reviews have been published looking specifically at CBT programs.

Comparisons of eSBIs and cognitive behavioral treatment programs

Although no systematic reviews have looked specifically at CBT programs, two meta-analyses have performed sub-analyses on type of intervention (eSBI or CBT program). The first of these found that CBT programs rendered a higher effect size ($g=0.61$) compared to eSBIs ($g=0.27$) [80], but the subsequent systematic review found no significant differences [75].

For a more elaborate overview of the effectiveness of alcohol internet interventions, see a recent review of systematic reviews [81] (also included in this thesis as Appendix).

1.5.4 The issue of therapist guidance

There is evidence suggesting that therapist guidance augments the effects of internet treatment [82], and that it can even be as effective as face-to-face treatment when it comes to psychiatric disorders such as depression and anxiety, and behavioral medicine conditions such as tinnitus and sleep difficulties [83]. This evidence has led to therapist-guided internet treatment being implemented within routine health care in countries such as Sweden [64],

Norway [84], Canada [85] and Australia [86]. However, only one review has addressed the significance of therapist guidance in interventions about alcohol problems [75]. In this review, no significant differences were found between internet interventions with and without guidance. However, the authors of the review conclude that there is still a shortage of studies on interventions with guidance and that more studies on this topic are warranted.

Only two studies investigating a full CBT program with therapist guidance for alcohol problems have been published. In the first study, one group had access to a CBT program and was also given 8 chat sessions with a therapist, one group was only offered the CBT program without therapist guidance and a third group was put on a waiting list. The results showed that there was a significant difference in alcohol consumption favoring the guidance group over the unguided group 6 months after randomization but not immediately after treatment. The differential effect size was moderate [87]. In the other study, one group was given access to a CBT program with synchronous messages from a therapist and one group was put on a waiting list. After treatment, the participants in the therapist group had reduced their consumption significantly compared to the waiting list control group. The differential effect size was large [88].

Neither of these two studies included proper diagnostic assessments of participants, but relied instead on self-report questionnaires and reports of recent alcohol consumption when assessing severity of alcohol problems. The most recent systematic review published noted the lack of studies that include therapist guidance and diagnostic assessments in internet treatment for alcohol problems [89].

1.5.5 What predicts outcome in alcohol internet interventions?

Two studies have investigated predictors of outcome in internet interventions for alcohol problems. Riper and colleagues found that female gender and a higher level of education predicted positive treatment outcomes 12 months after randomization [90]. Blankers and colleagues found that having a shared living situation and high interpersonal sensitivity predicted positive outcome six months after randomization [91]. Outcome has not been the only focus in prediction analyses. As internet interventions generally suffer from high attrition rates [92], several studies have investigated predictors of attrition (or its opposite – retention). Postel and colleagues found that higher treatment readiness, higher age and lower baseline consumption predicted retention [93] and Murray and colleagues found that higher age, being of female gender, having a university degree and not having children were related to retention [94].

1.6 RESEARCH QUESTIONS

Before this doctoral project started, the internet interventions for alcohol problems studied had mainly been aimed at college students or a less severe segment of the general population with alcohol problems [89]. There were no internet treatments that had been developed specifically for individuals with an AUD, i.e. a high level of severity. Further, there was still a knowledge gap concerning the relevance of therapist guidance in alcohol internet interventions. First, the question of whether therapist guidance has an additive effect was not clear, as the only study on a CBT program with and without therapist guidance showed a medium between-group effect size six months after randomization, while a meta-analysis showed no differences between guided and unguided interventions (the guided interventions included in this review were almost all eSBIs delivered within a primary care context). Second, no alcohol internet studies had included proper diagnostic assessments with participants, hampering generalizations to the clinical population. Thirdly, little is still known about which participants benefit most from this form of treatment. The general aim of this thesis was therefore to develop, test and evaluate therapist-guided internet treatment for people with a diagnosed AUD.

Specific research questions were:

Study I: Is a CBT program more effective in reducing alcohol consumption with therapist guidance than without for individuals with alcohol problems?

Study II: Is high-intensity therapist-guided internet treatment an acceptable, feasible and potentially effective treatment for individuals with AUD?

Study III: Is high-intensity therapist-guided internet treatment more effective than low-intensity non-guided treatment, and are both of these more effective than a wait list control group?

Study IV: What factors predict who benefits from internet-based treatment for AUD?

2. SUMMARY OF THE EMPIRICAL STUDIES

2.1 THE TREATMENT PROGRAMS

2.1.1 eChange (studies I and III)

This treatment program was a translation and adaptation of a program originally developed by Trimbos-Instituut in Holland, subsequently evaluated in an RCT [87]. The content of the program is based on traditional relapse prevention [76], i.e. analyzing risk situations and developing skills to cope with these situations (see Table 4 for module content). Each module consists of a text (equaling about 1-2 pages) with homework assignments and a worksheet. The program has a built-in message system where user and therapist can interact either synchronously or asynchronously. In study I, the program was delivered through a technical platform used within Stockholm Dependency Centre. In study III, the treatment was delivered through the technical platform within the Internet Psychiatry Clinic, a routine care clinic in Stockholm, Sweden since 2008. In the later study, a finishing module (Module 9) was added to eChange to make the comparison to adjust the time period to the other treatment (ePlus).

Table 4. Overview of treatment modules in eChange (Study I, III and IV)

Module	Purpose of module	Homework assignment
Module 1 Pros and cons of drinking	To help the participant reflect about pros and cons of drinking To inform about abstinence and how to deal with it (only Study III)	- Make a decisional balance
Module 2 Goal setting	To set a goal for alcohol consumption during the treatment	- Set an alcohol consumption goal during treatment (abstinence or moderate drinking) - Explore and formulate core values in life
Module 3 Self-control skills	To learn skills to control certain situations	- Make notes on how and when to practice these skills
Module 4 Analyzing risk situations	To learn what risk situations are, and how to analyze them	- Complete a behavioral analysis of one's own risk situations
Module 5 Dealing with craving	To learn about craving and ways of dealing with it	- Make notes on how to deal with craving: Who can you call when you feel craving? What can you do to distract yourself?
Module 6 Dealing with feelings about alcohol	To learn about what feelings commonly occur among people who have just begun changing their alcohol habits	- Make notes on which feelings about alcohol occur most frequently - Make a situational analysis and choose which specific coping strategies to use
Module 7 Dealing with social situations	To learn about why it can be hard to say no to alcohol in social situations	- Practice saying no with a friend or in front of a mirror - Write down answers to specific situations presented in the text
Module 8 Relapse plan	To learn about the concept of relapse, and predict situations that could make it harder to resist drinking	- Formulate a relapse plan
Module 9 Finishing module (study III)	To summarize the treatment and look towards the future	- Review the initial alcohol consumption goal formulated in Module 2 - Set goals for the future, after treatment

2.1.2 ePlus (studies II, III and IV)

This treatment program was developed by the research group after data collection for study I was complete. The purpose was to develop a more extended program than the previous one, specifically intended to be used with therapist guidance, and similar in length and intensity to other treatment programs implemented at the Internet Psychiatry Clinic in Stockholm [64]. The content was based on relapse prevention [76], with additional inspiration from other psychotherapeutic traditions such as cognitive therapy [95], Motivational Interviewing [43] and Acceptance and Commitment Therapy [96] (see Table 5 for module content). Each module consisted of a text about the module theme (equaling about 3-4 pages) and a worksheet with questions pertaining to the text, or space where the participant could report to the therapist about homework. Most modules also contained a film-clip that served to illustrate the module theme (for example “What is craving?”). In addition to the modules and worksheets, the program had a built-in message system where the participant and the therapist could interact asynchronously. The treatment was delivered through the technical platform within the Internet Psychiatry Clinic.

Table 5. Overview of treatment modules in ePlus (Study II, III and IV)

Module	Purpose of module	Homework assignment
Module 1 Alcohol Education	To learn about the effects of alcohol on body and mind and about tolerance and abstinence	- Questions pertaining to the text
Module 2 Pros and cons of drinking	To help the participant reflect about pros and cons of drinking	- Make a decisional balance
Module 3 Goals and values	To learn the difference between goals and values, and why these are important to establish at the beginning of treatment	- Set an alcohol consumption goal during treatment (abstinence/moderate drinking) - Explore/formulate core values in life
Module 4 Analyzing risk situations	To learn what risk situations are, and how to analyze them	- Complete a behavioral analysis of one's own risk situations
Module 5 Dealing with craving	To learn about craving and ways of dealing with it	- Make notes on how to deal with craving: Who can you call when you feel craving? What can you do to distract yourself?
Module 6 Dealing with thoughts about alcohol	To learn about what thoughts commonly occur among people who have just begun changing their alcohol habits	- Make notes on which thoughts about alcohol occur most frequently - Make a situational analysis and choose which specific coping strategies to use when the thoughts appear
Module 7 Dealing with social situations	To learn about why it can be hard to say no to alcohol in social situations	- Practice saying no with a friend or in front of a mirror - Write down answers to specific situations presented in the text
Module 8 Finding other activities	To learn about the "reward trap" (using alcohol as a reward), and the importance of finding other meaningful activities	- List activities to engage in that do not include alcohol - Draw up a time schedule for doing them
Module 9 Problem solving	To learn about stress, how it is sometimes associated with alcohol use, and about problem solving as a technique	- To, step by step, apply problem solving in at least one situation
Module 10 Negative thoughts and interpretation traps	To learn about negative thoughts and about coping strategies to deal with them, such as cognitive restructuring and other cognitive therapy skills	- Complete a behavioral analysis of negative thoughts and challenging these thoughts
Module 11 Seemingly irrelevant decisions	To learn about the importance of identifying small, seemingly irrelevant decisions that could lead to drinking	- Make notes on a situation where irrelevant decisions were involved in one's drinking
Module 12 Relapse plan	To learn about the concept of relapse, and predict situations that could make it harder to resist drinking	- Formulate a relapse plan
Module 13 Life without alcohol problems	To summarize the treatment and look towards the future	- Review the initial alcohol consumption goal formulated in Module 2 - Set goals for the future
Optional Module About relapses and setbacks	To reflect on the situation in which the relapse/setback occurred (for participants reporting a setback during treatment to the therapist)	- Make a situational analysis and prepare for how to cope with a similar future situation



