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**ALCOHOL DEPENDENCE:
BARRIERS TO TREATMENT
AND NEW APPROACHES
IN PRIMARY CARE**

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The picture on the front page illustrates changes in proportions of participants in each WHO drinking risk level from baseline (left), to six months (middle) and 12 months (right) in study III and IV.

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Alcohol Dependence: Barriers to Treatment and New Approaches in Primary Care

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“Make a difference about something other than yourselves”

Toni Morrison: Conversations

ABSTRACT

Alcohol dependence is highly prevalent worldwide, with an estimated prevalence of 4 % in the Swedish adult population. However, alcohol dependence has one of the largest gaps between the number of individuals affected and the number in treatment, where less than one in five seek treatment. The overarching aim of this thesis was to study possible strategies to reduce this treatment gap.

In study I, the aim was to investigate which type of treatment for alcohol problems, and setting, that was preferred in the general population. Also, reasons for not seeking treatment. In a cross-sectional design, 9005 individuals representative of the general population between 16-80 years of age were interviewed. The results showed that a majority of the participants preferred treatment for alcohol problems within the health care system, while only 5 % preferred the social services. Support groups, psychotherapy and residential treatment were the most endorsed types of treatments. Shame was the most common reason given for not seeking treatment.

In study II, the aim was to describe how individuals with alcohol dependence perceive treatment for alcohol use disorders and their reasons for seeking and not seeking treatment. 32 participants aged 18-62 with alcohol dependence were recruited via a market research company. Data was collected through focus group interviews and individual interviews. The results showed that shame and stigma were important barriers for seeking treatment. Additional barriers were; the perception that treatment meant accepting a goal of lifetime abstinence, low level of knowledge of health consequences associated with alcohol use and also low level of knowledge about treatment. Psychotherapy was the most preferred form of treatment.

In study III, the effects of treatment for alcohol dependence in primary care were investigated. 288 adults with alcohol dependence were randomized to treatment in primary care with the 15-method, a brief treatment adapted for generalist settings, or treatment at a specialized addiction unit. The hypothesis was that treatment in primary care was non-inferior to specialist care. At six month follow up, the results on the primary outcome measure, weekly alcohol consumption, were statistically inconclusive, and could not confirm non-inferiority. However, treatment in specialist care was not superior to primary care. Sub-analysis showed that primary care was non-inferior for low to moderate severity of dependence, while participants with high severity of dependence had better outcome after

specialist treatment.

In study IV, the long-term effect of treatment for alcohol dependence in primary care was investigated, as well as trajectories for change of alcohol consumption. The study was based on the 12 month follow up of the participants in study III. The results confirmed non-inferiority for the primary outcome measure; weekly alcohol consumption. The results for the secondary outcome measures were consistent with the primary outcome – a reduction from baseline to 12 month follow up with no differences between primary care and specialist care. The only exception was that patients randomized to specialist care were more satisfied with treatment. The analyses of trajectories showed that the main reduction in consumption occurred during the first six months and were maintained at the 12 month follow up.

In conclusion, treatment for alcohol dependence was seen as an issue for the health care services. Shame and stigma impose strong barriers to seeking treatment. The knowledge of health consequences associated with alcohol and treatment for alcohol dependence was limited. Common perceptions of treatment often stood in sharp contrast to preferred treatments among non-treatment seekers. Treatment for alcohol dependence in primary care with the 15-method is a promising approach. Five strategies are suggested in order to decrease the current treatment gap: reduce stigma; organize treatment in an attractive way; offer controlled drinking as a treatment goal; improve health literacy regarding alcohol use, health, alcohol dependence and treatment and finally - new ways to increase dissemination of alcohol interventions in primary care.

LIST OF SCIENTIFIC PAPERS

- I. Andréasson, S., Danielsson, A-K., Wallhed Finn, S. (2013). Preferences Regarding Treatment for Alcohol Problems. *Alcohol and Alcoholism* **48**: 694-699.
- II. Wallhed Finn, S., Bakshi, A-S., Andréasson, S. (2014). Alcohol Consumption, Dependence and Treatment Barriers: Perceptions Among Nontreatment Seekers With Alcohol Dependence. *Substance Use & Misuse* **49**:762-9.
- III. Wallhed Finn, S., Hammarberg, A., Andréasson, S. (2018). Treatment for Alcohol Dependence in Primary Care Compared to Outpatient Specialist Treatment – A Randomized Controlled Trial. *Alcohol and Alcoholism* doi: 10.1093/alcalc/agx126. [Epub ahead of print]
- IV. Wallhed Finn, S., Hammarberg, A., Andréasson, S. Treatment for Alcohol Dependence in Primary Care Compared to Outpatient Specialist Treatment – A Randomized Controlled Trial. 12 Months Follow Up. (Manuscript).

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LIST OF ABBREVIATIONS

AA	Alcoholics anonymous
ALT	Alanine amino transferase
AST	Aspartate amino transferase
APA	The American Psychiatric Association
AUDIT	Alcohol Use Disorders Identification Test
BI	Brief Intervention
CBT	Cognitive Behavioral Therapy
CCM	Chronic Care Model
CDT	Carbohydrate-Deficient Transferrin
DSM	The Diagnostic and Statistical Manuals of Mental Disorders
ICD	The International Classification of Diseases
ITT	Intention To Treat
GGT	Gamma-Glutamyl Transferase
GSC	Guided Self Change
HADS	Hospital Anxiety and Depression Scale
HDD	Heavy Drinking Day(s)
MET	Motivational Enhancement Therapy
MI	Motivational Interviewing
PEth	Phosphatidylethanol
PP	Per Protocol
RTC	Readiness To Change
SADD	Short Alcohol Dependence Data Questionnaire
SBI	Screening and Brief Intervention
SBIRT	Screening, Brief Intervention and Referral to Treatment
SIP	The Short Index of Problems
TLFB	Time Line Follow Back
WHO	The World Health Organization

1 BACKGROUND

1.1 ALCOHOL USE

In Sweden in 2016, the total alcohol consumption, which takes both recorded and unrecorded alcohol into account, was estimated to 9.0 litres of pure alcohol among individuals aged 15 years and older (1). Men tend to drink more than women, both the total consumption and the number of heavy drinking days, defined as drinking > 5 units (one unit equals 12 grams of alcohol) on one occasion. A decline in self-reported alcohol use has been seen among younger, while among the oldest there has been an increase. Between 2007 and 2016, there has been an eight per cent decline in the total alcohol consumption (2).

Globally, the total alcohol consumption, among individuals above 15 years of age, is 6.2 litres of pure alcohol per year (3). In all regions, women drink less alcohol than men. Europe, together with North and South America, are the regions with the highest alcohol consumption. Europe consume circa 25 % of the total alcohol consumption globally, while only 15 % of the global population over 15 years of age live in the region.

1.2 HAZARDOUS ALCOHOL USE

The term hazardous alcohol use describes a level of alcohol use that significantly increases the health risks associated with alcohol. The pattern of use is associated with different types of risks (4). High weekly alcohol consumption is mainly associated with health risks with different diseases, such as cancer, high blood pressure etcetera. Heavy drinking, i.e. drinking a large amount of alcohol at the same time, is rather associated with acute risks such as accidents and violence.

Sweden lacks official guidelines to define hazardous consumption. However, a definition suggested in a report from 2005 is often used and widely disseminated (5). Here, a weekly consumption above nine standard units (12 grams of alcohol) for women and above 14 units for men defines hazardous consumption. Heavy drinking is defined as ≥ 4 units for women and ≥ 5 for men on the same occasion.

In 2016, 13 % of men and 9 % of women in Sweden drank above these recommendations (1). Among the age group 17-29, the proportion of hazardous consumption decreased from 2004 to 2010, then increased and 2016 15 % had a hazardous consumption. Among the group 30-49 years old, the proportion of hazardous consumption has decreased from 13 % year 2004 to

9 % 2016. Individuals aged 50 years and older showed small variations over time. Within the EU, 15.3 % of men and 3.4 % of women consume alcohol at a level corresponding to hazardous use (6)

1.3 HARMFUL ALCOHOL USE

Alcohol use is one of the world's leading causes of disability and mortality (7). Alcohol use is associated with a vast number of diseases and injuries, for example liver cirrhosis, cancer, cardio vascular disease, dementia, depression and hypertension (4). Alcohol use is partially attributable to most of these diseases. For the majority of these diseases there is a dose-response relationship between alcohol use and harm; the higher consumption, the higher risk for harm. In addition, alcohol use also causes substantial harm to others (8, 9).

As alcohol related harms mainly are non-fatal, mortality rates tend to underestimate the harms. Because of this, disability adjusted life years (DALY) is suggested as a more accurate method to calculate the disease burden from alcohol (10). The measure disability adjusted life years (DALY), is a combination of years of life lost (YLL), premature death, and years lived with disability (YLD). Globally, 5.1 % of DALYs are attributable to alcohol (3). In the Nordic countries alcohol use disorders are the main contributor to the alcohol-attributed disease burden measured with DALY (11).

1.4 ALCOHOL DEPENDENCE

Alcohol dependence was first recognized as a disease in the end of the 18th century (12). In 1797, the North American physician Benjamin Rush described alcohol dependence, followed by the British physician Thomas Trotter in 1804. In 1849, the Swedish physician Magnus Huss was the first to systematically describe the symptoms, and named the disease "alcoholismus". In 1960, E.M. Jellinek, separated alcohol dependence into subcategories, where "gamma alcoholism" was characterized by impaired control and "delta alcoholism" rather the inability to abstain from alcohol. However, up until Edward and Gross, in 1976, proposed seven criteria for what they called "alcohol dependence syndrome", there was a lack of clear definitions of alcohol dependence. Edwards revised the description in 1986 and suggested the main two features of "alcohol dependence syndrome" were impaired control and the biological consequences as withdrawal and tolerance.

Today, there are two diagnostic manuals commonly used - the International Classification of Diseases (ICD) of the World Health Organization (WHO) (13) and the Diagnostic and

Statistical Manuals of Mental Disorders (DSM) of the American Psychiatric Association (APA) (14). In Swedish health care, the ICD version 10 is used. According to the ICD-10 the diagnosis of alcohol dependence is met if three or more of the following six criteria occur together over the past 12 months (13):

- A strong desire or sense of compulsion to use alcohol
- Impaired control over alcohol use
- Physiological withdrawal when alcohol use is reduced or ceased
- Tolerance
- Preoccupation with alcohol use
- Persistent substance use despite clear evidence of harmful consequences.

The definition of alcohol dependence in DSM-IV (15) was very similar to the definition in ICD-10. However, in the update to DSM-5, there were major changes to the definition of substance use disorder (16). The assumed hierarchical structure between abuse and dependence had been questioned, and analysis with item response theory showed the criteria of abuse and dependence measured one dimension rather than two. Thus, the criteria from abuse and dependence were combined into one disorder – alcohol use disorder. In this process, the legal criteria in abuse was removed, and a new criteria for craving was added. In total there are eleven criteria (14):

1. Used larger amounts or for longer time than intended
2. Repeated attempts to cut down or stop use
3. Much time spent getting, using, or recovering from alcohol
4. Cravings to use alcohol
5. Neglected major roles to use alcohol
6. Social/interpersonal problems related to use
7. Giving up important social, occupational, or recreational activities because of alcohol
8. Hazardous use
9. Physical or psychological problems related to alcohol use
10. Tolerance
11. Withdrawal symptoms.

In addition, there was a change from a dichotomous view of the diagnosis to a continuous one, where also severity is graded. To fulfill two or three criteria is considered a mild severity; four to five criteria moderate, and six or more severe.

There has been criticism of the classifications of alcohol dependence in the diagnostic manuals, and a proposal to abandon it in favor of a measure of alcohol consumption instead - "heavy use over time" (17). The argument is that it is heavy alcohol use that causes the harms of alcohol, and that even though the criteria for dependence are associated with alcohol use, there are also examples of individuals fulfilling the diagnostic criteria for dependence, but do not drink excessively. In addition, epidemiological research shows how social norms about drinking affect what is seen as problematic use or not. This gives very different estimates for prevalence of alcohol dependence in countries with similar total alcohol consumption, which gives rise to questions about the construct validity of the condition.

The prevalence of alcohol dependence according to ICD-10 criteria is estimated to be 2.3 % worldwide and the corresponding prevalence in Europe is 4.0 % (3). In Sweden, 4.0 % of the adult population is estimated to fulfill the diagnostic criteria for alcohol dependence (18). A majority of these, around 75 %, have a mild to moderate form of dependence; fulfilling three or four of the seven DSM-IV criteria for dependence, while a minority, circa 25 %, have a more severe form of dependence, fulfilling five or more criteria.

In cohort studies in the general population, the recovery rates from alcohol dependence are high (19-21). In a prospective cohort study in the general population in Holland, using DSM-5 criteria, 70 % who fulfilled criteria for alcohol dependence at baseline, had recovered at three-year follow up (21). Of those who had recovered, only 9 % abstained completely from alcohol. Risk factors for relapse are previous severe dependence (22) and hazardous use of alcohol (22, 23). In a Swedish clinical sample, Nordström and Berglund (24) interviewed 70 patients with a stable social situation 20 years after they had been treated for alcohol dependence in Lund. In this group there were twice as many social drinkers as complete abstainers. On the other hand, a 20 year follow up of 850 patients treated for alcohol dependence in Catalonia showed abstinence was the most common and stable outcome, which one third of the initial sample had achieved at the follow up (25).

1.5 TREATMENT SYSTEM IN SWEDEN

Sweden passed its first law for treatment of alcohol dependence in 1913 (26). Historically, the system was designed to protect society and families of drinkers, rather than to offer treatment. This was targeted mainly at people of lower socioeconomic background. From the 1960's and onwards there has gradually been more focus on treatment for individuals with dependence.

Today, the responsibility for treatment of substance use disorders is shared between municipal social services, regulated in the Social Services Act, and the county councils or regional counties, regulated in Health and Medical Services Act (27). Services offered by social services vary considerably between regions in Sweden, but usually include outpatient counseling as well as residential treatment provided by private or not for profit providers. The health care services are responsible for medical treatment. This includes treatment for serious withdrawal, pharmacological treatment and treatment for medical complications due to high alcohol consumption, e.g. liver disease, neurological disorders, affective disorders, etc. However, the shared responsibility is implemented in different ways across the country, with local collaborations between social services and specialized addiction units, specialist psychiatric units or primary care. Most health care providers offer some form of preventive services, even if these are vary in scope.

1.6 A LARGE TREATMENT GAP

Alcohol dependence has, compared to other psychiatric disorders, one of the largest gaps between the number of individuals affected and the number in treatment (28). Estimates from 26 countries worldwide suggest only 7 % of individuals with substance use disorders receive treatment (29). Among patients in primary care in six European countries, less than one in five with alcohol dependence were in treatment (30). Similar conclusions are drawn from surveys in the general population in North America (31).

Individuals in treatment typically have a more severe form of dependence, higher alcohol consumption, co-morbid disorders and are less well socially integrated (32, 33). On the other hand, individuals with mild to moderate alcohol dependence tend to have less co-morbidities, are better socially integrated and do not seek treatment to the same extent. This phenomenon has been called “the two worlds of alcohol problems” (33), as the characteristics of these two groups are so different from one another.

In order to reduce alcohol related harm, it is important to improve treatment coverage. By treating two out of five with alcohol dependence, rather than today's one in five, it is estimated 12 000 lives in the EU can annually be saved (6). From a public health perspective, it is important to investigate why individuals do not seek treatment.

1.7 PUBLIC PERCEPTIONS OF ALCOHOL DEPENDENCE AND TREATMENT FOR ALCOHOL DEPENDENCE

The public both encourages and discourages treatment seeking for alcohol dependence in a number of different ways. One way of increasing the understanding of alcohol dependence and addiction treatment is through understanding public perceptions better.

In a survey from Alabama, most responders preferred informal help for milder problems and formal treatment for more severe problems (34). Results from a survey in Australia, show strong support for all types of treatment for alcohol dependence, where most saw alcohol dependence as a disease (35). This is in line with a survey from Spain, where the vast majority of respondents (87 %) also viewed alcohol dependence as a disease, and a minority (9 %), viewed it as a bad habit (36). A majority of the responders (68 %), and especially women and older, viewed primary care as suitable for treatment.

In a case vignette study from North America, the general public was found to endorse non-pharmacological treatments for alcohol dependence, as psychotherapy, talk to family/friends and self-help groups to the largest extent (37). The choices of treatments were strongly related to perceptions of causes of alcohol dependence. Similar conclusions are drawn in studies from Brazil, where a majority of participants express a view of alcohol dependence as a psychosocial and moral issue and where help from lay-people or psychologists are preferred (38, 39). Public perceptions of treatment for other psychiatric conditions, as depression and schizophrenia, resembles the ones for alcohol dependence, with a preference for psychotherapy to pharmacological treatment, and an association between treatment preference and the understanding of the cause of the condition (40).

1.8 BARRIERS TO TREATMENT

In order to increase the rate of treatment seeking, and decrease the treatment gap, there is a need to understand why individuals with alcohol dependence do not seek treatment. One approach is to investigate which barriers to seeking treatment are reported. Saunders et al. (41) have proposed a model of treatment seeking, consisting of four steps with unique barriers at each step. The first step is recognizing having an alcohol problem. The second, deciding change is needed, followed by the decision that treatment is needed. The fourth and last step is seeking treatment. The barriers are divided into “person-related” and “treatment-related”. Person-related barriers include cognitive or emotional features, such as not recognizing one’s alcohol use is problematic or shame. Treatment-related barriers include scarce availability of treatment or negative emotions towards the types of treatment offered. Person-related barriers are most common in the first two steps of treatment seeking, while the latter two steps often include a combination of person-related and treatment-related barriers. Individuals in population surveys predominantly tend to report person-related barriers to seeking substance use treatment (42, 43).

A recurring person-related barrier is not recognizing problems related to alcohol and not perceiving a need for treatment (29, 44-46). Problem severity has been suggested as a gradient, where not perceiving a need for treatment is more common at lower problem severity compared to higher problem severity (31, 45). In addition, there are indications that age is an important factor, as younger (age 26-34) and older (65 +) are less likely to perceive a need for treatment (47). Another barrier is the wish to handle alcohol problems on one’s own (44, 46).

One of the most important person-related barriers to treatment is shame and the stigma surrounding alcohol dependence and addiction treatment (45, 46). One study has found older people (65+) less likely to report stigma as a barrier to seeking treatment (47). Stigma will be discussed in more detail in the next section.

Among treatment-related barriers, a lack of knowledge about available treatment options plays a role, as do concerns about treatment content, such as treatments with only abstinence as a goal (48). Among older people (65+) the main reason given for not seeking treatment was “not ready to stop use” (47), a reason also common in a survey in a primary care setting in Spain (49).

A structural, treatment-related, barrier in many parts of the world is lack of access to treatment (29). Little is known about barriers to treatment among different ethnic minorities. A survey from North America found African Americans and Latino/os reported more structural rather than attitudinal barriers to treatment (50). In addition, consumer dissatisfaction with existing services, rather than lack of availability, can impede utilization (34).

1.9 STIGMA

Alcohol dependence is among the most highly stigmatized mental health disorders in the Western world (51). Individuals with alcohol dependence are viewed as being more responsible for their disorder and elicit more social rejection and more negative emotions compared to other disorders. This can lead to discrimination towards affected individuals, where they have more difficulties gaining work, housing or receiving health care. This stigmatization has been found stable over time (52). In the modern era, alcohol dependence has been associated with a loss of control over one's drinking and also loss of control over one's life, which are aspects that constitute parts of the moralization and stigma (53). Also, the view that alcohol dependence is associated with being "irresponsible" has been suggested a core component of the stigma (52).

Stigma is a social process of rejection and degradation of certain groups in society. Irving Goffman defines stigma as "a mark that leads to spoiled identity" (54). Goffman differentiates "discredited" stigma from "discreditable" stigma. The first refers to a visible mark, such as biological gender leading to discrimination. The latter refers to a concealed mark, where others cannot judge the presence or absence of the mark from the outside of the person. In the case of discreditable stigma, which alcohol dependence is an example of, the labeling is often via association.

Health-related stigma is the stigmatization of people affected by different health conditions (55). Public stigma and self-stigma are two different aspects of health-related stigma. Public stigma is negative perceptions and stereotypes about a specific group by the population (56). A person with a medical condition may internalize the public stigma, a process called self-stigma (57). There are four different stages of self-stigma: the first, stereotype awareness (aware), which describes whether the individual is aware of the stereotype of the public stigma. The second stage, is stereotype agreement (agree), and describes whether the individual agrees with the stereotype or not. The third stage, self-concurrence (apply),

describes whether the individual applies the stereotype to themselves. Stage four describes self-esteem decrement (harm), whether applying the stereotype causes negative consequences to the individual. Self-stigma among people with alcohol dependence has been shown to lead to lower self-efficacy and lower drinking-refusal skills (58). Higher level of self-stigma is also associated with more severe substance use, and has been suggested as a possible factor influencing outcome of substance use treatment (59). As described above, shame and stigma are also important barriers to seeking treatment for alcohol dependence (45, 46)

Even though alcohol dependence is among the most highly stigmatized disorders, research in the field is scarce. Recently there have been calls for more research in order to understand these processes more fully, especially how stigma affects individuals with dependence (60, 61).

1.10 TREATMENT PREFERENCES AMONG INDIVIDUALS WITH DEPENDENCE

A complement to studies of barriers to treatment is to investigate treatment preferences. However, this topic has received little attention, even though there have been calls for more consumer-oriented approaches (34). Involving problem drinkers who are not treatment seekers can be one possible way of increasing treatment engagement.

A vignette study from North America, including treatment naïve individuals with alcohol dependence, showed that around 20 % were positive to seek treatment in primary care (62). In a survey of individuals with hazardous or problematic alcohol use identified in primary care, the majority were positive to seek treatment in primary care and would prefer pharmacological treatment that would help them cut down without making them feel ill if they drank alcohol (63). A sample of participants in an internet-intervention to reduce drinking expressed a preference to receive treatment at their level of problems and also treatments that make it possible to maintain their everyday lives (64). Also, they preferred treatment services that allowed a goal of moderated alcohol consumption rather than abstinence-only.

1.11 INTERVENTIONS TO REDUCE ALCOHOL USE IN PRIMARY CARE SETTINGS

Primary care has for a long time been emphasized as a setting with the potential of reaching a large proportion of individuals with excessive alcohol use (65). Firstly, primary care has contact with a large proportion of the population. Secondly, alcohol is a relevant factor for many health issues treated in primary care (4). Thirdly, patients seeking treatment in primary care, for other conditions than problematic alcohol use, have been found to have a higher prevalence of alcohol dependence, compared to the general population (30). This contributes to primary care having an important role, both in regards to interventions aimed at prevention and treatment of excessive alcohol use.

1.11.1 Brief interventions

Brief interventions (BI) is a secondary prevention intervention aimed to reduce alcohol use among individuals with hazardous use by enhancing the patient's motivation to change their drinking (66). Many individuals are unaware that their level of drinking is potentially harmful for their health, and also of how their alcohol use might affect the medical conditions they present for in primary care. Brief intervention is aimed at patients who are not primarily treatment seekers for their alcohol consumption, where the health care staff raises the issue of alcohol. This is also known as opportunistic screening.

The WHO has pursued brief interventions in primary care, starting with the development of the AUDIT questionnaire in the 1980's (67) and the following WHO brief intervention study (68). This trial showed promising results, that brief interventions significantly can reduce alcohol consumption. In the large SAMHSA (the US Substance Abuse and Mental Health Services Administration) project that has been ongoing since 2003, Referral to Treatment was added to the model, expanding it to Screening, Brief Interventions and Referral to Treatment (SBIRT) (69). The focus on Referral to Treatment was to guarantee individuals in need would have access to specialist care. In addition, brief treatment was also added to the SBIRT model.