Figure 4. Screenshot of eChange in the platform used in study I

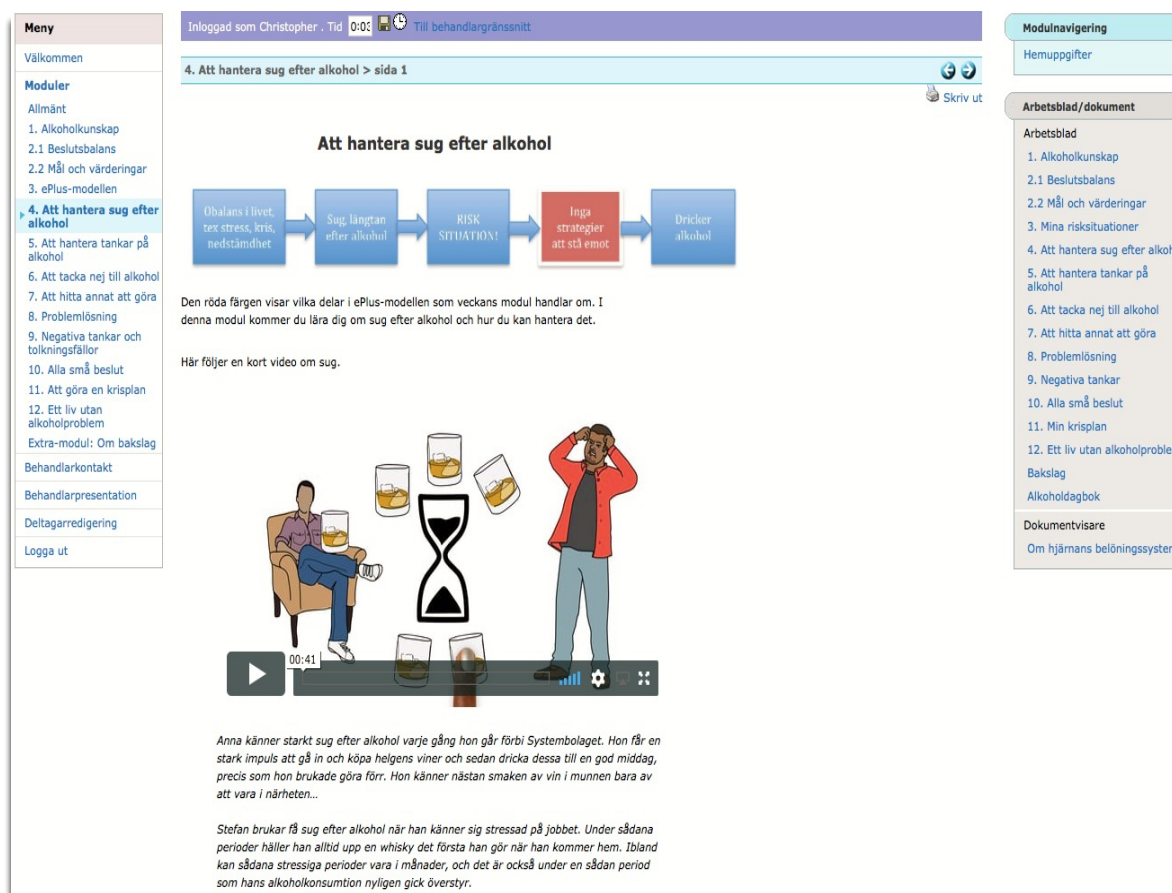


Figure 5. Screenshot of ePlus in the platform used in studies II, III and IV

2.2 MEASURES

Primary outcome

The primary outcome in all studies was alcohol consumption as measured with the Time Line Follow Back (TLFB), a calendar method where the participant reports number of drinks consumed during a given time frame [97, 98]. In all studies, the given time frame was the preceding week. In study II and III, heavy drinking days (HDD), defined as ≥ 4 drinks per day for women/ ≥ 5 drinks per day for men, was also aggregated. In study IV, the outcome “low-risk drinking” was calculated from TLFB, and was defined as ≤ 9 drinks preceding week and no HDD for women and ≤ 14 drinks preceding week and no HDD for men.

Secondary outcomes

Several other secondary outcome measures were used in these studies but are not presented here, see relevant scientific papers in the thesis.

2.3 THE STUDIES

Table 6. Characteristics of the three outcome studies

	Study I	Study II	Study III
Study aim	To evaluate effects of eChange with and without guidance	To evaluate acceptability and preliminary effects of high-intensity internet treatment (ePlus with guidance)	To evaluate effects of high-intensity (ePlus with guidance) vs low-intensity (eChange with no guidance) internet treatment and a wait list control group
Sample source	Visitors to self-help site	Visitors to self-help site	Internet help-seekers
Design	RCT, three groups	Open study, one group	RCT, three groups
Assessment points	Screening-Post	Screening - Pre-treatment - Mid1 - Mid2 – Post - Three-month Follow-up	Screening - Pre-treatment - Mid1 - Mid2 – Post - Three-month Follow-up
Sample size	80	13	166
Female	60%	69%	51%
Age	42.3	49.5	53.2

Study I

Aim

The aim of study I was to evaluate the effects of eChange with and without guidance for people with problematic alcohol use.

Methods

The eight-module internet-based program eChange was tested among 80 participants with an Alcohol Use Disorders Identification Test (AUDIT) score of ≥ 6 for women and ≥ 8 for men, recruited online from the open access website www.alkoholhjalpen.se and then randomized into three different groups. All groups were offered eChange, but participants in two of the three groups also received therapist guidance. One of the guidance groups was

given a choice between receiving guidance via asynchronous text messages or via synchronous text-based chat, while the other guidance group received guidance via asynchronous text messages only. Participant data were collected at screening and immediately post-treatment.

Results

In the choice group, 65% (13 of 20 participants) chose guidance via asynchronous text messages. Participants in the therapist-guided group completed 58% of the module work sheets and the non-guided group completed 21%. Attrition was 39% at post-treatment (10 weeks). An intention-to-treat (ITT) analysis showed that participants in the two guidance groups (choice and messages) combined reported significantly lower past week alcohol consumption compared to the group without guidance; $m=10.8$ drinks ($sd=12.1$) versus $m=22.6$ drinks ($sd=18.4$); $p \leq 0.001$; Cohen's $d = 0.77$. A higher proportion of participants in the guidance groups said that they would recommend the treatment to a friend compared to the group without guidance (87% vs 47%).

Methodological considerations

Attrition was quite large in this study, and we handled this statistically by performing multiple imputation. Imputation is always a second-hand option in analyses and constitutes a limitation to any interpretation of data. Further, with an attrition of 20% in the combined guidance group and 52.5% in the self-help group, differential attrition was high. Differential attrition is a threat to internal validity as it may be related to for example perceived efficacy or tolerability of the interventions. Differences in attrition in this study might have also been a result of the fact that participants were informed at recruitment that two groups would receive guidance from a therapist and one group would not. Those who at recruitment were interested in receiving such guidance but were randomized to self-help, may have discontinued the intervention for that very reason. Another limitation is the absence of a parallel wait-list control group. Any causal effect of the intervention beyond the added effects of guidance was thus not possible to assess. It is possible that the reductions in alcohol consumption observed in either of the groups would have been similar in a wait-list control group. Furthermore, as we only included a follow-up at post-treatment, we cannot say whether the changes observed were temporary or long-term.

Study II

Aim

The aim of study II was to evaluate the feasibility and preliminary effects of ePlus for people with alcohol use disorder.

Methods

The 13-module internet-based program ePlus was tested among thirteen participants recruited through the alcohol self-help web site www.alkoholhjalpen.se and, after initial internet screening, diagnostically assessed by telephone. Inclusion criteria were 1) having an AUDIT score of ≥ 14 for women and ≥ 16 for men and 3) having ≥ 2 positive AUD criteria in a diagnostic telephone assessment. Eligible participants were offered access to ePlus with therapist guidance.

Results

According to the diagnostic assessments, 62% of participants had a severe AUD (more than 5 positive criteria). Participants completed 59% of the module work sheets. No attrition occurred in this study. Significant reductions in alcohol consumption were found post-treatment ($m=10.3$ drinks; $sd=10.8$; $p \leq 0.001$; Cohen's $d = 1.00$) and at the three-month follow-up ($m=5.1$ drinks; $sd=7.9$; $p \leq 0.001$; Cohen's $d = 1.20$).

Methodological considerations

This was a pilot study intended to test feasibility and preliminary effects, as preparation for a proper randomized trial. The sample size was small, and obviously limits any conclusions about effects. A limitation inherent in the design is the lack of control group. Use of a control group is always necessary to establish causality, as changes observed among participants could be due to the treatment but could also be due to the passage of time or other co-occurring factors. A control group might even be particularly important when attempting to establish efficacy of interventions for alcohol problems, given that many people seem to be able to stop or reduce their drinking on their own without any or little help. Further, the average alcohol consumption at screening was 23.1 drinks during preceding week among participants, which is low compared to most studies of this kind. As alcohol consumption during the preceding week was not an inclusion criterion, three participants had a very low or no alcohol consumption at screening. The inclusion of these participants meant that there was little or no room for them to change in the primary outcome. It might also indicate that some participants in this trial may have had a lower severity of problems compared to our other studies.

Study III

Aim

The aim of study III was to compare alcohol outcomes between ePlus (therapist-guided high-intensity internet treatment), eChange (non-guided low-intensity internet treatment) and a waitlist control group, for people with AUD. We also wanted to study potential negative effects of treatment [99].