SBI usually includes questions covering the patient's level of alcohol use, consequences of drinking or a questionnaire, as the AUDIT (66, 70). This is then followed by normative feedback on the patient's alcohol use in comparison to national guidelines for low risk drinking or health risks associated with drinking, and advice how to cut down. As the name

suggests, SBI can be delivered in a short time within a regular consultation in generalist health care settings, for example primary care. For patients with alcohol use disorders, referral to specialist treatment is suggested.

The effects of brief interventions for individuals with hazardous consumption of alcohol has been well studied. A recent meta-analysis including 15 197 participants in 34 randomized controlled trials, showed that brief interventions reduce alcohol consumption by around 20 grams per week at 12 months follow up compared to a minimal intervention (70). The effects seem to be larger for individuals with hazardous use at higher consumption level.

The results from BI trials have sparked hope that disseminating alcohol interventions into routine clinical practice can substantially reduce alcohol related harm. However, there are issues regarding the application of SBIRT in primary care settings.

The first issue is the difficulties implementing SBI in regular clinical practices despite great efforts (71). One example is the Swedish Risk Drinking Project that was carried out between 2004 and 2010 (72). This was a large-scale implementation project of SBI in primary care, occupational health and maternity care. In occupational health and maternity care, SBI has been better implemented compared to primary care. Despite this large implementation effort, few individuals in the general population (13-14 %) reported having discussed their alcohol consumption at their last health care visit (73, 74). Data from a telephone survey to the general population in one county council, Uppsala, indicates the level of activity in primary care increased during the time-period of the project (75). The rate of individuals who respond they have been screened during visits in health care settings increased from 15 to 33 %, however the rate of BI only marginally increased from 3.2 % to 4.2 %. More studies have now focussed on understanding factors which increase SBI activities among primary care clinicians, where for example training, support and financial reimbursement have been found important (76). In the SAMHSA SBIRT project, the programs tended to hire specially trained staff to deliver SBI and brief treatment (69, 77). A need to broaden the delivery of SBIRT from general practitioners to other staff was highlighted, as well as the need to develop for example digital interventions (77).

The second issue is the absence of evidence for the effects on alcohol consumption for individuals who have developed alcohol dependence (78, 79). In addition, there is a lack of evidence that screening and brief interventions lead to a higher rate of treatment utilization in

specialist care among problem drinkers, independent of problem severity (80). This highlights the question of whether primary care can provide treatment for alcohol dependence, and with which effects.

1.11.2 Models for treatment of alcohol dependence

As described above, most treatment studies in primary care have included individuals with hazardous or harmful consumption, and less focus have been made on models for treatment of alcohol dependence.

In an early trial of treatment for alcohol dependence in primary care in Great Britain, Drummond et al. (81), found no difference in reduction of alcohol consumption for patients treated by general practitioners compared to specialist treatment. However, the study has several methodological limitations. In a Canadian study, general practitioners proactively screened patients' with a history of trauma, for alcohol use (82). At 12 months follow up, patients randomized to three hours of cognitive behavioural therapy showed a greater reduction of alcohol use compared to those randomized to advice. A majority of the patients, 60 %, fulfilled criteria for alcohol dependence.

1.11.2.1 Pharmacological treatment

To our knowledge, three randomized controlled trials have evaluated the effects of pharmacological treatment in primary care delivered by generalists without specialist training in addiction medicine. Two studies of acamprosate showed mixed results (83, 84). One trial with nalmefene combined with a minimal psychosocial intervention was found to reduce the number of heavy drinking days compared to placebo (85).

1.11.2.2 Integrated psychosocial treatment with pharmacological treatment

In order to improve compliance to treatment for alcohol use disorders in general and pharmacological treatment specifically, integrating psychosocial treatment with pharmacological treatment has been suggested (86, 87).

The best known model is probably the manual for medical management from the COMBINE study (87, 88). The content of the sessions focus on:

- Medication compliance
- Side effects
- Laboratory tests
- Progress of the treatment/assessment on drinking
- Education
- Support.

The goal of treatment according to the manual is abstinence only, and participation in support groups, as AA, is advocated. The initial visit lasts up to 60 minutes, and the following visits 15-25 minutes. Pharmacological treatment in combination with medical management has been found to be effective in reducing alcohol consumption (88). Medical management was developed to be delivered by generalist staff, in order to be readily implemented in generalist settings. However, the COMBINE trial was performed in specialist care setting.

A slightly different approach from medical management is the BRENDA model, which is based on six components (86, 89):

1. Assessment
2. Feedback
3. Empathy
4. Identify patient's needs
5. Advice to patient
6. Assess reaction of advice, and adjust advice if needed.

In this model moderated alcohol use can also be a goal. Each session is approximately 15 minutes, with slightly longer for the first session. O'Malley et al., studied effects of treatment with naltrexone combined with behavioural interventions in primary care compared to specialist care (90). The behavioural intervention was a type of medical management similar to the one described in the BRENDA model, and was delivered by generalists without specialist training in treatment for alcohol dependence. The caregivers were regularly supervised. The authors found an advantage for specialist care on the primary outcome measure per cent days abstinent, but no differences on the secondary drinking outcomes during the first 10 weeks of treatment.

1.11.2.3 Chronic Care Model

The Chronic Care Model (CCM) gives a framework for management of chronic conditions in primary care, first described by Wagner et al. (91). This is a patient-centred model, which often includes; identification, attempts to engage the patient in care, monitoring and treatments according to the patient's needs. A multidisciplinary team consisting of psychiatrist, psychologist, social worker and nurse can deliver the care, and it is then often referred to as "collaborative care" (92, 93). As suggested by the name, the team collaborates with the primary care staff around the care of the patient.

Willenbring adapted the CCM to management of alcohol dependence, where it mainly has been applied to management of severe alcohol dependence, in populations where medical, psychiatric and social issues are common (92, 94-98). The intervention often lasts 12 months. CCM has shown mixed results in trials. Willenbring compared CCM to regular primary care, and a reduction of alcohol consumption was shown for the whole sample at 24 months follow up compared to baseline assessment, with a larger proportion of abstinent patients in the CCM group (95). Oslin et al. (97) found that treatment in primary care was more effective in reducing heavy drinking days compared to specialist care. Also, retention to treatment was significantly higher in primary care. A recent study showed that care based on similar principles increased treatment utilization and abstinence among individuals with alcohol dependence (98). In contrast to these studies, Saitz et al. (94) found no benefit for CCM compared to usual care, nor did Bradley et al. (99). The differences in outcomes between trials can be explained by differences in patient characteristics, where severe psychiatric comorbidities and dependence on illicit drug can hamper effects (99).

1.11.2.4 Stepped care

Stepped care has been suggested as a cost effective approach to treatment for alcohol problems (100). Stepped care is an individualized approach, which begins with a low intensity intervention and continues up to more intense interventions if no progress is made. Thus, how the patient's alcohol use develops during treatment, rather than his or her pre-treatment characteristics, guides the type and amount of interventions that are delivered. As there is a lack of evidence for the hypothesis of matching patients to treatment based on their characteristics, stepped care is a viable option. One important question in stepped care models concerns the criteria for moving to the next step, and thus how success is defined. Even though this model can be one way of making alcohol interventions available to a larger group of the population, there are few studies of stepped care models in primary care.

In a feasibility study in primary care units in Wales, a 5-minute minimal intervention was compared to a stepped care model in three steps, consisting of a single session, four motivational enhancement therapy (MET) sessions and in the third step referral to specialist care (101). Male patients with an AUDIT score of eight or more, or an alcohol diagnosis were opportunistically recruited. At follow-up both groups showed a reduction in alcohol consumption, however there were no significant difference between groups. Following this feasibility study, a larger study (n=529) with the same design, but targeting individuals aged 55 years and older, was conducted, the AESOPS (102). A majority of the sample, 80 %, were male and 8 % had an AUDIT score of at least 20. Again, no differences in average drinks per day were found between the two conditions at 12 month follow up.

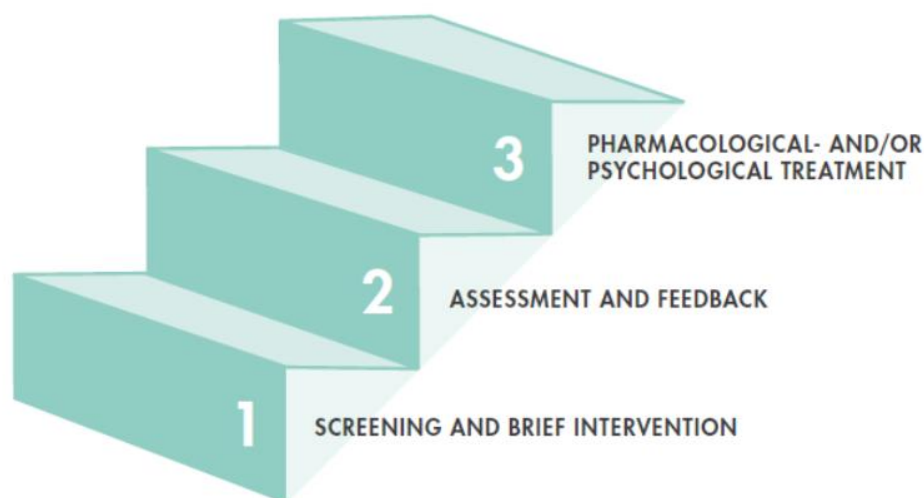
In a study in primary care units in Luebeck and Kiel, opportunistically recruited participants were randomised to stepped-care, full care or control group with no treatment (103). The stepped care consisted of a computer-based intervention plus up to three 40-minute telephone-based motivational interviewing (MI), depending on success. Full care consisted of the same computer based intervention plus four 30 min telephone based MI sessions. At 12 month follow up, patients with hazardous consumption or alcohol abuse who received stepped care or full care significantly reduced their alcohol consumption, compared to the control group. However, no effects were found for patients with alcohol dependence.

1.11.2.5 Low- and middle-income countries

Most research on alcohol interventions has been conducted in high-income countries in the Western World. Low- and middle-income countries face different challenges compared to high-income countries, for example low availability of specialist care and lack of trained staff. Research from Goa in India, showed that brief psychological treatment in primary care, delivered by lay counsellors, can be effective in reducing alcohol consumption among hazardous and harmful drinkers (104). The effect was sustained, and even improved, at 12 month follow up (105).

1.11.3 Theoretical framework and rationale for the 15-method

There is thus robust evidence that BI gives a small but clinically significant effect on reducing alcohol use among individuals with hazardous consumption (70). However, there is lack of evidence that referral to treatment increases utilization of specialist care (80). Most studies on treatment for alcohol dependence in primary care have focused on individuals with severe alcohol dependence, often with co-morbidities (92, 94-99). Stepped care model has the possibility of disseminating alcohol interventions to larger populations of individuals with alcohol use disorders (100). However, there are no studies of brief treatments integrated with pharmacological treatment delivered in a stepped care model. With this background, our group has developed a manual for management of hazardous drinking and alcohol use disorders in primary care – the 15-method (106). The model consists of three steps, starting with a brief intervention and moving to the next, more extensive, step if needed. The name refers both to the length of the sessions, 15 minutes, and that the target group for the intervention in the second and third steps are patients who score above 15 points on the AUDIT (67).



The first step, is screening followed by a brief intervention (SBI) (70). From a public health perspective, SBI can play an important role as a secondary prevention intervention, reducing alcohol consumption among hazardous consumption. However, for individuals who have developed more a problematic drinking, a more intensive intervention is in many cases called for. In the 15-method, moving to step two is suggested for patients scoring above 15 points on the AUDIT (67), or who express concern about their alcohol use.

Step two, is an assessment with self-report questionnaires and biological markers, focusing on the consequences of alcohol consumption, followed by a feedback session (107, 108). Many individuals with excessive alcohol use express ambivalence about changing their alcohol use, and ambivalence about entering treatment. This intervention can be a suitable first step in to treatment; a possibility to assess problems associated with alcohol use and enhance the patient's motivation to change.

The assessment focuses on the following areas, which in previous studies have been shown to be clinically relevant for treatment of alcohol dependence:

- a) Alcohol use
- b) Biological markers
- c) Severity of dependence
- d) Mental health
- e) Motivation to change

a) Alcohol use

Time Line Follow Back 30 days (TLFB30) measures frequency and intensity of alcohol consumption (109), where the patient self-rates their drinking in standard units for each day, during the previous 30 days (110). TLFB30 also gives an overview of drinking pattern and HDD.

b) Biological markers

Hans Kristenson et al. (111) was one of the first to show that monitoring biomarkers in combination with a brief intervention could reduce alcohol consumption among men with excessive alcohol use, of whom many probably had developed alcohol dependence.

Biological markers can also play an important role in enhancing motivation to reduce alcohol use.

Carbohydrate-deficient transferrin (CDT) and phosphatidylethanol (PEth) are alcohol specific biomarker (112). Alanine amino transferase (ALT), aspartate amino transferase (AST) and gamma-glutamyl transferase (GGT) are enzymes mainly found in the liver (113-115). Elevated levels are a marker for liver dysfunction and a possible indicator for excessive alcohol use.

c) Severity of dependence

Patients who have developed alcohol dependence, compared to those with hazardous or harmful use, often have more difficulties reducing their alcohol consumption. They can need treatment that is more extensive. In addition, it is important to assess severity of dependence, as this has shown a predictive value for drinking outcomes (116). A mild to moderate severity has been predictive of moderate drinking outcomes, while stable outcomes associated with severe dependence has rather been complete abstinence. Two questionnaires measure severity of dependence: ICD-10 criteria for alcohol dependence (13) and Alcohol Use Disorders Identification Test (AUDIT) (67).

d) Mental health

Depression and anxiety are overrepresented among individuals with excessive alcohol use (31). Concurrent psychiatric disorders are associated with a worse outcome for the dependency treatment (117). An additional reason to assess depression and anxiety is that deterioration in psychological health can be one reason why the patient has chosen to seek treatment. This is therefore important to pay attention to, in order to be able to enhance the patient's motivation to change. Hospital Anxiety and Depression Scale (HADS) measures symptoms of anxiety and depression (118).

e) Motivation to change

The transtheoretical model for change is the base for the concept of Readiness to Change (RTC) (119). RTC includes both how important the patient perceives making a change is, in this case alcohol use, and how the patient perceives their self-efficacy in making this change. The evidence for how RTC relates to outcome is mixed. Some studies have found high RTC before start of treatment associated with lower alcohol consumption at follow up, while other studies have not found an association (120, 121). There are evidence that the different aspects of RTC have different predictive value, where self-efficacy has the most predictive value (116). Readiness rulers measure RTC, where the patient rates, on a visual analogue scale (VAS) how important change is and their self-efficacy in making the change (122).

The feedback session in step 2, is based on FRAMES, an acronym for components that have been found common in brief interventions (123):

- Feedback of personal risk
- emphasis on personal Responsibility for change
- offer Advice to change
- giving a Menu of alternatives for how to change
- showing Empathy from the treatment provider
- enhancing Self-efficacy

The feedback session focuses on the patient's motivation to change, using motivational interviewing (MI). The key principles in MI are expressing empathy, develop discrepancies, avoid argumentation, to roll with resistance and support self-efficacy to change (124). The session can also include handing over self-help material. Self-help material, or bibliotherapy, has been shown to reduce alcohol consumption among people with moderately severe problems, especially among participants recruited via advertising (125).

This type of intervention - a single feedback session based on short questionnaires and laboratory tests, also known as the Drinker's Check Up, has been found to decrease alcohol consumption (107, 108). However, this intervention is not sufficient for all individuals with problematic drinking. Miller et al. (108) found that many participants reported persisting problems at follow up. For patients requesting more support to change their alcohol use, step 3 is offered.

Step 3 draws on the observation that evidence-based treatments for alcohol dependence have low to moderate effectiveness, and that from what is known today – one treatment cannot be seen as the Gold Standard and recommended prior the others. Rather, a patient centered approach where the treatment provider offers a menu of available psychological and pharmacological treatments and lets the patient's preference guide the choice seems the best choice. Therefore, in step 3 the patient chooses whether to receive psychological treatment, pharmacological treatment or a combination of the two.

Linda and Mark Sobell developed brief cognitive behavior therapy, or Guided Self-Change (GSC), in the early 1980's (126). GSC aims to facilitate self-change, and has been shown to reduce alcohol use among individuals with mild to moderate alcohol problems (126-128). Most GSC manuals include goal setting, self-monitoring drinking, identifying risk factors and

coping skills. Often techniques from motivational interviewing are also integrated. GSC is based on CBT principles and therefore overlaps with themes that are included in other CBT manuals, for example identifying antecedents/stimuli that elicit problematic drinking when working with risk factors and problem solving. However, the model differs from other cognitive behavioral therapies for alcohol use disorders, in that it does not emphasize behavioral coping skills to the same extent as, for example relapse prevention or coping skills training (129). GSC has mainly been studied among problem drinkers and mild to moderate dependence. The assumption has been that this group does not have the same need for training coping skills in order to change their problematic drinking. Rather, GSC is mainly a help to self-help by strengthening the patient's own resources and self-efficacy to change. GSC can also be suitable for generalist staff, as it is an easy protocol and structure to follow.

For the manual of the 15-method, four sessions is suggested. Each session contains a theme to facilitate behavior change: goal setting, self-monitoring of alcohol consumption, identifying risk situations and problem solving. The goal setting is performed in a patient centered approach where the patient chooses the goal – moderated consumption or abstinence.

For patients who prefer pharmacological rather than psychological treatment, or a combination of the two, these four sessions can be combined with pharmacological treatment approved by the Swedish Medical Products Agency for treatment of alcohol dependence in Sweden; acamprosate, disulfiram, nalmefene or naltrexone.

The pharmacological anti-craving treatments draw on neurobiological understandings of dependence, and all aim to reduce the rewarding effects of alcohol. Naltrexone is an opiate receptor antagonist, which has shown efficacy in reducing risk of heavy drinking and reducing alcohol consumption among individuals with alcohol dependence (130). Acamprosate is a putative glutamate modulator, which has shown to reduce risk of drinking (131). A meta-analysis concluded acamprosate as more efficacious in maintaining abstinence compared to naltrexone, while naltrexone was found more efficacious in reducing heavy drinking (132). Nalmefene is, as naltrexone, an opioid antagonist. Randomized controlled studies of as-needed use show a reduction of heavy drinking days and overall alcohol consumption compared to placebo (133, 134). Disulfiram inhibits the liver enzyme aldehyde dehydrogenase, and intake of alcohol during treatment causes unpleasant somatic reactions. The mechanism can also be understood from a behavioral paradigm; where treatment can

lead to a reinforcing experience of abstinence for the patient, or a punishing experience of alcohol intake. Meta-analysis has shown supervised treatment to have some effect on drinking outcomes (135). Medical management is a part of all pharmacological treatment, where the practitioners monitor the progress of treatment in a structured way (87).

2 AIMS

The overarching aim of this thesis was to study possible strategies to involve a larger proportion of individuals with alcohol dependence with treatment.

Specific aims of the four studies were to:

Study I: Investigate what type of treatment for alcohol problems, and what setting, is preferred in the general population, and also the reasons for not seeking treatment for alcohol problems.

Study II: Describe and explain how people with alcohol dependence perceive and discuss treatment for alcohol use disorders and their reasons for seeking and not seeking treatment.

Study III: Investigate if treatment for alcohol dependence in primary care is as effective as standard treatment delivered in specialist care at six month follow up.

Study IV: Investigate if treatment for alcohol dependence in primary care is as effective as standard treatment delivered in specialist care at 12 month follow up. In addition, trajectories for change of alcohol consumption were investigated.

3 METHODS

In the four studies in this thesis, both quantitative and qualitative research methods have been applied in order to study the research questions. In study I, we used a cross sectional research design, in study II we used focus group interviews and individual interviews, and study III and IV were designed as a randomized controlled trial.

The Regional Ethics Board in Stockholm approved all studies.

Study I: Dnr 2012/1759-31/5.

Study II: Dnr 2011/1524-31/4.

Study III and IV: Dnr 2012/1760-31/1.

Each subject provided an informed consent before the study procedures began.

In this section, I will describe the methods used in more detail and discuss ethical issues in each study. As study III and IV are based on the same trial, I will describe the method for these studies jointly.

3.1 STUDY I: PREFERENCES REGARDING TREATMENT FOR ALCOHOL PROBLEMS

In study I, the aim was to investigate what type of treatment for alcohol problems and which treatment settings, the general population prefer. We also wanted to study the reasons for not seeking treatment for alcohol problems. Furthermore, we wanted to study whether level of alcohol consumption, education, employment status and income would influence these preferences. As described previously, only a minority of all individuals with alcohol dependence seek treatment (29). However, knowledge about how the general population perceive treatment for alcohol dependence and barriers to seeking treatment is scarce.

3.1.1 Method

Data for this study were collected as a part of a cross-sectional, interview survey of the Swedish general population, aged 16–80 years (136). Alcohol consumption was measured with 18 questions on volume and frequency of consumption during the previous 30 days. Regarding preferred type of treatment, the respondents could choose the following alternatives (one to five); help via the Internet; support group [e.g. alcoholics anonymous (AA)]; psychotherapy; pharmacotherapy and residential treatment. For preferred source of treatment four alternatives were given; social services; psychiatry or addiction specialist treatment; primary health care and occupational health services. The respondents were given four alternatives regarding reasons for not seeking treatment; did not believe there is any effective treatment; concerns about confidentiality; would be ashamed to seek help for alcohol problems and did not know where to seek help.

3.1.2 Participants

From April to September in 2010 1500 new, randomly selected Swedish-speaking respondents were interviewed each month, Response rates were on average 62 %. In total, 9005 persons aged 16–80 were included in the analyses. During the first month of data collection, direct questions regarding the treatment questions resulted in very few responses. This resulted in a decision to change the question, so that the respondents were asked the treatment questions in an indirect way, with regard to someone they know, a friend or relative, as opposed to preferences were they themselves to develop alcohol problems. This gave a higher frequency of responses.

3.1.3 Data analyses

Proportions of respondents, preferring a certain treatment; a certain source of treatment and giving reasons for why people do not seek treatment for alcohol dependence were calculated in relation to the number of standard drinks, employment, education and income. All analyses were completed for men and women separately, and, in most cases, separately for different age groups. Chi square analyses were used to examine possible gender and/or group differences. Bonferroni correction was used to test for spurious significances.

All analyses were performed with SPSS version 20.

3.2 STUDY II: ALCOHOL CONSUMPTION, DEPENDENCE AND TREATMENT BARRIERS: PERCEPTIONS AMONG NON-TREATMENT SEEKERS WITH ALCOHOL DEPENDENCE

In Study II, the aim was to continue the line of research regarding barriers to seeking treatment and treatment preferences, and to study how people with alcohol dependence perceive and discuss treatment for alcohol use disorders and their reasons for seeking and not seeking treatment. We also analyzed the results in relation to the participants' severity of alcohol dependence, age and occupational status. The background to this study, as in study I, draws on the observation that few individuals seek treatment for alcohol dependence, and specifically that few studies have investigated treatment preferences. Qualitative research method has the possibility to give greater nuances to the understanding of these phenomena, and possibly generate new hypotheses.

3.2.1 Method

Focus group discussions were used to elicit points of view as well as socially shared representations of alcohol consumption and treatments (137). However, as focus group discussions between strangers may not always generate personal accounts (138), individual interviews were also conducted to enrich the data.

Semi-structured questions based on eleven themes were developed for the group discussions. The themes covered different aspects of the participants' views on alcohol consumption, alcohol problems and dependence, treatment options and settings. For the individual interviews the same questions were used, but with a greater focus on individual experiences.

3.2.2 Participants

Our goal was to recruit participants outside of the treatment systems, and therefore enlisted a market research company with access to a panel, consisting of approximately 115 000 people living in Stockholm county, Sweden. In total 32 participants, age 18-62 with a hazardous alcohol consumption measured with AUDIT-C (67) and fulfilling DSM-IV criteria (15) for alcohol dependence were included. The participants were allocated to seven focus groups according to: number of DSM-IV criteria for alcohol dependence met, age and occupational status. Due to difficulties recruiting participants fulfilling five to seven criteria, one group was mixed in regards to occupational status. All participants were

offered to also attend an individual interview, which almost all participants were interested in. Two participants from each focus group were randomly chosen. In total 14 individual interviews were carried out. Data was collected between December 2011 and May 2012.