Methods

In this study, 166 participants were recruited online through Google Adwords, information posts on Facebook and the health app Remente. Inclusion criteria were 1) having a past week alcohol consumption of ≥ 11 standard drinks for women and ≥ 14 standard drinks for men, 2) having an AUDIT score of ≥ 14 for women and ≥ 16 for men and 3) having ≥ 2 positive AUD criteria in a diagnostic telephone assessment. Included participants were randomized to three groups; 1) ePlus (high-intensity treatment) 2) eChange (low-intensity treatment) and 3) a wait-list control group.

Results

According to the diagnostic interviews, 75% had a severe AUD (more than 5 positive criteria). Participants in ePlus and eChange completed 65% and 66% of the module work sheets respectively. Negative effects were reported by 8% in the high-intensity group, and 7% in the low-intensity group. Attrition was 13% at post-treatment and 24% at the three-month follow-up. An ITT analysis showed that participants in ePlus consumed significantly fewer standard drinks compared to WLC (-10.11 drinks per week, $p \leq 0.01$, Cohen's $d=0.74$) and significantly fewer HDD compared to both WLC (-1.30 HDD/week, $p \leq 0.01$, Cohen's $d=0.79$) and eChange (-0.61 HDD/week, $p \leq 0.05$, Cohen's $d=0.35$). At the three-month follow up, no significant differences in alcohol consumption (standard drinks or HDD) were observed between ePlus and eChange.

Methodological considerations

To our knowledge, this is the first time that a thorough diagnostic assessment of AUD was used as an inclusion criterion in a randomized trial of an internet treatment focused on reducing alcohol consumption, at least among studies conducted outside of the clinical context. This makes generalizations to the clinical population more valid than previously conducted studies on internet interventions for alcohol problems. Although our recruitment method enables generalization to people with AUD recruited over the internet, this group may not be representative for the population seen in a clinic. Unlike previous studies, we included a wait-list control-group. However, wait-lists are not an optimal form of control

group, as participants may ‘postpone’ any changes, while awaiting the intervention, thereby inflating treatment effects [100]. An attention control, such as a discussion forum or supportive online counselling, would perhaps have been preferable. A limitation to interpretation of follow-up results is that the control group received their treatment after 12 weeks. Including a follow-up of the control group at three months would have facilitated evaluation of longer-term treatment effects in relation to the waitlist condition. However, the waitlist control group was offered treatment three months after recruitment for ethical reasons. Lastly, we cannot say anything about long-term effects. One- and two-year follow-ups including diagnostic telephone interviews, still to be conducted, may show changes over the longer term in drinking levels.

Study IV

Aims

The aim of study IV was to investigate predictors of 1) adherence and 2) low-risk drinking in internet treatment for people with AUD.

Methods

Data were obtained from study III, and participants in the treatment groups were combined into one. Twenty-seven candidate predictors were then run in univariate logistic regressions with two dependent outcomes: 1) adherence (defined as having completed more than 60% of module work sheets) and 2) “low-risk drinking” at post-treatment and three-month follow-up, as dependent outcomes. Significant predictors were then entered hierarchically through domain-specific logistic regressions. In the final analysis, predictors still showing significant effects were run in multiple logistic regressions.

Results

One factor emerged as predicting adherence to treatment; experiencing the treatment as highly credible. Four factors emerged as significantly predicting low-risk drinking post-treatment: early abstinence, being of male gender and two personality factors, having a low degree of antagonism and a high degree of alexithymia. Only one of the significant predictors – pre-treatment abstinence – was also significant in the three-month follow-up multiple regression.

Methodological considerations

In this study, we combined participants from the two groups in order to increase power. However, this may have introduced problems in the interpretations of results, as participants may have reacted differently to the two treatments. A solution to this would

have been to investigate treatment as a moderator, but this would have decreased power and reduced chances of finding predictors overall. Another issue that merits concern is the explorative approach, which increased the risk for mass significance. As this was an exploratory study with almost 30 potential predictors and three outcome variables, a large number of significance tests were performed, raising the possibility of chance findings. Furthermore, although we collapsed the two treatment groups into one thus increasing power, the sample is still relatively small. The results should therefore be interpreted with caution.

Table 7. Summary of alcohol consumption outcomes preceding week in studies I-III

Study	Measure	Group	Screening	Post	3FU	Within-group effect size	
			M (sd)	M (sd)	M (sd)	Screening-Post	Screening-3FU
I	Standard drinks	Guidance	28.9 (18.2)	10.8 (12.2)	n/a	1.23	n/a
		No guidance	29.8 (15.4)	22.6 (18.4)	n/a	0.43	n/a
II	Standard drinks	Guidance	23.4 (15.1)	10.3 (10.8)	5.1 (7.9)	1.00	1.20
	Heavy drinking days		3.5 (2.5)	1.5 (2.2)	0.7 (1.7)	0.82	1.30
III	Standard drinks	High intensity	34.2 (17.3)	10.7 (11.8)	17.4 (16.0)	1.59	0.95
		Low intensity	33.9 (16.4)	14.8 (15.4)	14.8 (15.9)	1.23	1.21
		Wait list	32.0 (16.6)	20.8 (19.2)	n/a	0.64	n/a
	Heavy drinking days	High intensity	4.0 (2.0)	1.1 (1.4)	1.9 (2.0)	1.69	1.06
		Low intensity	4.0 (2.1)	1.7 (2.0)	1.7 (2.1)	1.09	1.06
		Wait list	3.4 (2.0)	2.4 (2.3)	n/a	0.45	n/a

2.4 ETHICAL CONSIDERATIONS

The ethical considerations in this project mostly concerned the welfare and well-being of the participants, and of those who wished to participate but were for some reason excluded. It was important that the research group could provide practical support to participants who, for example, may have felt worse during treatment due to abstinence symptoms. In studies II and III, participants were informed about what abstinence is and what risks it entails, what signs to look for and when they should consider seeking help for detoxification. Furthermore, in the therapist guidance group in study III, participants were obliged to fill out Montgomery Asberg Depression Rating Scale on a weekly basis. If a high score on the item reflecting thoughts about suicide or self-harm, was reported, the participant was ‘flagged’ on the platform. The therapist was then immediately informed about this when logging in, and was able to take some form of action. Another important ethical aspect was for the research group to function as mediators of referral to other treatment if such was deemed necessary for participants for whom the Internet treatment was not enough. If someone in internet treatment for example felt that they were in need of some other form of help, or if they were initially

excluded, then the research group would offer assistance in helping the participant establish a contact with relevant health care providers.

3. GENERAL DISCUSSION

3.1 Primary findings

The overarching aim of this thesis was to investigate feasibility, acceptability and efficacy of therapist-guided internet treatment for individuals with AUD. Three separate trials were conducted; one pilot study and two RCTs.

3.1.1 Differences between guided and unguided internet treatment in studies I- III

Taken together, results from the pilot study and the two RCTs suggest that therapist-guided internet treatment has a small to medium effect on alcohol consumption as measured immediately after treatment compared to the unguided groups in these studies, but this effect may not last beyond treatment completion.

Briefly stated, results from the three trials show that:

- At post-treatment, the therapist-guided groups in studies I and III had reduced their alcohol consumption to a significantly greater degree than the unguided groups (study I: drinks; study III: heavy drinking days)
- Only studies II and III included a three-month follow-up
- Study II showed a further decline in alcohol consumption for the (guided) high-intensity group at the three-month follow-up, but this study was small and did not include a comparison group
- In study III, the (guided) high-intensity group showed a small increase in consumption (drinks and heavy drinking days) at three-month follow-up compared to post-treatment, while the (unguided) low-intensity group reported virtually the same level of alcohol consumption as at post-treatment

How come participants in the high-intensity group in study III increased their alcohol consumption between post-treatment and the three-month follow-up while the low-intensity group remained on the same level? A speculation is that participants in the high-intensity group were more easily able to reduce their alcohol consumption initially with the help of guidance and support from the therapist but that this resulted in an increased likelihood of relapse when the therapist guidance eventually ended, while the low-intensity group, receiving no therapist guidance, had a slightly slower reduction curve during and after treatment but were nevertheless able to maintain this reduction on their own. Although the results are a noteworthy observation, it should be stressed that differences between the treatment groups at the three-month follow-up were quite small and non-significant. Also, these results are the exact opposite of the previously mentioned study conducted in Holland,

where significant differences in favor of guided internet treatment instead were found at the three-month follow-up, but not post-treatment [87].

3.1.2 Differences between the unguided groups in studies I and III

Effect sizes are a useful tool when attempting to compare results across studies. Some observations stand out when comparing effect sizes in standard drinks between the two unguided groups in study I and III:

- Between-group effect sizes between the guided and unguided groups were more than twice as large in study I compared to study III (0.77 vs 0.30)
- The within-group effect size for the unguided groups was moderate in study I (0.43) and large in study III (1.23), even though the groups received the exact same treatment content (eChange)
- The unguided group in study III had the same within-group effect size as the guided group in study I (1.23)
- The within-group effect size for the wait-list control-group in study III was higher than the within-group effect size for the unguided group in Study I (0.64 vs 0.43)

Further, there were large differences in adherence and attrition in the unguided groups. In the unguided group in Study I, participants completed a mean of 1.5 modules (21%) while participants in the unguided group in Study III completed a mean of 5.9 modules (66%), roughly the same percentage as those in the guided group in the same study. The amount of attrition in the unguided group in Study I was 47.5% and in Study III it was 14%.

What can these large differences between two unguided groups receiving the exact same treatment be attributed to? Although there are several possible explanations, the different inclusion processes in the studies is the most likely. In study III, all potential participants underwent a diagnostic assessment interview with a psychologist, usually about 45 minutes long. The purpose of this interview was to only include individuals with a diagnosed AUD. However, assessment has been shown to also have a therapeutic effect, a phenomenon commonly referred to in the alcohol treatment literature as assessment reactivity [101]. It has for example been shown that comprehensiveness of assessment is directly related to subsequent engagement in treatment [102-104]. Likely, the comprehensive diagnostic assessment in Study III had a therapeutic effect on participants which perhaps promoted engagement that added to, or synergized with, the subsequent effect of the treatment. A less likely, but possible, explanation is that studies I and III had slightly different samples, due to differing inclusion criteria. In Study III we wanted to reach a population with more severe

alcohol problems. Therefore, a higher inclusion score on AUDIT was used, and in addition to this, participants also had to have at least two positive AUD criteria according to the diagnostic interview. However, despite these differences, the two instruments that were applied in both studies (TLFB and AUDIT) were comparable at screening, suggesting that participants in the studies had a similar severity of alcohol problems.