3.2.3 Data analyses

The interviews were transcribed verbatim. Data analysis was performed using thematic analysis as described by Braun & Clarke (139). Data was read repeatedly to identify categories of relevance to the research aim. These categories were then grouped accordingly to coherence in topic, as well as in relation to the research aim, and themes were thereby constructed. The themes were defined as a result of interplay between the data, research aim, and theory.

3.3 STUDY III: TREATMENT FOR ALCOHOL DEPENDENCE IN PRIMARY CARE COMPARED TO OUTPATIENT SPECIALIST TREATMENT – A RANDOMIZED CONTROLLED TRIAL

In Study III, the aim was to investigate if treatment for alcohol dependence in primary care was as effective as standard treatment delivered in specialist care, at six month follow up. The hypothesis was that treatment for alcohol dependence in primary care with the 15-method was non-inferior to specialist care. The majority of studies on alcohol interventions in primary care have focused on individuals with hazardous alcohol consumption, while few models for treatment of alcohol dependence have been studied.

The trial was registered at Controlled Trials.com, ISRCTN84490505.

3.3.1 Method

Randomized controlled non-inferiority trial, between groups parallel design.

During the planning phase of the trial we thoroughly discussed the choice of non-inferiority limit. At that time we found no published studies in the alcohol field with a non-inferiority design. The study we judged to be closest in characteristics of the participants and the intervention, to the study we planned, was a previous study from our research group (127). In this trial, socially well-adjusted heavy drinkers, with moderate levels of dependence severity, received either four sessions of guided self-change or one session of advice. Guided by the characteristics and results, we deemed a difference in alcohol consumption of 50 grams, or approximately four standard drinks, between groups, clinically non-significant in this heavy drinking population. Therefore, the non-inferiority limit was set to a difference of 50 grams of alcohol per week on the pre-specified primary outcome weekly alcohol consumption. Later, we have discussed the choice of non-inferiority limit with an expert panel of international researchers within the field. Their opinion was that the set limit was quite conservative, meaning that the study will not conclude non-inferiority, even at clinically very small differences between groups.

The manual for the intervention in primary care in this trial was adapted from the 15-method (106), which is a model for treatment of hazardous drinking and alcohol dependence in primary care. The name refers both to the length of the sessions, 15 minutes, and that the target group for the intervention in the second and third steps are patients who score above 15 points on the Alcohol Use Disorders Identification Test (67).

For this study, where participants were mainly recruited by advertisement, and had already completed intake assessment as a part of study procedures, the first step of the manual was redundant. The treatment according to the study manual consisted of a maximum of five sessions or 90 minutes over 24 weeks, starting on step 2 with the feedback session.

In order to keep the study naturalistic we wanted to collaborate with regular primary care units. During the spring of 2013 we sent out information about the trial by post to all primary care units in Stockholm county, asking whether they were interested in participating. We only received two replies; neither of the two generated a primary care unit that was interested in participating. After this, we decided to make contact via telephone to the head of primary care clinics, and asked permission to make a short personal visit and give an introduction to the study. This was a more successful strategy. During the autumn of 2013, we had set up collaborations with 12 primary care units in Stockholm, which was two more than we had aimed for. In total, 29 general practitioners received an eight hour training in the manual and in the study protocol during the autumn of 2013.

The specialist care was delivered by the regular clinical staff at Riddargatan 1, an alcohol treatment clinic within the Stockholm Centre for Dependence Disorders. The treatment in the study started with a visit to a physician, with feedback of the baseline assessment. Then, information was given about the pharmacological and psychological treatments, and shared decision-making guided the choice of treatment. The pharmacological treatments were identical to the ones in primary care regarding substances and dosage, however, with 30 minutes per visit. The manual based psychological treatments were either motivational enhancement treatment (four sessions) (140), guided self-change (four sessions) (126), relapse prevention (six to eight sessions) (129), behavioural self-control training (four to five sessions) (141) or 12-step treatment (12 sessions) (142). Each session in the psychological treatments lasted 45 minutes.

The primary outcome was change in weekly alcohol consumption measured in grams of alcohol before inclusion compared to six months after start of treatment. The secondary outcomes were: HDD (women > 3/men > 4 standard units of 12 g of alcohol) per month; severity of dependence; consequences of drinking; symptoms of anxiety and depression; health related quality of life; satisfaction with treatment and biomarkers.

3.3.1.1 Questionnaires

Time Line Follow Back 30 days (TLFB30) measures self-reported alcohol use during the previous 30 days (109). TLFB30 was used to assess weekly alcohol consumption and HDD. The questionnaire has been evaluated in a Swedish population with patients in treatment for alcohol dependence, and have sound psychometric qualities (110).

Severity of alcohol dependence was assessed with Alcohol Use Disorders Identification Test (AUDIT) (67); the ICD-10 criteria for alcohol dependence (13) and Short Alcohol Dependence Data Questionnaire (SADD) (143). As AUDIT and the ICD-10 criteria assess the last 12 months, these questionnaires were re-worded for the six month follow up to only cover the past six months.

Alcohol Use Disorders Identification Test (AUDIT) measures alcohol use and hazardous drinking. AUDIT has been developed by the WHO (67), and translated and validated in Swedish (144). The questionnaire consists of ten questions, scored 0-4, with a total score between 0 and 40. Reliability and validity have been found to be good (145, 146).

ICD-10 is a diagnostic manual used in Swedish health care settings (13). To fulfil the criteria for alcohol dependence three or more of the diagnostic criteria need to be fulfilled during the last 12 months.

Short Alcohol Dependence Data Questionnaire (SADD) measures severity of alcohol dependence (143, 147). This is a 15-item self-rate questionnaire, measuring different aspects associated with alcohol dependence. The items are scored from zero to three, and the total score range between 0 and 45. SADD has not been validated in Swedish.

The Short Index of Problems (SIP) is a 15-item short version of the 50-item DrInC (Drinker Inventory of Consequences) developed by Miller et al. (148). SIP was developed by choosing the three items with strongest item correlation to each subscale of DrInC; interpersonal, intrapersonal, physical, impulse control and social. The questionnaire measures self-reported alcohol-related consequences during the last three months independently of severity of dependence or the amount of alcohol consumed. Each item is scored from 0 to 3 and the total score range from 0 to 45. Test retest reliability and intraclass correlations have been found to be moderate (149). There are, however, no validation studies completed in Swedish.

Symptoms of anxiety and depression were assessed with Hospital Anxiety and Depression Scale (HADS) (118). HADS has a total of 14 questions, seven measuring symptoms of anxiety and seven measuring symptoms of depression. The patient grades each item between 0 and 3. Maximum total score is 21 for each subcategory, i.e. anxiety and depression. Sensitivity, specificity and other psychometric properties have shown to be acceptable (150, 151). Lisspers et al. (152) have validated the questionnaire in a Swedish sample.

EuroQol 5 Dimensions (EQ-5D) (153) is a health related quality of life questionnaire, which is non-disease specific. It measures five health related dimensions; mobility, self-care, activities, pain/discomfort and anxiety/depression, and emphasizes physical health rather than psychological. Each dimension has five response categories ranging from no problems to extreme problems. The instrument is designed for self-completion, and respondents also rate their overall health on the day of the interview on a 0–100 hash-marked, vertical visual analogue scale (EQ-VAS). It has strong psychometric properties, but limited ability to discern small to moderate differences in health status (154, 155). The questionnaire has been validated in a Swedish population (156).

The transtheoretical model for change is the base for the concept of Readiness to Change (RTC) (119). Readiness to change was assessed with a visual analogue scale (range: 0–100), in which importance and confidence to reach ones goal [regarding alcohol] were rated (122).

Client Satisfaction Questionnaire (CSQ-8) is an eight item questionnaire measuring satisfaction with treatment (157). The items are scored from one to four, with a minimum score of eight and the maximum 32. The questionnaire has been correlated with treatment drop out, number of sessions attended and with change of symptoms (158). CSQ-8 has been validated in a Dutch population of patients in substance abuse treatment, and found to have high internal consistency (159). However, the authors note that this type of measurement suffers from strong ceiling effects. There are though no validation studies completed in Swedish.

3.3.1.2 *Biological markers*

Blood was analyzed for levels of carbohydrate-deficient transferrin (CDT), gamma-glutamyl transferase (GGT); aspartate amino transferase (AST) and alanine amino transferase (ALT).

CDT is an alcohol specific biomarker, where prolonged excessive alcohol consumption, on average at least 40 grams per day for two weeks or more, alter the pattern of serum transferrin (160). The half-life of transferrin is 1.5-2 weeks and after abstinence the levels normalizes (161). To reach a stable baseline level may require abstinence for one month or more (162).

GGT is an enzyme found in the liver and also other organs (115). Elevated levels is as a marker for liver dysfunction and an indicator for possible excessive alcohol consumption. However, the sensitivity and the specificity are low, as various other factors can elevate the level, such as medical conditions, individual factors and pharmacological treatment (113). The half-life of GGT is 2-3 weeks and after abstinence, the levels will normalize within a month.

ALT and AST are enzymes involved in amino acid metabolism, and mainly found in the liver (113). Elevated levels indicate liver injury, where high alcohol consumption is one common cause (114). The sensitivity and specificity as alcohol markers are low, as there are many other factors that can elevate the levels, such as obesity and pharmacological treatment (113).

3.3.1.3 Sample size

Sample size was calculated for the primary outcome based on Andreasson et al. (127), assuming a standard deviation of 140 g. A total of 250 patients were necessary to accomplish 80% power to confirm non-inferiority at a 95% confidence level. Assuming a dropout rate of around 20%, the aim was to include 300 participants.

3.3.2 Participants

Between October 2013 and March 2015, 288 participants were included. The participants were recruited via advertisement in newspapers, posters/leaflets at the primary care study sites or a direct question at a primary care consultation. After an initial telephone screening with a research nurse, eligible individuals were scheduled for an assessment. The inclusion criteria were: alcohol dependence according to ICD-10; ≥ 18 years old and living within Stockholm county. The exclusion criteria were: need of continuous support from the social services (homeless, financial support); previous severe withdrawal symptoms (seizures, hallucinations, delirium); misuse or dependence of narcotics or prescription drugs (ICD-10); severe somatic or psychiatric condition; or not able to understand Swedish.

Participants who gave informed consent and completed the baseline assessment were randomized to treatment either at primary care or specialist care. Participants randomized to primary care chose the primary care center that was geographically most convenient for them.



The poster/flyer used to recruit participants in primary care.

Translation of the text: "Do You Know Someone Who Wants To Cut Down Their Drinking?"

3.3.3 Data analyses

The primary analysis was based on the intention-to-treat (ITT) data set, using data from all available cases as randomized, i.e. all participants who completed follow-up measures at six months regardless of protocol adherence. The analysis of the primary outcome was performed using an analysis of covariance (ANCOVA) with the consumption at six months as the dependent variable, group as a factor variable, adjusting for baseline consumption. The same statistical model was used for analyses of secondary outcomes. Factors related to the primary outcome was analyzed with a regression model. Additional analyses used t-tests and chi-square tests. All analyses used two-sided tests and a significance level of $P < 0.05$. In-group effect sizes were calculated with Cohen's d .

Two sensitivity analyses were performed on the primary outcome. In the first, the ITT data set was used with multiple imputation by predictive mean matching (163). The second analysis was based on a per protocol (PP) principle, where participants with at least one treatment visit, no concurrent treatment for alcohol dependence during the six month follow up period and who completed the follow-up measures were included.

Statistical analyses were conducted with R, Version 3.1.0.

3.4 STUDY IV: TREATMENT FOR ALCOHOL DEPENDENCE IN PRIMARY CARE COMPARED TO OUTPATIENT SPECIALIST TREATMENT – A RANDOMIZED CONTROLLED TRIAL. 12 MONTH FOLLOW UP.

This is the 12 month follow up from the same trial as study III, where we wanted to investigate whether effects of treatment were sustained over time. The aim of this study was to investigate if treatment for alcohol dependence in primary care was as effective as standard treatment delivered in specialist care at 12 month follow up. In addition, trajectories for change of alcohol consumption were investigated, using WHO drinking risk levels as primary measure. A reduction of at least one WHO drinking risk level can be considered as significant, both from a clinical and public health perspective (164, 165).

WHO drinking risk levels.

WHO risk level (grams of alcohol per day)	<i>Females</i>	<i>Males</i>
Abstinence	0	0
Low risk	1 – 20	1 – 40
Medium risk	21 - 40	41 – 60
High risk	41 – 60	61 – 100
Very high risk	61 >=	101 >=

Results from studies in specialist care indicate that change occurs during the active treatment period (166), and is sustained up to 12 months (142, 167). Studies from primary care show similar results (94, 95, 105). However these results might not be applicable to the participants in this trial who mainly had more moderate severity of alcohol dependence and also received a shorter intervention compared to the other studies. The hypothesis was that treatment for alcohol dependence in primary care with the 15-method was non-inferior to specialist care. We hypothesized that the main reduction of alcohol consumption would occur during the treatment period for both treatment conditions, and sustained at 12 months follow up.

3.4.1 Method

This study is a part of the same trial as study III, therefore the method is described in detail previously.

3.4.2 Participants

The same participants as in study III were included in the analyses, with the addition of data from 231 participants who completed the 12 month follow up.

3.4.3 Data analyses

The primary analysis was based on the intention-to-treat (ITT) data set, using data from all available cases as randomized, i.e. all participants who completed follow-up measures at six months and 12 months regardless of protocol adherence. The analyses of the primary and secondary outcomes were performed using multilevel mixed effects linear regression. Treatment condition and time were set as fixed effects, while random effects estimated differences in change between individuals. Additional analyses used t-tests and chi-square tests. All analyses used two-sided tests and a significance level of $P < 0.05$.

Two sensitivity analyses were performed on the primary outcome. In the first, the ITT data set was used with multiple imputation by predictive mean matching (163). The second analysis was based on a per protocol (PP) principle, where participants with at least one treatment visit, no concurrent treatment for alcohol dependence during the six month follow up period and who completed the follow-up measures were included.

Statistical analyses were conducted with Stata version 13.1.

3.5 ETHICAL ASPECTS

In this section, I will discuss the ethical aspects of the four studies. First, I will discuss the general aspects of all studies, and then specifically for each study.

In all studies, the participants were informed of the aim of the respective study, that it was voluntary to participate and that they could at any time withdraw from the study without any negative consequences. As study I was a telephone survey, the participants gave a verbal informed consent before any of the study questions were asked. In the other three studies the consent was both verbal and written. All studies have been approved by the Regional Ethical Review Board in Stockholm.

In Study I, there was a risk that the participants could feel that their personal integrity was violated, as questions regarding alcohol can be sensitive. In addition to emphasize that it was voluntary to participate, data collection was performed by a private company with long experience of telephone surveys. Another risk was the handling of data. The private company removed all information that could identify a participant, and gave each one a code for identification in the study. Thus, the data was anonymous when handed over to the researchers. We believe these precautions minimized the risks for the participants.

Also in study II, there was a risk that the participants could feel that their personal integrity was violated, as some of the questions about their alcohol use could be sensitive. The participants received thorough information, both written and verbal, about the study and that it was voluntary to participate. During the focus group interviews, there were two moderators, where one lead the discussion and the other observed the group, in order to observe the participant reactions and intervene if someone seemed to feel unease. A specific ethical aspect in this study, was that the participants' self-rated that they fulfilled the diagnostic criteria for alcohol dependence, but were not treatment seekers. As treatments were one of the topics discussed, the participants also received verbal information about where to seek treatment for problematic alcohol use.

In study III and IV the most important ethical issues were whether any participant risked harm from participating in the study. We discussed these issues thoroughly at the planning stage of the trial. This was especially important as it was general practitioners, without prior experience of treatment of alcohol dependence, who were going to treat half of the participants. We were careful to review the literature on treatment outcomes, and define

exclusion criteria to make sure that we would minimize the risk of including participants who were very likely to need specialist treatment. We also developed guidelines for the general practitioners, for when they should refer a patient they treated to specialist care. In addition, we monitored harms during the trial, both reported from the clinicians and from the patients. Another issue we discussed was whether to include a third arm in the trial, with a no-treatment-control group in order to disentangle the treatment effect from the treatment seeking effect. However, as alcohol dependence is a severe condition, and the participants had actively sought treatment in applying to the trial, we decided for ethical reasons to only compare two active treatment arms.

Overall, we assessed the possible gains of the studies outweighed the risks for the participants. In the first two studies, our aim was to allow target groups to voice their own opinions and preferences about treatment. This could strengthen their participation in the enhancement of treatments for alcohol dependence, and thereby improve treatment services to better match people's needs. By offering treatment in a primary care setting, a larger proportion of all individuals with alcohol dependence can be reached with interventions. As alcohol dependence has one of the largest treatment gaps of all psychiatric disorders, this can play an important role in improving public health.

4 RESULTS

In this section, I will give a summary of the results in each study. The results are presented extensively in the articles I to IV.

4.1 STUDY I

A majority, 50 – 65 %, of the participants would recommend psychiatric or specialist addiction treatment. Primary care was endorsed by 10-11 %. 20 % of the women and 25 % of the men recommended occupational health services. Circa 5 % would recommend social services. Participants with higher income and higher education were more likely to choose specialist care, psychiatric or dependence, and less likely to choose primary care.

The types of treatments preferred were; support groups, psychotherapy and residential treatment. Among participants in the high consumption group, psychotherapy was most preferred. Few preferred pharmacological treatment and very few treatment via the Internet.

The most common reason given why people would not seek help for alcohol problems was they "would be ashamed".

Overall, few differences were found in regards to level of alcohol consumption.



4.2 STUDY II

A dominant theme was how alcohol dependence and seeking treatment were closely linked to shame and stigma. To have a need for treatment was seen shameful, and treatment seeking was associated with failure and social deprivation. By seeking treatment, the participants described a change of identity, toward the stereotype of "the alcoholic", often described as a drunk man on a park bench.

Another barrier to seeking treatment, especially in the youngest age group 18-34 years, was the perception that treatment meant to accept a goal of lifetime abstinence. Many were open to moderated alcohol consumption. Other barriers to treatment were; the view that alcohol problems is a bad habit, that one change without seeking treatment, and low knowledge about the health impacts of excessive alcohol use.

Internet based treatment and telephone help lines were seen as attractive alternatives for assessment and guidance to treatment. However, the participants preferred a personal meeting if they were to seek treatment. Psychotherapy was the most preferred type of treatment, while pharmacological treatment with antabuse (disulfiram) was viewed negatively. Few had heard of medications as acamprosate and naltrexone before, but they were viewed positively.

Specialist care was most preferred, while views on treatment in primary care were divided, and mainly seen as attractive among the oldest age group 40-65 years. Students viewed student health services as attractive, while treatment in occupational health care was seen less appealing because of fear of negative career consequences. Components of attractive treatments were; confidence in the treatment provider, easy access, a high degree of autonomy and the possibility to maintain everyday life.

Overall, there were few differences in the data in regards to severity of dependence, occupational status or age.



4.3 STUDY III

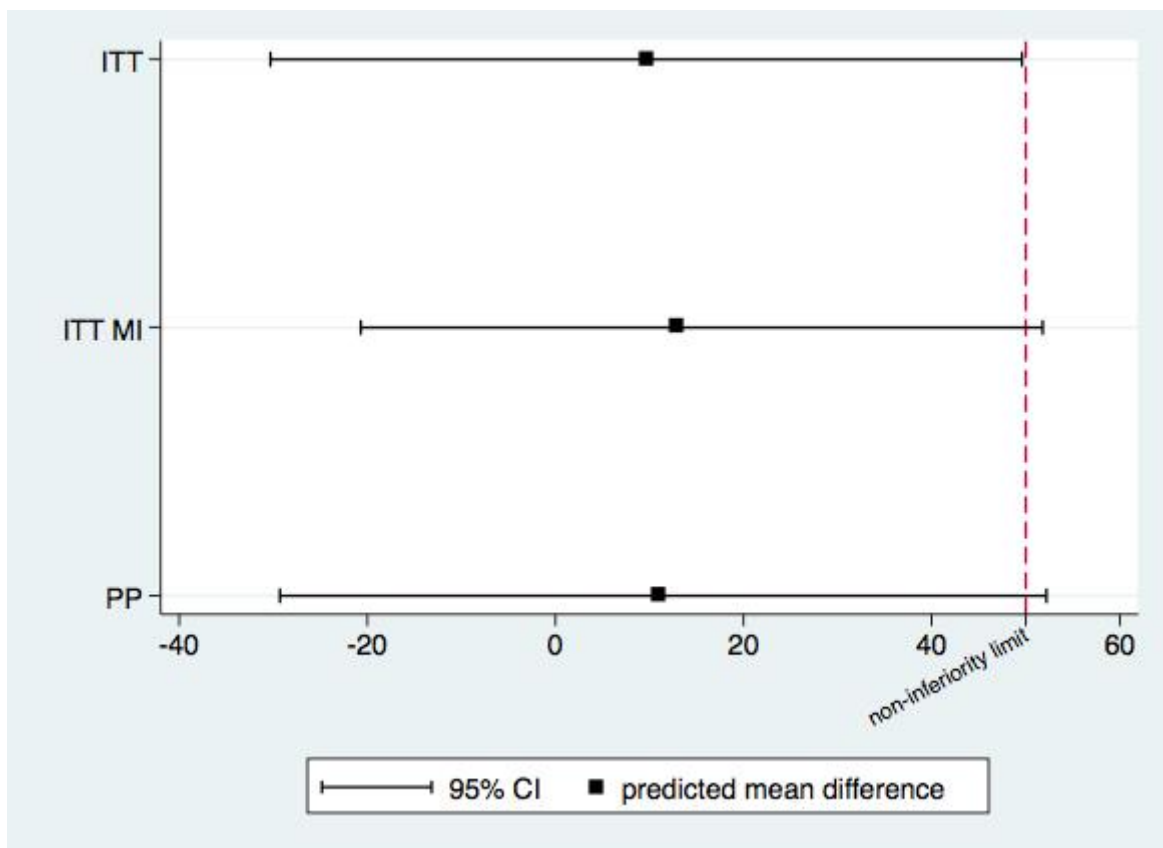
At six months, 232 participants completed follow up. Four of these were missing data on the primary outcome measure, thus 228 were included in the intention-to-treat analysis (ITT). This analysis was statistically inconclusive, and could not confirm non-inferiority for the primary outcome, as the high end of the confidence interval exceeded 50, and thereby the pre-specified non-inferiority limit. Estimated mean weekly alcohol consumption was 30 grams higher in primary care compared to specialist care; 95% confidence interval -10.2; 69.7. However, treatment in specialist care was not significantly superior to primary care ($p = 0.15$). The two sensitivity analyses only slightly altered the results.

The secondary outcome measures followed the same pattern – a reduction from baseline to six month follow up, with no significant differences between primary care and specialist care. The only exception was satisfaction with treatment, where participants randomized to specialist care were more satisfied with treatment compared to participants randomized to primary care.

Sub analysis suggested treatment in primary care was non-inferior for participants with low to moderate severity of dependence, while specialist care was superior for patient with high severity of dependence. In both primary care and specialist care, a higher number of sessions predicted a lower alcohol consumption at follow up (-12.7; 95% CI: -21.8; -3.6, $p = 0.01$). However, the length of treatment measured in minutes did not predict alcohol consumption at six months (-0.2, 95% CI: -0.4; 0.1, $p = 0.15$). When controlling for number of sessions, primary care was non-inferior to specialist care (4.7; 95% CI: -38.7; 48.2, $p = 0.83$).