3.1.3 Is internet treatment for AUD acceptable and feasible?

The short answer is yes. In both studies II and III, a validated instrument of client satisfaction, CSQ-8, was used [105], and results indicated that treatment satisfaction was excellent. In study III, treatment satisfaction was significantly higher for the (guided) high-intensity group compared to the (non-guided) low-intensity group. Few participants expressed clear dismay with the treatment or other aspects of the study. Concerning feasibility in studies II and III, attrition was low and adherence to treatment (modules completed) was acceptable and similar to other internet treatments [106].

To illustrate participants' perception of the therapist guidance specifically, some quotes from telephone interviews in Study II are presented below:

- I had not expected the therapist contact to feel so personal. It was suddenly easier to reach someone than ever before! Without that contact I might as well just have gone to the library.
- I like writing, I didn't feel the need to talk. ... I wouldn't have been able to have face-to-face therapy, as my work situation is so irregular.
- If it would have been talk therapy, I would have dropped out. Here, it was I who decided the pace. When someone else demands an answer from you immediately (like in regular psychotherapy), you don't have time to think.
- When you write it down, you see it yourself. It's very frustrating. Talking... can be easier. When you write, it gives you more anxiety.
- People talk so much. It's nice to just be able to write down what's important.... I'm an inquisitive person, in a conversation I would have maybe asked too many questions.

3.1.4 Are there negative effects of internet treatment for AUD?

Whenever a new treatment is investigated, potential negative effects should be studied. Although this is standard when developing new pharmacological treatments, when it comes to psychological treatments it is still rare [107]. Regarding internet treatment, exploration of negative effects is even rarer, although it has received sizeable attention in recent years [99,

108]. In this thesis, negative effects were evaluated in two studies; In study II, negative effects were evaluated in post-treatment interviews; there was only one participant mentioning a negative effect, and this individual dropped out of treatment due stress and anxiety. In study III, negative effects were evaluated via an online questionnaire. Six individuals in the high-intensity group and five in the low-intensity group reported negative effects. The negative effects mostly consisted of disappointment with the progress made during treatment. In comparison to other types of internet treatment, this was similar both in prevalence and content [99].

3.1.5 Which individuals benefit most from internet treatment for AUD?

The purpose of Study IV was to investigate factors that might predict adherence and low-risk drinking among participants in Study III. We found that one factor predicted adherence: rating high credibility of treatment. Four factors predicted low-risk drinking post-treatment; pre-treatment abstinence, male gender and two personality variables. Of these, pre-treatment abstinence was the only factor predictive at both post-treatment and at the three-month follow-up. Although this result is purely associative and not causal, this result could imply that individuals should be encouraged to abstain from alcohol in the initial part of treatment. This is supported by recent research showing that early abstinence in treatment is associated with positive outcomes after treatment [109].

Another noteworthy finding was that men were significantly more likely to have a low-risk drinking post-treatment than women. This is in conflict with some literature that has found women to be more helped by treatment [60], but not with other [110]. The question of the impact of gender is further complicated by the fact that men and women usually have different cut-offs for inclusion and treatment response categorizations. This may lead to an underestimation of effects on women, as it will be harder for women to reduce their consumption to below the cut-off, than it will be for men [111]. In this study, the low-risk drinking variable was indeed created based on these cut-offs, and may thus have unintended consequences for the low-risk drinking outcome. By way of a sensitivity analysis looking at change scores (screening - post-treatment) instead of low-risk drinking as outcome, we assessed robustness of the finding that male gender was predictive of low-risk drinking. This analysis showed that men and women had made comparable quantitative reductions, implying that the treatment effect was similar among men and women. Although it is a matter of debate which of these two analyses is preferable, it can at least be argued that in future trials where different gender cut-offs are used to assess eligibility and/or generate treatment

outcome, gender differences may be explored further with appropriate sensitivity analyses to assess robustness of findings.

Two personality variables of the five-factor model were found to predict low-risk drinking; alexithymia (corresponding to the FFM factor openness) and antagonism (corresponding to the FFM factor agreeableness). Alexithymia denotes a difficulty in identifying and communicating feelings, and has been linked to AUD factors [112]. Concerning psychotherapy, it has been found to negatively predict outcomes following psychodynamic psychotherapy, but not following CBT. The second factor associated with outcome, low degree of antagonism, was unexpected, as this domain has not previously been associated with either alcohol problems [113] or with alcohol treatment outcomes [114, 115]. Although both alexithymia and antagonism were predictive of low-risk drinking, their predictive value occurred in opposite directions, which was unanticipated and somewhat confusing as these factors are theoretically similar and were highly correlated in our study ($r=0.414$, $p<0.0001$).

3.2 Strengths and limitations

There are several strengths to the studies included in this thesis that hopefully can serve to move the field forward. One strength already mentioned is that we targeted a more severely affected population, and used diagnostic interviews to achieve this. This increases generalizability to the AUD population, and hopefully paves the way for more clinically oriented research agendas on internet treatment for AUD. Another strength was that we had very low attrition in study III compared to many internet trials on alcohol problems. A third strength is that we investigated negative effects in studies II and III, which is still rare in internet trials.

Many limitations have been discussed separately for the four studies in the previous sections, but two additional limitations that the studies have in common are presented below.

The first limitation concerns outcomes. In most alcohol treatment studies, self-report of alcohol consumption is the primary outcome. Although such self-reports have been shown to be both valid and reliable, there is always the risk that such instruments introduce bias. People may not always accurately reflect their alcohol consumption, and this may be due to social desirability or cognitive misjudgments. Particularly when drinking is heavy, consumption may be underestimated [116]. This is a problem that is by no means specific to the studies included in this thesis, but rather reflects a common methodological limitation to

the field. A possible solution would be to verify self-reports with biological tests. Although valuable, such tests require a clinical infrastructure that the current studies did not have.

The second limitation concerns the design of studies I and III. The conceptualization of these two studies differed in one important aspect. In study I, therapist guidance was simply added to the same treatment program as the other group received (eChange). In study III, however, the treatment program differed across the two treatment groups (eChange and ePlus), creating a confound between guidance and program. Consequently, the results of the high-intensity group in study III may not (only) reflect the effect of therapist guidance, but may instead reflect effects of the treatment program, or these may have had a synergistic effect. Bearing this limitation in mind, our intent in this specific study was to conceptualize intensity, as this is a recurring concept in alcohol treatment, and the current design fitted that purpose.

3.3 Future directions

The results from Study III showed that participants in the guided group were able to reduce their alcohol consumption at post-treatment but that they then increased their consumption at the three-month follow-up, as opposed to the unguided group that remained on the same consumption level. These results raise important clinical questions relevant for future studies on therapist-guided internet treatment for AUD. Could therapist-guidance have an initial positive effect that is then reversed when the guidance disappears? Future studies would benefit from more closely studying the change processes involved in both guided and unguided internet treatment by way of qualitative interviews [117]. Questions that would be relevant to explore are: How is the therapist-guidance perceived by participants during versus after treatment? Are experiences unequivocally positive, or are there negative experiences when treatment is ended and the participant is left on his/her own? Such research could enable more definitive conclusions about what role, if any, therapist-guidance should have in the development of future digital treatment models for AUD. Indeed, the level of intensity or the timing of guidance may be more important factors than the guidance per se, as indicated by the apparent added benefit of the diagnostic assessment in Study III. Future studies could consequently aim to further dissect and optimize the therapist-guidance component, for example by examining guidance with different levels of intensity (guidance once a week, guidance on demand etc.) or guidance with different “timings” (guidance during the initial weeks of treatment, guidance after treatment completion/continuing care etc.).

Our aim with these studies was to reach a population with severe alcohol problems, similar to those found in clinics. Although participants in the studies were self-referred, and results are

not fully generalizable to a clinical population, about half of participants in study III stated that they had previously sought treatment for alcohol problems. Half of participants also reported having had alcohol problems for more than five years, and 75% of participants had a severe AUD according to the diagnostic assessments. Although we cannot from this generalize to a strict clinical population, as individuals found in clinics are often more afflicted by other problems than problem drinkers in the general population for example by being more likely to be divorced and unemployed [118], it at least shows that there are individuals with a long history of severe AUD and experience form treatment, who are willing, able and seem to be able to benefit from both high- and low intensity internet treatment.

Although most internet interventions on alcohol problems have had a public health approach, recent years have seen an upsurge in publications conducted in clinical settings; for example Kiluk and colleagues published an RCT on an unguided internet treatment for individuals with AUD as an add-on to treatment as usual with promising outcomes in terms of percent days abstinent [119], and Gustafson and colleagues conducted a study on a mobile app intended as continuing care, and found that, compared to treatment as usual, the app resulted in fewer risky drinking days [120]. Before internet treatment for AUD can be legitimately disseminated as a treatment alternative to face-to-face or group treatment in routine health care several important steps need to be taken. First, comparisons of internet treatment and face-to-face treatment in non-inferiority designs are needed, as they are a prerequisite to start building the case for internet treatment as a clinical alternative to regular psychotherapy. Further, predictors of outcome should be studied further. Long-term follow-ups are also sorely needed, as few studies have included follow-ups more than 6 months [89]. Lastly, therapist guidance obviously means a cost for therapist time, and to justify such a cost, the additive effect must be verified in several studies. With health care costs currently spiraling due to an aging population, cost-effectiveness studies are increasingly considered important as a market tool when promoting new treatment models to stakeholders.