4.4 STUDY IV

At 12 months, 233 participants completed follow up. Two of these were missing data on the primary outcome measure. The intention-to-treat analysis (n=231) confirmed non-inferiority for the primary outcome at 12 month follow up. Weekly alcohol consumption in primary care (n=111) was 9.7 grams higher compared to specialist care (n=120), (95% CI: -30.3; -49.6, p = 0.64). The two sensitivity analyses resulted in a slightly higher predicted mean difference, 13 grams for the ITT with multiple imputation (95% CI: -20.7; 51.8, p = 0.40) respectively 11 grams for the per protocol (PP) analysis (95% CI: -29.3; 52.2, p = 0.28), and are thus statistically inconclusive.

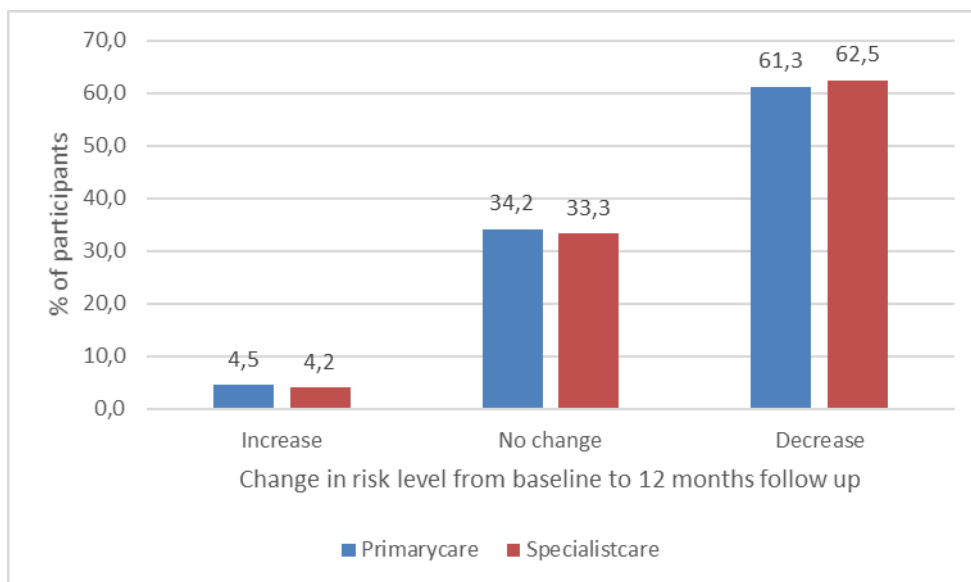


Predicted mean difference at 12 month follow up, for the primary outcome measure weekly alcohol consumption, in primary care compared to specialist treatment. A positive value of the estimate indicates a higher predicted mean in primary care compared to specialist care. ITT data set with available cases. ITT data set with multiple imputation. PP analysis.

The results from the secondary outcomes measures are consistent with the primary outcome – a reduction from baseline to 12 month follow up, and no differences between primary care and specialist care except patients randomized to specialist care were more satisfied with treatment.

The analyses of trajectories showed that the main part of change in consumption occurred from baseline to the six month follow up and were maintained to the 12 month follow up. There were no differences between the two treatment conditions.

A majority of the participants decreased their alcohol consumption at least one WHO risk level. There were no differences between treatment conditions ($\chi^2 = 0.04$; $p = 0.98$).



Change in WHO risk level from baseline to 12 month follow up.

Per cent of participants in primary care and specialist care.

5 DISCUSSION

The overarching aim of this thesis was to study possible strategies to involve a larger proportion of individuals with alcohol dependence with treatment. More specifically the included studies investigated barriers to seeking treatment and treatment preferences in the general population respectively among non-treatment seekers with alcohol dependence. In addition, the effects of treatment with the 15-method for alcohol dependence in primary care, were studied.

5.1 TREATMENT BARRIERS AND PREFERENCES IN THE GENERAL POPULATION

The results from study I showed that a majority in the general population would recommend treatment for alcohol dependence in psychiatric care, including addiction services. One in five would recommend occupational health care, 10-11 % would recommend primary care and 5 % social services. Thus, a majority perceived health care services as best suited to manage treatment for alcohol dependence. This suggests that people in general view alcohol dependence as a health issue, rather than a social issue; a finding supported by other research (35, 36). This, however is not reflected in the way treatment services for substance use disorders are organized in Sweden today; where the responsibility is shared between the social services and health care services. Signaling that alcohol dependence is a social issue can therefore impose a barrier to seeking treatment.

In study I, fewer participants endorsed treatment in primary care compared to the results found in other studies (36, 62, 63). This disparity can be due to methodological differences in data collection between the studies. Gual et al. (36) and Lieberman et al. (63) collected data in primary care settings. Individuals who already are in treatment in primary care for other conditions might be more positive to also seek treatment for alcohol dependence in primary care. Barry et al. (62) included treatment naïve individuals with alcohol dependence, and used vignettes to describe alternatives for treatment. This method is probably closer to a real situation of treatment seeking, compared to our indirect questions. Obviously, there may also be differences between countries in views of preferred services.

The general population most frequently endorsed traditional types of treatments such as support groups, psychotherapy and residential treatment. Shame was the most frequently mentioned barrier to seeking treatment.

5.2 TREATMENT BARRIERS AND PREFERENCES AMONG NON-TREATMENT SEEKERS WITH ALCOHOL DEPENDENCE

The results in study II showed that shame and stigma were strongly associated with problematic alcohol use and important barriers to seeking treatment among individuals with dependence, confirming previous research (46, 51, 53). One can speculate whether the difficulties with data collection in both studies also reflect issues of shame and stigma associated to alcohol use. In study I, the difficulties were reflected in the low rate of answers to direct questions about treatment and in study II, the high drop out rate during recruitment. Study II contributed to a greater understanding of the nature of stigma. To realize that one needs treatment, and needs to seek treatment, was seen as shameful and linked to failure and social deprivation, which seem to be the base of the stigma. A change of identity was described when seeking treatment, an example of the self-stigma process, which is similar to findings from studies of individuals seeking treatment for illicit drug use (168). The perception of alcohol dependence associated with a man on a park bench has been described in North American research over 30 years ago (169). In that study, participants regarded dependence as a disease, which could affect anyone. However, when asked to describe a person with this condition, a similar stereotype of an old man with a severe form of dependence, also suffering from poverty and homelessness was depicted. This illustrates the persistence of the perception of the man on the bench, and how the public stigma of alcohol dependence transcends time periods and cultures.

An additional barrier to seeking treatment, especially among younger participants, was the perception that treatment meant accepting the goal of life-long abstinence. Participants were more positive to seeking treatments with the goal of moderated alcohol use. A preference for moderated drinking as a goal, has been found in other studies (48, 63, 64). Treatments with only abstinence as a goal can therefore be regarded as a barrier to seeking treatment. Another barrier, found in study II, was that the participants were unaware of health consequences related to alcohol, which confirms findings in other studies (170-172). This suggests that health literacy regarding alcohol use and health is low and needs to be improved.

The participants' knowledge of treatment was limited to lifelong abstinence, pharmacological treatment with Disulfiram and residential treatment. These treatments stood in sharp contrast to the participants' preferences; methods with a high degree of autonomy, the possibility to maintain everyday life during treatment, and as already discussed, controlled drinking as a goal. The most endorsed type of treatment, in both study I and II, was psychological

treatment, which emphasizes the importance of offering this type of treatment. In both study I and II, few endorsed pharmacological treatments. These findings are in line with how the public view treatment of other psychiatric disorders – a preference for psychological treatment and low rates of endorsement for pharmacological treatments (173). In study II the participants clearly expressed more positive views after they received more information about the available options, which suggests the low endorsement rate is associated with lack of knowledge rather than negative views of pharmacological treatments per se. This suggests that health literacy regarding alcohol dependence and treatment needs to be improved.

5.3 EFFECTS OF TREATMENT IN PRIMARY CARE

The results from study III and IV show largely similar outcome after treatment in primary care compared to specialist care. The outcomes showed a non-significant trend towards slightly better results for participants randomized to specialist care. In study IV, the 12 month follow up showed treatment in primary care to be non-inferior to specialist care – but only barely so. The results from study III were, at six month follow up, statistically inconclusive, and could not conclude non-inferiority. However, treatment in specialist care was not found to be superior to primary care. The reason for these equivocal results regarding non-inferiority can be found in the group with high severity of dependence. Sub analyses showed severity of dependence to be an important factor for outcome in different settings at the first follow up. At six months, treatment in primary care was non-inferior to specialist care for patients with low to moderate severity of dependence, while patients with a high severity of dependence had a significantly better outcome after treatment in specialist care. The secondary outcome measures followed the same pattern at both six and 12 month follow up, with a reduction compared to baseline in both treatment conditions and no differences between groups.

The results show that the 15-method is a promising approach for treatment of alcohol dependence in primary care. This also confirms previous studies, showing treatment in primary care can have beneficial outcomes for individuals with low psychiatric co-morbidities and without dependence on illicit drugs (95, 97, 98). The findings in study III and IV indicate that treatment for alcohol dependence can be simplified, for this group of patients with low to moderate severity of dependence and few psychiatric co-morbidities. The 15-method includes fewer and briefer sessions compared to existing models of treatment in primary care (92, 94, 95, 97, 98). In addition, the general practitioners only received a brief one-day training, which means the model can be readily implemented.

Even though the two treatment conditions were different in terms of intensity of treatment and practitioners' expertise and experience, the participants' outcomes were non-inferior at 12 month follow up. The lack of association between intensity of treatment and outcome has been found in other studies (142, 174). The similarities in outcomes suggest the factors that facilitated change may have been general treatment factors, rather than specific to one particular method. Implications that general factors play an important role are found in other studies. Participants in the UKATT study attributed change in their alcohol use to general factors, such as their commitment to change or feeling comfortable talking about their alcohol use, rather than specific factors of a treatment method (175). There are also implications that assessments can promote change (123, 176, 177), which is a general factor shared in both treatment conditions. Another important general factor is treatment seeking, which in itself seems to facilitate change (178, 179). Further research is needed in order to understand how treatment systems can enhance this impact by understanding which components reinforce mechanisms of change. In treatment of anxiety and depression, recent findings indicate organizational factors, at the service provider level, impact treatment outcome, for example waiting time to start treatment (180).

The only significant difference found between the two treatment groups was satisfaction with treatment; where patients randomized to specialist care were more satisfied with treatment compared to those randomized to primary care both at six and 12 month follow up. It is not possible to draw conclusions from the available data on what the differences in satisfaction can be ascribed to. A possible hypothesis is that briefer length of treatment in primary care or staff training can have affected the level of satisfaction, but future studies should investigate this further.

The results of these studies have important implications. They suggest that treatment of alcohol dependence largely can be managed by general practitioners, where only a minority of severe cases need to be referred to specialists'. This implies a division of labor between generalists and specialists, that is the norm in most medical fields, is feasible but has not been accepted for addiction medicine yet.

5.4 REDUCTION SUSTAINED AT 12 MONTHS

The significant reduction in alcohol use for the majority of the participants occurred during the first six months of treatment, and was sustained at 12 month follow up. This is in line with findings in other studies (105, 142, 166, 167). Circa 60 % of the participants reduced their alcohol use in a clinically significant way, at least one WHO drinking risk level. One third did not change drinking risk level and circa 4 % increased their alcohol use. These are smaller proportions of change compared to the COMBINE trial, where 87 % reported a reduction of at least one risk level, while 12 % had not changed and 1 % had increased their risk level (165). These two studies differ in a number of important ways. Firstly, the treatment goals differed, moderated alcohol use was accepted in the current trial, but in COMBINE the goal was only abstinence. It is unlikely this difference affected the outcome, as treatment goal stated in the intervention has not been found to effect outcome (141, 181, 182). However, there is support for an association between the patient's goal at baseline and outcome (183). Secondly, the participants in study III & IV had a lower weekly alcohol consumption and few psychiatric co-morbidities compared to the COMBINE trial and many other clinical trials of treatment for alcohol dependence. Lower alcohol use at baseline implies a smaller margin for change, a factor which also have been discussed recently regarding effects of BI (70). This is a more likely explanation to the differences in change between the current trial and COMBINE. It is of concern that 4 % increased their alcohol use after start of treatment. However, this is partially due to the methodological flaw of not having alcohol use as inclusion criteria in the study. Around half of the group who had increased at 12 months, had stopped drinking before inclusion, thus not allowing for any improvement after treatment.