We were surprised at the high mean age of participants in Study II and III ($m=49.5$ and $m=52.8$) respectively), compared to previous studies conducted by the research group and others, where the mean age commonly has been around 40. This can reflect both that more older people in society are developing severe alcohol problems or that older people use the internet to a greater degree than previously. Either way, it is thought-provoking to reflect on the current epidemiological trends. In relation to age: research suggests that alcohol consumption is actually increasing in the elderly population in Sweden [121], in contrast to

the development among young people where a sharp decrease has been observed for several years [122]. Nevertheless, with age being one of the most important factors in the development and maintenance of alcohol problems [22], perhaps future studies on internet interventions would do well in specifically addressing, and adjusting treatment to, older age groups.

Lastly, security of personal information is surprisingly little discussed in the literature. Although no major database seems to have been hacked and leaked on the internet, it is important to reflect on what the consequences of such an incident would have for willingness to participate in research and clinical internet treatment. Importantly, there are simple ways to make interventions more secure. In internet treatment clinics, double authentication, as commonly used when logging in to your bank account by for example providing a password sent to your phone, is commonly used. Another variant of increasing security in a clinical setting is to provide patients with physical note pads and booklets, while not saving any personal information on the actual platform (for example just a user name and a random password), but just using it for conveying information.

4. CONCLUSIONS

The purpose with this thesis was to study therapist-guided internet treatment for people with AUD, i.e. a more severe population than is commonly targeted in internet interventions for alcohol problems. The studies provide support for therapist-guided internet treatment for AUD, in that it was feasible, acceptable and more effective in reducing alcohol consumption compared to non-guided treatment at post-treatment.

In sum, the studies demonstrate the following:

- Study I showed that adding therapist guidance to an internet based CBT treatment program leads to greater reductions in alcohol consumption measured in number of drinks after treatment
- Study II showed that high-intensity therapist-guided treatment for individuals with a diagnosed AUD is acceptable, feasible and leads to few negative effects. Further, it also leads to significant reductions in alcohol consumption measured in number of drinks and heavy drinking days
- Study III showed that high-intensity treatment is more effective than a wait-list control in reducing number of drinks and number of heavy drinking days, and more effective than low-intensity treatment in reducing number of heavy drinking days. However, there were no significant differences between the two treatment groups at the three-month follow-up
- Study IV showed that treatment credibility predicted adherence to treatment in terms of completion of module work sheets. Male gender, pre-treatment abstinence and two personality variables (a high degree of alexithymia and a low degree of antagonism) were predictive of low-risk drinking

Hopefully, results from the studies included in this thesis can contribute to the development of new, dynamic and innovative treatment models that can attract individuals who suffer from alcohol problems, whether they seek formal treatment or not.

5. ACKNOWLEDGEMENTS

Anne Berman. Not many people are responsible for changing the course of one's life. You are such a person to me. I am so thankful that I failed those early PTP interviews and instead ended up in your research group. I am privileged and proud to have had you as a supervisor. Thank you for seeing my potential. Your optimism is contagious! Hope our paths will continue to cross for many years ahead, whether it be in Stockholm, Copenhagen, Rome, Melbourne, London, Toronto, Koster islands... P.S. will add you on Facebook now ☺

Viktor Kaldo. Thank you for having been immensely supportive, creative and kind throughout this journey. Everything has run so smoothly working with you and Martin, it's been a real "treat". You are also highly ambitious and would of course never settle for anything less than perfection ;)

Paul Wallace. So deeply, unapologetically British (it's a compliment!). Always professional and focused, but also always personal and caring. Thank you for taking the time to listen to me babbling about research and life in general. Apart from co-supervisor you are also a friend. Next time we take a stroll in Notting Hill, pub lunch is on me.

Göran Hagman, my mentor. Thank you for never-ending lunches, and for encouraging me to take a PhD in those early days when I was a research assistant contemplating the pros and cons of it all. Your knowledge and passion for neuropsychology was inspiring, and made the choice to do a PhD much easier.

Martin Kraepelien and Niels Éek. Well, I guess I could have done it without you two, but it wouldn't have been half as fun and not nearly as good. Thank you for all the work you put into these studies, theoretically as well as practically. I truly feel we've accomplished something great together. We have a good vibe, let's nurture it!

Karolina Sörman. Guess what, the little CPF gnome is leaving... he will miss the daily chats. Let's keep in touch.

Mikael Gajecki. My wife asked me to stop singing Wonderwall to her. I said maybe.

Maria Beckman and Miriam Jakobson, thank you for participating as therapists in study III, you contributed a lot with your clinical competence. We'll meet again!

Berit Scott of Uppsala University. Thank you for encouraging me to continue with research when I did my Master's Thesis. Turns out it was a good decision!

Shout out and thanks to the National Research School in Clinical Psychiatry and all the colleagues I met for the first time there. Started from the bottom now we're HERE!

European School of Addiction Research Dresden (ESADD)/Dresden Technische Universität for an excellent research school experience and for providing me with colleagues all over Europe that I now consider my friends (in particular Max, Judit and Malou). Thank you for bringing me closer to Europe, physically and mentally.

Friends from the AARON network. Thank you for inspiring talks over the years, and for allowing me to participate in a dynamic conversation that I hope will continue in one way or another.

Fellow doctoral students in Anne's group: Olof Molander, Viktor Månsson, Elisabeth Petersén and Karoline Kolaas. Looking forward to your work. Good luck!

Zarnie Khadjesari and Matthijs Blankers. Wow, writing our review felt so easy and playful! Research should always be like that, shouldn't it? ☺

Shout out to all my wonderful colleagues at CPF/KI (and I know some of you are thinking: But he was always having coffee and chatting in the kitchen area... When did he have time to write his thesis??)

Friends for emotional (etc.) support in times of need during these four years (in no particular order): Ella Petersson & Anton Hultberg (in no particular order), Niklas Ahlgren, Hordokht Moravejzadeh, Peter Holm, Viktor Jondal. I consider you my base ☺

Tove Persson and family.

Family for being there: my sisters Anniela, Agneta, Gunilla and their families (think mom would have been proud?). And of course, the True Unicorns of the family: dear aunt Eva, uncle Staffan & Inga.

Finally, thank you to all participants in the studies. I truly hope that we made a difference for the better!

6. REFERENCES

1. Global status report on alcohol and health 2014. World Health Organization, 2014.
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373(9682):2223-33. Epub 2009/06/30. doi: 10.1016/s0140-6736(09)60746-7. PubMed PMID: 19560604.
3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2224-60. PubMed PMID: WOS:000312387000017.
4. Room R, Babor T, Rehm J. Alcohol and public health. *Lancet*. 2005;365(9458):519-30. Epub 2005/02/12. doi: 10.1016/s0140-6736(05)17870-2. PubMed PMID: 15705462.
5. O'Keefe JH, Bhatti SK, Bajwa A, DiNicolantonio JJ, Lavie CJ. Alcohol and cardiovascular health: the dose makes the poison...or the remedy. *Mayo Clinic proceedings*. 2014;89(3):382-93. Epub 2014/03/04. doi: 10.1016/j.mayocp.2013.11.005. PubMed PMID: 24582196.
6. Chikritzhs T, Stockwell T, Naimi T, Andreasson S, Dangardt F, Liang W. Has the leaning tower of presumed health benefits from 'moderate' alcohol use finally collapsed? *Addiction*. 2015;110(5):726-7. Epub 2015/01/24. doi: 10.1111/add.12828. PubMed PMID: 25613200.
7. Rehm J, Baliunas D, Borges GL, Graham K, Irving H, Kehoe T, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction*. 2010;105(5):817-43. Epub 2010/03/25. doi: 10.1111/j.1360-0443.2010.02899.x. PubMed PMID: 20331573; PubMed Central PMCID: PMC3306013.
8. Babor T CR, Casswell S, Edwards G, Giesbrecht N, Graham K, Grube J, Hill L, Holder H, Ross H, Livingston M, Österberg E, Ehm J, Room R, Rossow I. *Alcohol: No ordinary commodity*. 2 ed. New York: Oxford University Press; 2010. 360 p.
9. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1575-86. doi: 10.1016/s0140-6736(13)61611-6. PubMed PMID: WOS:000326623900029.
10. Room R. Measurement and distribution of drinking patterns and problems in general populations. *Alcohol-Related Disabilities*. 1977;32:61-87.
11. Jellinek EM. Phases of alcohol addiction. *Quarterly journal of studies on alcohol*. 1952;13(4):673-84. Epub 1952/12/01. PubMed PMID: 13014274.
12. Leshner AI. Addiction is a brain disease, and it matters. *Science (New York, NY)*. 1997;278(5335):45-7. Epub 1997/10/06. PubMed PMID: 9311924.
13. Volkow ND, Koob G. Brain disease model of addiction: why is it so controversial? *The lancet Psychiatry*. 2015;2(8):677-9. Epub 2015/08/08. doi: 10.1016/s2215-0366(15)00236-9. PubMed PMID: 26249284; PubMed Central PMCID: PMC34556943.
14. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th edition ed. Washington, DC: American Psychiatric Association; 2013.

15. Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. *British medical journal*. 1976;1(6017):1058-61. Epub 1976/05/01. PubMed PMID: 773501; PubMed Central PMCID: PMCPMC1639901.
16. West RB, J. *Theory of Addiction*. 2 ed. West Sussex: John Wiley & Sons; 2013. 263 p.
17. Buhringer G, Wittchen HU, Gottlebe K, Kufeld C, Goschke T. Why people change? The role of cognitive-control processes in the onset and cessation of substance abuse disorders. *International journal of methods in psychiatric research*. 2008;17 Suppl 1:S4-s15. Epub 2008/06/11. doi: 10.1002/mpr.246. PubMed PMID: 18543358.
18. Goldstein RZ, Craig AD, Bechara A, Garavan H, Childress AR, Paulus MP, et al. The neurocircuitry of impaired insight in drug addiction. *Trends in cognitive sciences*. 2009;13(9):372-80. Epub 2009/09/01. doi: 10.1016/j.tics.2009.06.004. PubMed PMID: 19716751; PubMed Central PMCID: PMCPMC2844118.
19. Skog OJ. The collectivity of drinking cultures: a theory of the distribution of alcohol consumption. *British journal of addiction*. 1985;80(1):83-99. Epub 1985/03/01. PubMed PMID: 3856453.
20. Edwards G. How the 1977 World Health Organization report on alcohol-related disabilities came to be written: a provisional analysis. *Addiction*. 2007;102(11):1711-21. Epub 2007/10/16. doi: 10.1111/j.1360-0443.2007.02003.x. PubMed PMID: 17935579.
21. Rose G. *Rose's Strategy of Preventive Medicine*. 2 ed. New York: Oxford University Press; 1992. 171 p.
22. Cunningham JA, McCambridge J. Is alcohol dependence best viewed as a chronic relapsing disorder? *Addiction*. 2012;107(1):6-12. Epub 2011/10/11. doi: 10.1111/j.1360-0443.2011.03583.x. PubMed PMID: 21981681; PubMed Central PMCID: PMCPMC3272223.
23. McCrady BS, Owens MD, Borders AZ, Brovko JM. Psychosocial approaches to alcohol use disorders since 1940: a review. *Journal of studies on alcohol and drugs Supplement*. 2014;75 Suppl 17:68-78. Epub 2014/02/26. PubMed PMID: 24565313.
24. Miller WR, Wilbourne PL. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction*. 2002;97(3):265-77. Epub 2002/04/20. PubMed PMID: 11964100.
25. Alcoholics anonymous. *Jama*. 1976;236(13):1505-6. Epub 1976/09/27. PubMed PMID: 785048.
26. Miller WR, Kurtz E. Models of alcoholism used in treatment: contrasting AA and other perspectives with which it is often confused. *Journal of studies on alcohol*. 1994;55(2):159-66. Epub 1994/03/01. PubMed PMID: 8189736.
27. Ferri M, Amato L, Davoli M. Alcoholics Anonymous and other 12-step programmes for alcohol dependence. *The Cochrane database of systematic reviews*. 2006;(3):Cd005032. Epub 2006/07/21. doi: 10.1002/14651858.CD005032.pub2. PubMed PMID: 16856072.
28. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors*. 2 ed. New York: Guilford Press; 2005. 416 p.
29. Kadden RM. Behavioral and cognitive-behavioral treatments for alcoholism: research opportunities. *Addictive behaviors*. 2001;26(4):489-507. Epub 2001/07/18. PubMed PMID: 11456073.
30. Smith JE, Meyers RJ, Miller WR. The community reinforcement approach to the treatment of substance use disorders. *The American journal on addictions*. 2001;10 Suppl:51-9. Epub 2001/03/28. PubMed PMID: 11268821.

31. Meyers RJ, Roozen HG, Smith JE. The community reinforcement approach: an update of the evidence. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*. 2011;33(4):380-8. Epub 2011/01/01. PubMed PMID: 23580022; PubMed Central PMCID: PMC3860533.
32. Babor TF, McRee BG, Kassebaum PA, Grimaldi PL, Ahmed K, Bray J. Screening, Brief Intervention, and Referral to Treatment (SBIRT): toward a public health approach to the management of substance abuse. *Substance abuse*. 2007;28(3):7-30. Epub 2007/12/14. doi: 10.1300/J465v28n03_03. PubMed PMID: 18077300.
33. Heather N. Breaking new ground in the study and practice of alcohol brief interventions. *Drug and alcohol review*. 2010;29(6):584-8. Epub 2010/10/27. doi: 10.1111/j.1465-3362.2010.00204.x. PubMed PMID: 20973840.
34. Cunningham JA, Breslin FC. Only one in three people with alcohol abuse or dependence ever seek treatment. *Addictive behaviors*. 2004;29(1):221-3. Epub 2003/12/12. PubMed PMID: 14667433.
35. Heather N. Toward an understanding of the effective mechanisms of alcohol brief interventions. *Alcoholism, clinical and experimental research*. 2014;38(3):626-8. doi: 10.1111/acer.12336. PubMed PMID: 24428398.
36. Chafetz ME, Blane HT, Abram HS, Golner J, Lacy E, Mc CW, et al. Establishing treatment relations with alcoholics. *The Journal of nervous and mental disease*. 1962;134:395-409. Epub 1962/05/01. PubMed PMID: 13877834.
37. McCambridge J, Cunningham JA. The early history of ideas on brief interventions for alcohol. *Addiction*. 2014;109(4):538-46. Epub 2013/12/21. doi: 10.1111/add.12458. PubMed PMID: 24354855; PubMed Central PMCID: PMC3992901.
38. Nilssen P, Wahlin S, Heather N. Implementing brief interventions in health care: lessons learned from the Swedish Risk Drinking Project. *International journal of environmental research and public health*. 2011;8(9):3609-27. Epub 2011/10/22. doi: 10.3390/ijerph8093609. PubMed PMID: 22016706; PubMed Central PMCID: PMC3194107.
39. O'Donnell A, Wallace P, Kaner E. From efficacy to effectiveness and beyond: what next for brief interventions in primary care? *Front Psychiatry*. 2014;5:113. Epub 2014/09/16. doi: 10.3389/fpsy.2014.00113. PubMed PMID: 25221524; PubMed Central PMCID: PMC3992901.
40. Kaner E, Bland M, Cassidy P, Coulton S, Dale V, Deluca P, et al. Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial. *BMJ (Clinical research ed)*. 2013;346:e8501. Epub 2013/01/11. doi: 10.1136/bmj.e8501. PubMed PMID: 23303891; PubMed Central PMCID: PMC3541471.
41. Bien TH, Miller WR, Tonigan JS. Brief interventions for alcohol problems: a review. *Addiction*. 1993;88(3):315-35. Epub 1993/03/01. PubMed PMID: 8461850.
42. O'Donnell A, Anderson P, Newbury-Birch D, Schulte B, Schmidt C, Reimer J, et al. The impact of brief alcohol interventions in primary healthcare: a systematic review of reviews. *Alcohol and alcoholism*. 2014;49(1):66-78. Epub 2013/11/16. doi: 10.1093/alcalc/agt170. PubMed PMID: 24232177; PubMed Central PMCID: PMC3865817.
43. Hettima J, Steele J, Miller WR. Motivational interviewing. *Annual review of clinical psychology*. 2005;1:91-111. Epub 2007/08/25. doi: 10.1146/annurev.clinpsy.1.102803.143833. PubMed PMID: 17716083.
44. Jorgensen CH, Pedersen B, Tonnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcoholism, clinical and experimental research*.

- 2011;35(10):1749-58. Epub 2011/05/28. doi: 10.1111/j.1530-0277.2011.01523.x. PubMed PMID: 21615426.
45. Rosner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. The Cochrane database of systematic reviews. 2010;(9):Cd004332. Epub 2010/09/09. doi: 10.1002/14651858.CD004332.pub2. PubMed PMID: 20824837.
46. Roozen HG, de Waart R, van der Windt DA, van den Brink W, de Jong CA, Kerkhof AJ. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2006;16(5):311-23. Epub 2005/12/20. doi: 10.1016/j.euroneuro.2005.11.001. PubMed PMID: 16361086.
47. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Jama*. 2006;295(17):2003-17. Epub 2006/05/04. doi: 10.1001/jama.295.17.2003. PubMed PMID: 16670409.
48. Mann K, Lemenager T, Hoffmann S, Reinhard I, Hermann D, Batra A, et al. Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. *Addiction biology*. 2013;18(6):937-46. Epub 2012/12/13. doi: 10.1111/adb.12012. PubMed PMID: 23231446.
49. Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of studies on alcohol*. 1997;58(1):7-29. Epub 1997/01/01. PubMed PMID: 8979210.
50. Effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). *BMJ (Clinical research ed)*. 2005;331(7516):541. Epub 2005/09/10. doi: 10.1136/bmj.331.7516.541. PubMed PMID: 16150764; PubMed Central PMCID: PMCPMC1200586.
51. Edwards G, Orford J, Egert S, Guthrie S, Hawker A, Hensman C, et al. Alcoholism: a controlled trial of "treatment" and "advice". *Journal of studies on alcohol*. 1977;38(5):1004-31. Epub 1977/05/01. PubMed PMID: 881837.
52. Drummond DC, Thom B, Brown C, Edwards G, Mullan MJ. Specialist versus general practitioner treatment of problem drinkers. *Lancet*. 1990;336(8720):915-8. Epub 1990/10/13. PubMed PMID: 1976937.
53. Imel ZE, Wampold BE, Miller SD, Fleming RR. Distinctions without a difference: direct comparisons of psychotherapies for alcohol use disorders. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors*. 2008;22(4):533-43. Epub 2008/12/17. doi: 10.1037/a0013171. PubMed PMID: 19071978.
54. Wampold BE, Mondin GW, Moody M, Stich F, Benson K, Ahn H-n. A meta-analysis of outcome studies comparing bona fide psychotherapies: Empirically, "all must have prizes.". *American Psychological Association*; 1997.
55. Magill M, Longabaugh R. Efficacy combined with specified ingredients: a new direction for empirically supported addiction treatment. *Addiction*. 2013;108(5):874-81. Epub 2012/10/18. doi: 10.1111/add.12013. PubMed PMID: 23072622; PubMed Central PMCID: PMCPMC3566277.
56. Magill M, Kiluk BD, McCrady BS, Tonigan JS, Longabaugh R. Active Ingredients of Treatment and Client Mechanisms of Change in Behavioral Treatments for Alcohol Use Disorders: Progress 10 Years Later. *Alcoholism, clinical and experimental research*. 2015;39(10):1852-62. Epub 2015/09/08. doi:

- 10.1111/acer.12848. PubMed PMID: 26344200; PubMed Central PMCID: PMCPMC4592447.
57. Kiluk BD, Carroll KM. New developments in behavioral treatments for substance use disorders. *Current psychiatry reports*. 2013;15(12):420. Epub 2013/11/01. doi: 10.1007/s11920-013-0420-1. PubMed PMID: 24173656; PubMed Central PMCID: PMCPMC3878068.
58. Dale V, Heather N, Adamson S, Coulton S, Copello A, Godfrey C, et al. Predicting drinking outcomes: Evidence from the United Kingdom Alcohol Treatment Trial (UKATT). *Addictive behaviors*. 2017;71:61-7. Epub 2017/03/09. doi: 10.1016/j.addbeh.2017.02.023. PubMed PMID: 28273487.
59. Gibbs L, Flanagan J. Prognostic indicators of alcoholism treatment outcome. *The International journal of the addictions*. 1977;12(8):1097-141. Epub 1977/12/01. PubMed PMID: 344234.
60. Adamson SJ, Sellman JD, Frampton CM. Patient predictors of alcohol treatment outcome: a systematic review. *Journal of substance abuse treatment*. 2009;36(1):75-86. Epub 2008/07/29. doi: 10.1016/j.jsat.2008.05.007. PubMed PMID: 18657940.
61. Andersson G. Using the Internet to provide cognitive behaviour therapy. *Behav Res Ther*. 2009;47(3):175-80. Epub 2009/02/24. doi: 10.1016/j.brat.2009.01.010. PubMed PMID: 19230862.
62. Hedman E. Therapist guided internet delivered cognitive behavioural therapy. *BMJ (Clinical research ed)*. 2014;348:g1977. Epub 2014/03/13. doi: 10.1136/bmj.g1977. PubMed PMID: 24614338.
63. Andersson G, Cuijpers P. Pros and cons of online cognitive-behavioural therapy. *The British journal of psychiatry : the journal of mental science*. 2008;193(4):270-1. Epub 2008/10/02. doi: 10.1192/bjp.bp.108.054080. PubMed PMID: 18827286.
64. Andersson G, Bergström J, Buhrman M, Carlbring P, Holländare F, Kaldö V, et al. Development of a New Approach to Guided Self-Help via the Internet: The Swedish Experience. *Journal of Technology in Human Services*. 2008;26(2-4):161-81. doi: 10.1080/15228830802094627.
65. Cunningham JA, Kypri K, McCambridge J. The use of emerging technologies in alcohol treatment. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*. 2011;33(4):320-6. Epub 2011/01/01. PubMed PMID: 23580017; PubMed Central PMCID: PMCPmc3860543.
66. Kypri K, Sitharthan T, Cunningham JA, Kavanagh DJ, Dean JI. Innovative approaches to intervention for problem drinking. *Current opinion in psychiatry*. 2005;18(3):229-34. Epub 2006/04/28. doi: 10.1097/01.yco.0000165591.75681.ab. PubMed PMID: 16639145.
67. Cunningham JA, Sobell LC, Sobell MB, Agrawal S, Toneatto T. Barriers to treatment: why alcohol and drug abusers delay or never seek treatment. *Addictive behaviors*. 1993;18(3):347-53. Epub 1993/05/01. PubMed PMID: 8393611.
68. Heather N. Interpreting null findings from trials of alcohol brief interventions. *Front Psychiatry*. 2014;5:85. doi: 10.3389/fpsy.2014.00085. PubMed PMID: 25076917; PubMed Central PMCID: PMCPMC4100216.
69. O'Malley PM, Johnston LD. Epidemiology of alcohol and other drug use among American college students. *Journal of studies on alcohol Supplement*. 2002;(14):23-39. Epub 2002/05/23. PubMed PMID: 12022728.
70. Bhoohibhoya A, Hayes L, Branscum P, Taylor L. The Use of the Internet for Prevention of Binge Drinking Among the College Population: A Systematic Review

- of Evidence. *Alcohol and alcoholism*. 2015;50(5):526-35. Epub 2015/06/07. doi: 10.1093/alcalc/agn047. PubMed PMID: 26047832.
71. Carey KB, Scott-Sheldon LA, Elliott JC, Bolles JR, Carey MP. Computer-delivered interventions to reduce college student drinking: a meta-analysis. *Addiction*. 2009;104(11):1807-19. Epub 2009/09/12. doi: 10.1111/j.1360-0443.2009.02691.x. PubMed PMID: 19744139; PubMed Central PMCID: PMC2763045.
72. Tait RJ, Christensen H. Internet-based interventions for young people with problematic substance use: a systematic review. *The Medical journal of Australia*. 2010;192(11 Suppl):S15-21. Epub 2010/07/14. PubMed PMID: 20528701.
73. Khadjesari Z, Murray E, Hewitt C, Hartley S, Godfrey C. Can stand-alone computer-based interventions reduce alcohol consumption? A systematic review. *Addiction*. 2011;106(2):267-82. Epub 2010/11/19. doi: 10.1111/j.1360-0443.2010.03214.x. PubMed PMID: 21083832.
74. Vernon ML. A review of computer-based alcohol problem services designed for the general public. *J Subst Abuse Treat*. 2010;38(3):203-11. Epub 2009/12/18. doi: 10.1016/j.jsat.2009.11.001. PubMed PMID: 20015607; PubMed Central PMCID: PMC2835799.
75. Riper H, Blankers M, Hadiwijaya H, Cunningham J, Clarke S, Wiers R, et al. Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: a meta-analysis. *PloS one*. 2014;9(6):e99912. doi: 10.1371/journal.pone.0099912. PubMed PMID: 24937483; PubMed Central PMCID: PMC4061051.
76. Larimer ME, Palmer RS, Marlatt GA. Relapse prevention. An overview of Marlatt's cognitive-behavioral model. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*. 1999;23(2):151-60. Epub 2000/07/13. PubMed PMID: 10890810.
77. Wallace P, Murray E, McCambridge J, Khadjesari Z, White IR, Thompson SG, et al. On-line randomized controlled trial of an internet based psychologically enhanced intervention for people with hazardous alcohol consumption. *PLoS One*. 2011;6(3):e14740. doi: 10.1371/journal.pone.0014740. PubMed PMID: 21408060; PubMed Central PMCID: PMC3052303.
78. Riper H, Kramer J, Smit F, Conijn B, Schippers G, Cuijpers P. Web-based self-help for problem drinkers: a pragmatic randomized trial. *Addiction*. 2008;103(2):218-27. Epub 2008/01/18. doi: 10.1111/j.1360-0443.2007.02063.x. PubMed PMID: 18199300.
79. Sinadinovic K, Wennberg P, Johansson M, Berman AH. Targeting individuals with problematic alcohol use via Web-based cognitive-behavioral self-help modules, personalized screening feedback or assessment only: a randomized controlled trial. *Eur Addict Res*. 2014;20(6):305-18. Epub 2014/10/11. doi: 10.1159/000362406. PubMed PMID: 25300885.
80. Riper H, Spek V, Boon B, Conijn B, Kramer J, Martin-Abello K, et al. Effectiveness of E-self-help interventions for curbing adult problem drinking: a meta-analysis. *Journal of medical Internet research*. 2011;13(2):e42. Epub 2011/07/02. doi: 10.2196/jmir.1691. PubMed PMID: 21719411; PubMed Central PMCID: PMC2763045.
81. Sundström C, Blankers M, Khadjesari Z. Computer-Based Interventions for Problematic Alcohol Use: a Review of Systematic Reviews. *International journal of behavioral medicine*. 2016. Epub 2016/10/21. doi: 10.1007/s12529-016-9601-8. PubMed PMID: 27757844.
82. Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis.

- Psychol Med. 2007;37(3):319-28. Epub 2006/11/23. doi: 10.1017/s0033291706008944. PubMed PMID: 17112400.
83. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2014;13(3):288-95. Epub 2014/10/03. doi: 10.1002/wps.20151. PubMed PMID: 25273302; PubMed Central PMCID: PMC4219070.
84. Nordgreen T, Gjestad R, Andersson G, Carlbring P, Havik OE. The implementation of guided Internet-based cognitive behaviour therapy for panic disorder in a routine-care setting: effectiveness and implementation efforts. *Cogn Behav Ther*. 2017:1-14. Epub 2017/07/18. doi: 10.1080/16506073.2017.1348389. PubMed PMID: 28714775.
85. Hadjistavropoulos HD, Pugh NE, Nugent MM, Hesser H, Andersson G, Ivanov M, et al. Therapist-assisted Internet-delivered cognitive behavior therapy for depression and anxiety: translating evidence into clinical practice. *Journal of anxiety disorders*. 2014;28(8):884-93. Epub 2014/12/03. doi: 10.1016/j.janxdis.2014.09.018. PubMed PMID: 25445078.
86. Titov N, Dear BF, Staples LG, Bennett-Levy J, Klein B, Rapee RM, et al. MindSpot Clinic: An Accessible, Efficient, and Effective Online Treatment Service for Anxiety and Depression. *Psychiatric services (Washington, DC)*. 2015;66(10):1043-50. Epub 2015/07/02. doi: 10.1176/appi.ps.201400477. PubMed PMID: 26130001.
87. Blankers M, Koeter MW, Schippers GM. Internet therapy versus internet self-help versus no treatment for problematic alcohol use: A randomized controlled trial. *Journal of consulting and clinical psychology*. 2011;79(3):330-41. doi: 10.1037/a0023498. PubMed PMID: 21534652.
88. Postel M, de Haan H, ter Huurne E, Becker E, de Jong C. Effectiveness of a Web-based Intervention for Problem Drinkers and Reasons for Dropout: Randomized Controlled Trial. *Journal of Internet Medical Research*. 2010;12(4):e68.
89. Dedert EA, McDuffie JR, Stein R, McNeil JM, Kosinski AS, Freiermuth CE, et al. Electronic Interventions for Alcohol Misuse and Alcohol Use Disorders: A Systematic Review. *Annals of internal medicine*. 2015;163(3):205-14. Epub 2015/08/04. doi: 10.7326/m15-0285. PubMed PMID: 26237752.
90. Riper H, Kramer J, Keuken M, Smit F, Schippers G, Cuijpers P. Predicting successful treatment outcome of web-based self-help for problem drinkers: secondary analysis from a randomized controlled trial. *Journal of medical Internet research*. 2008;10(4):e46. Epub 2008/11/27. doi: 10.2196/jmir.1102. PubMed PMID: 19033150; PubMed Central PMCID: PMC2629366.
91. Blankers M, Koeter MW, Schippers GM. Baseline predictors of treatment outcome in Internet-based alcohol interventions: a recursive partitioning analysis alongside a randomized trial. *BMC public health*. 2013;13:455. doi: 10.1186/1471-2458-13-455. PubMed PMID: 23651767; PubMed Central PMCID: PMC3662562.
92. Eysenbach G. The law of attrition. *Journal of medical Internet research*. 2005;7(1):e11. Epub 2005/04/15. doi: 10.2196/jmir.7.1.e11. PubMed PMID: 15829473; PubMed Central PMCID: PMC1550631.
93. Postel MG, de Haan HA, ter Huurne ED, van der Palen J, Becker ES, de Jong CA. Attrition in web-based treatment for problem drinkers. *Journal of medical Internet research*. 2011;13(4):e117. Epub 2011/12/29. doi: 10.2196/jmir.1811. PubMed PMID: 22201703; PubMed Central PMCID: PMC3278103.
94. Murray E, White IR, Varaganam M, Godfrey C, Khadjesari Z, McCambridge J. Attrition revisited: adherence and retention in a web-based alcohol trial. *Journal of*

- medical Internet research. 2013;15(8):e162. Epub 2013/09/03. doi: 10.2196/jmir.2336. PubMed PMID: 23996958; PubMed Central PMCID: PMC3815435.
95. Beck AT. The current state of cognitive therapy: a 40-year retrospective. *Archives of general psychiatry*. 2005;62(9):953-9. Epub 2005/09/07. doi: 10.1001/archpsyc.62.9.953. PubMed PMID: 16143727.
96. Hayes SC, Wilson KG. *Acceptance and Commitment Therapy: an experiential approach to behavior change*. New York: Guilford Press; 1999.
97. Sobell LC, Sobell MB. *Timeline Follow-Back: A Technique for Assessing Self-Reported Alcohol Consumption*. In: Litten R, Allen J, editors. *Measuring Alcohol Consumption*. Totowa, NJ: The Humana Press; 1992.
98. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug and alcohol dependence*. 1996;42(1):49-54. doi: [http://dx.doi.org/10.1016/0376-8716\(96\)01263-X](http://dx.doi.org/10.1016/0376-8716(96)01263-X).
99. Rozental A, Andersson G, Boettcher J, Ebert DD, Cuijpers P, Knaevelsrud C, et al. Consensus statement on defining and measuring negative effects of Internet interventions. *Internet Interventions*. 2014;1(1):12-9.
100. Cunningham JA, Kypri K, McCambridge J. Exploratory randomized controlled trial evaluating the impact of a waiting list control design. *BMC medical research methodology*. 2013;13:150. Epub 2013/12/10. doi: 10.1186/1471-2288-13-150. PubMed PMID: 24314204; PubMed Central PMCID: PMC4029562.
101. Kypri K, Langley JD, Saunders JB, Cashell-Smith ML. Assessment may conceal therapeutic benefit: findings from a randomized controlled trial for hazardous drinking. *Addiction*. 2007;102(1):62-70. Epub 2007/01/09. doi: 10.1111/j.1360-0443.2006.01632.x. PubMed PMID: 17207124.
102. Clifford PR, Maisto SA, Davis CM. Alcohol treatment research assessment exposure subject reactivity effects: part I. Alcohol use and related consequences. *Journal of studies on alcohol and drugs*. 2007;68(4):519-28. Epub 2007/06/15. PubMed PMID: 17568955.
103. Maisto SA, Clifford PR, Davis CM. Alcohol treatment research assessment exposure subject reactivity effects: part II. Treatment engagement and involvement. *Journal of studies on alcohol and drugs*. 2007;68(4):529-33. Epub 2007/06/15. PubMed PMID: 17568956.
104. Epstein EE, Drapkin ML, Yusko DA, Cook SM, McCrady BS, Jensen NK. Is alcohol assessment therapeutic? Pretreatment change in drinking among alcohol-dependent women. *Journal of studies on alcohol*. 2005;66(3):369-78. Epub 2005/07/29. PubMed PMID: 16047526.
105. Attkisson CC, Zwick R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. *Evaluation and program planning*. 1982;5(3):233-7. Epub 1981/12/12. PubMed PMID: 10259963.
106. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. *Journal of medical Internet research*. 2009;11(2):e13. Epub 2009/05/01. doi: 10.2196/jmir.1194. PubMed PMID: 19403466; PubMed Central PMCID: PMC2762797.
107. Bystedt S, Rozental A, Andersson G, Boettcher J, Carlbring P. Clinicians' perspectives on negative effects of psychological treatments. *Cogn Behav Ther*. 2014;43(4):319-31. Epub 2014/09/11. doi: 10.1080/16506073.2014.939593. PubMed PMID: 25204370; PubMed Central PMCID: PMC4260663.

108. Rozental A, Magnusson K, Boettcher J, Andersson G, Carlbring P. For better or worse: An individual patient data meta-analysis of deterioration among participants receiving Internet-based cognitive behavior therapy. *Journal of consulting and clinical psychology*. 2017;85(2):160-77. Epub 2016/10/28. doi: 10.1037/ccp0000158. PubMed PMID: 27775414.
109. Dunn KE, Harrison JA, Leoutsakos JM, Han D, Strain EC. Continuous Abstinence During Early Alcohol Treatment is Significantly Associated with Positive Treatment Outcomes, Independent of Duration of Abstinence. *Alcohol and alcoholism*. 2017;52(1):72-9. Epub 2016/08/28. doi: 10.1093/alcalc/agw059. PubMed PMID: 27567268; PubMed Central PMCID: PMC5169033.
110. Kaner EF, Beyer F, Dickinson HO, Pienaar E, Campbell F, Schlesinger C, et al. Effectiveness of brief alcohol interventions in primary care populations. *The Cochrane database of systematic reviews*. 2007;(2):Cd004148. Epub 2007/04/20. doi: 10.1002/14651858.CD004148.pub3. PubMed PMID: 17443541.
111. Cunningham JA. Unintended impact of using different inclusion cut-offs for males and females in intervention trials for hazardous drinking. *Addiction*. 2017;112(5):910-1. Epub 2017/02/09. doi: 10.1111/add.13760. PubMed PMID: 28168847.
112. Thorberg FA, Young RM, Sullivan KA, Lyvers M. Alexithymia and alcohol use disorders: a critical review. *Addictive behaviors*. 2009;34(3):237-45. Epub 2008/11/18. doi: 10.1016/j.addbeh.2008.10.016. PubMed PMID: 19010601.
113. Ruiz MA, Pincus AL, Dickinson KA. NEO PI-R predictors of alcohol use and alcohol-related problems. *Journal of personality assessment*. 2003;81(3):226-36. Epub 2003/11/26. doi: 10.1207/s15327752jpa8103_05. PubMed PMID: 14638447.
114. Fisher LA, Elias JW, Ritz K. Predicting relapse to substance abuse as a function of personality dimensions. *Alcoholism, clinical and experimental research*. 1998;22(5):1041-7. Epub 1998/09/03. PubMed PMID: 9726270.
115. Bottlender M, Soyka M. Impact of different personality dimensions (NEO Five-Factor Inventory) on the outcome of alcohol-dependent patients 6 and 12 months after treatment. *Psychiatry research*. 2005;136(1):61-7. Epub 2005/07/19. doi: 10.1016/j.psychres.2004.07.013. PubMed PMID: 16023734.
116. Northcote J, Livingston M. Accuracy of self-reported drinking: observational verification of 'last occasion' drink estimates of young adults. *Alcohol and alcoholism*. 2011;46(6):709-13. Epub 2011/09/29. doi: 10.1093/alcalc/agr138. PubMed PMID: 21949190.
117. Orford J, Hodgson R, Copello A, John B, Smith M, Black R, et al. The clients' perspective on change during treatment for an alcohol problem: qualitative analysis of follow-up interviews in the UK Alcohol Treatment Trial. *Addiction*. 2006;101(1):60-8. Epub 2006/01/06. doi: 10.1111/j.1360-0443.2005.01291.x. PubMed PMID: 16393192.
118. Weisner C. Toward an alcohol treatment entry model: a comparison of problem drinkers in the general population and in treatment. *Alcoholism, clinical and experimental research*. 1993;17(4):746-52. Epub 1993/08/01. PubMed PMID: 8214407.
119. Kiluk BD, Devore KA, Buck MB, Nich C, Frankforter TL, LaPaglia DM, et al. Randomized Trial of Computerized Cognitive Behavioral Therapy for Alcohol Use Disorders: Efficacy as a Virtual Stand-Alone and Treatment Add-On Compared with Standard Outpatient Treatment. *Alcoholism, clinical and experimental research*. 2016;40(9):1991-2000. Epub 2016/08/05. doi: 10.1111/acer.13162. PubMed PMID: 27488212; PubMed Central PMCID: PMC5008977.

120. Gustafson DH, McTavish FM, Chih MY, Atwood AK, Johnson RA, Boyle MG, et al. A smartphone application to support recovery from alcoholism: a randomized clinical trial. *JAMA psychiatry*. 2014;71(5):566-72. Epub 2014/03/29. doi: 10.1001/jamapsychiatry.2013.4642. PubMed PMID: 24671165; PubMed Central PMCID: PMC4016167.
121. Raninen J, Leifman H, Ramstedt M. Who is not drinking less in Sweden? An analysis of the decline in consumption for the period 2004-2011. *Alcohol and alcoholism*. 2013;48(5):592-7. Epub 2013/06/05. doi: 10.1093/alcalc/agt051. PubMed PMID: 23729672.
122. Norström T, Svensson J. The declining trend in Swedish youth drinking: collectivity or polarization? *Addiction*. 2014;109(9):1437-46. Epub 2014/02/14. doi: 10.1111/add.12510. PubMed PMID: 24521087.