The difference of the participants' characteristics compared to other trials can partially be due to the main method of recruitment which was advertisement, which is known to attract individuals with lower severity (184). Method of recruitment is important in regards to outcome (185), where active treatment seekers show more favorable outcomes. The level of alcohol use in study III and IV corresponds to patients found in primary care who fulfill criteria for alcohol dependence, but are not in treatment for their dependence (30). The study was not blinded, meaning the participants were aware of the two treatment conditions when applying to participate in the study. This indicates that treatment in primary care may be seen as an attractive alternative for this group, that is rarely reached with interventions.

5.5 LOW UPTAKE IN PRIMARY CARE

One important future challenge is the low uptake of alcohol interventions in primary care settings (71, 186). Barriers to implementing alcohol interventions that have been identified are; lack of knowledge and training (187-190), doubts about whether the interventions are effective (188, 189), the view that pharmacological treatment for alcohol dependence is difficult to manage (189, 190) and would not fit in the time frames of primary care (190). Factors identified in facilitating implementation are; training (188, 191-193), financial incentives (76, 193), on-the-job experience (193), local champions (194) and changing attitudes (193). In addition, involvement of other professions than only general practitioners, for example nurses or psychologists, can also enhance implementation (188, 191). Currently, great amount of research is focused on implementation, where attention has been drawn to the need of also addressing the context where implementation of alcohol intervention takes place (195).

5.6 IMPLICATIONS

This section is divided into five strategies for reaching a larger proportion of individuals with alcohol dependence with treatment, drawing on the results in the thesis.

5.6.1 Reduce stigma

The persistence of shame and stigma, and how these become barriers to seeking treatment, which was found in study I and II, emphasizes the need for actions to reduce stigma at a societal level. Increased health literacy has the potential to reduce public stigma (60), and strategies for how to achieve this will be discussed in later section of the thesis. Suggestions have been made that framing dependence as a brain disease can reduce stigma (196). However, as stigma has not decreased since the brain disease model was introduced, this strategy does not seem effective (52). This suggests that the stigma of alcohol dependence may have different mechanisms compared to the stigmatization of other psychiatric disorders, where the brain disease model seems to reduce stigma (35). A more radical strategy would be, as suggested by Rehm et al (17), to redefine the concept of alcohol use disorders, and only discuss levels of alcohol use. The advantage of this approach would be to avoid the dichotomous view of alcohol problems, which is prone to reinforce stigma, and instead use a continuum of levels of alcohol use, which is suggested to reduce stigma. Others have emphasized the need to understand stigma better, and how the transition from hazardous use to dependence impact stigma (61). As indicated in the results from study II, one key message, in order to reduce the public stigma, can be that alcohol dependence does not equal social deprivation, as this association seems important for the perception of stigma. To adjust treatment services to better suit the needs for individuals of the whole range of severity of dependence, can possibly also be an effective strategy to reduce stigma, as this can challenge the perception that alcohol dependence means social deprivation. Suggestions for adjustments of treatment services will be discussed in the coming paragraphs. An additional strategy to change public stigma is to emphasize recovery (60). Alcohol dependence is often described as a "chronic relapsing disorder" (196), even though this assumption seems to mostly be applicable to the smaller group with severe dependence but not the larger group with low to moderate severity (197). To increase the public's knowledge about recovery and also broaden the understanding of recovery beyond the common misinterpretation that it is limited to abstinence only, can possible reduce stigma. Clearly, there is a need to increase knowledge about stigma associated with alcohol use and alcohol dependence, and how this can be reduced (60, 61, 198).

5.6.2 Making treatment attractive

In order to reach a larger proportion of individuals in need, the treatment services need to be made more attractive. In Sweden, reorganizing the responsibility for addiction treatment into one body responsible for providing treatment within the health care services can possibly facilitate treatment seeking. Clearly, in cases of severe addiction, combined with psychiatric comorbidity and social problems, collaboration is necessary with the social services as well as other agencies. However, in the majority of cases, such collaboration is not called for. The same proposal has been made in a Swedish Government Official Report in 2011 (27). Placing addiction treatment within health care could also possibly reduce the public stigma of alcohol dependence, weakening the association between alcohol dependence and social deprivation. In addition, the general public in Sweden support implementation of alcohol prevention in health care settings (199), which strengthens the conclusion that questions regarding alcohol is seen as an issue for health care services. Alcohol related harm is more pronounced among individuals with lower socioeconomic status (200), which emphasizes the need to reach this group with treatment. In study I, a majority of individuals with lower socioeconomic status also endorsed treatment within health care settings, and only a minority endorsed social services. In addition, those with lower socioeconomic status, compared to higher, were more positive to seek treatment in primary care, which implies that offering treatment in primary care may contribute to reduced health disparities.

5.6.3 Controlled drinking as a goal in treatment

Another way to lower the threshold to seeking treatment is to offer moderated drinking as a goal of treatment. The perception that seeking treatment means accepting life long abstinence imposed an important barrier among especially younger participants in study 2. Traditionally, treatments for alcohol dependence have mainly been focused on the goal of abstinence. There are several reasons for this, firstly that a majority of individuals in existing treatment programs have a severe form of dependence, where abstinence is a more realistic goal (201). Moreover, moderated, or controlled, drinking has been historically controversial both in public discussions and in the research field (202). However, controlled drinking as a feasible outcome of treatment has gained more attention over the past years (201, 203). Post hoc analysis of data from COMBINE, Project MATCH and UKATT show that individuals with low risk drinking during treatment reported equal outcomes, at 12 month follow up, to those who achieved abstinence (204). Baseline factors that predicted low risk drinking at follow up were; lower severity of dependence, lower alcohol consumption at baseline, fewer heavy drinkers in the social network and lower negative mood symptoms (201). These results

emphasize that the goal of controlled drinking has an important role in the treatment regime. From a public health perspective it needs to be stressed that heavy drinking is a strong risk factor for mortality, and that any decrease in consumption is associated with a reduced risk for mortality, especially among individuals with the heaviest consumption (205, 206).

5.6.4 Increase mental health literacy

Mental health literacy deals with the public's knowledge and beliefs about mental disorders: how to prevent, recognize them, available treatments, self-help strategies, and how to support those affected (207). As suggested by the results in study I and II, mental health literacy regarding alcohol use, alcohol dependence and treatment is low. Many individuals with hazardous consumption who are trying to reduce their alcohol use, state concern for future health problems as a reason (208). Increasing the public's knowledge of health consequences of alcohol can possibly increase motivation for a larger proportion of the population to reduce their alcohol use. For this purpose, the Internet has a possible large outreach, as more than 90 % of the Swedish population use the Internet (209). The Internet is also viewed positively by participants in study II, and mentioned as a suitable first step for assessment and information, before entering treatment. In addition, there are examples of media campaigns about detrimental health effects of alcohol, that were associated with increased knowledge, increased number of individuals expressing an intention to cut down, however no reduction of actual alcohol use (210). Health care settings in general, and primary care specifically, are important arenas for increasing mental health literacy related to alcohol use. For example, nearly one in ten, who is trying to reduce their alcohol use, state advice from health care services as a reason for a reduction (208). There is a need to develop a range of different strategies in order to reach different segments of the population, not the least minorities. In addition, there is a need to more fully understand how the public perceive risks associated to alcohol, where the individual's context and subjective experiences often play an important role (211).

5.6.5 New ways to increase dissemination in primary care

Implementation of SBI in primary care has progressed slowly over the past 30 years. In order to increase uptake, new strategies needs to be developed and tested. One strategy to investigate in the future, is whether increased knowledge and experience in treatment of alcohol dependence among primary care staff can enhance implementation of SBI. General practitioners might feel reluctant to bring up the issue of alcohol when it is difficult to refer to specialist care, and one's own knowledge of how to manage alcohol problems is rudimentary.

By improving general practitioners skills in managing the whole spectra of alcohol use, the barrier to asking about alcohol in the first place can possibly be lowered.

A topic often overlooked in the literature is whether stigmatizing attitudes among health care staff, affect implementation of alcohol interventions in generalist settings. Staff in primary care, rate working with substance use disorders as lower status compared to other health conditions (212). Working with individuals using illicit drugs is rated lower than alcohol use disorders. Moreover, general practitioners also express more stigmatizing attitudes towards patients with substance use disorders compared to staff in specialist addiction care and psychiatry (213). In a qualitative study, stigmatizing attitudes among physicians were identified as a barrier to implement pharmacological treatment in primary care (190). We suggest more attention to this topic in future research.

So far implementation strategies have mainly focused on health care professionals. Less attention has been given to how to attract people with dependence to seek treatment. Methods used in marketing science have the potential to contribute to the development of new methods in this field (214). The concepts of “push” versus “pull” marketing are the base for direct-to-customer (DTC) marketing (215). DTC shifts the focus from “pushing” alcohol interventions through the health care professionals, to instead increasing the customers, i.e. individuals with alcohol dependence, awareness of evidence based alcohol interventions. The customers will then request it and “pull” it through the health care system. This has been proposed as a strategy to increase pharmacological treatment for alcohol dependence (187), and also demand for treatment among parents to adolescents with substance use disorders (216). However, caveats in using DTC in health care services have been highlighted (217). There is support for that both strategies, i.e. push and pull, are complementary and both are needed for successful dissemination and implementation (214). This suggests the possibilities and limitations of DTC should be further explored.

5.7 STRENGTHS AND LIMITATIONS

In study I, the switch to an indirect question about treatment preferences is an important limitation. Even though the responses can give public perceptions on treatment, it does not answer the question of how the individual themselves would choose if they were to seek treatment. From the design of the study, it is not possible to understand the reasons the participants had for giving the answers. For example, it is possible the informants had limited knowledge about some alternatives, which influenced how they answered.

The study had a non-response rate of 38%, which is high but similar to other surveys about alcohol. Previous research of non-responders in this data material (136), has shown that a non-response rate of 40 to 55 % does not change the estimate for alcohol consumption. However, it is possible that the 5-10 % of non-responders, who have not been reached at all, differ from responders in important ways.

The strength of the study is the large sample from the general population, with both information about alcohol use and demographic factors.

In study II, one limitation is that the recruitment process had a large number of drop outs. Of 812 eligible individuals who met the inclusion criteria, 248 agreed to participate. But only 32 actually did participate. The choice of collecting data at a specialized alcohol clinic might have hampered the recruitment process.

The strengths of the study were the recruitment of non-treatment seekers individuals from the general community. An additional strength is the combination of focus group discussions, where the participants discussed shared perceptions, and individual interviews, where more personal experiences were discussed. Also, the mix of individuals who were treatment naïve and individuals who had experiences of seeking treatment was fruitful.

In study III and IV the main strength was the naturalistic set up of the trial. The general practitioners were regular clinicians, who received a one-day training in the manual. The generalizability to clinical settings is therefore very good.

A limitation of the trial is the choice of comparison condition. The specialist unit in the trial was a special research and development unit, developed to make addiction treatment more attractive. This possibly improved retention to treatment in specialist care and thus outcomes,

compared to if the participants had been randomized to regular specialist care. Another limitation is that identification of patients in primary care was not included in the study. The majority of participants were recruited via advertisement, and the results cannot be generalized to opportunistically recruited patients.

Without a control group that did not receive any treatment, we cannot rule out regression to the mean as an explanation for the results. Nor can we, without a no-treatment control group, rule out that the change we have observed was the natural process, rather than effects of treatment. This is an important issue, that needs further attention in future trials.

In order to keep the treatments as naturalistic as possible, and to minimize the risk of assessment reactivity, self-reported data on alcohol consumption was only collected at baseline assessment and the two follow ups, and is limited to only measure 30 days previous these time points. No data on alcohol use during the treatment period was collected. The analyses of trajectories can thus only broadly answer the question as to when change occurred. In addition, alcohol use was not an inclusion criteria, and some participants had already reduced their consumption by the time of the baseline measure, as some reported either a very low or no alcohol consumption at all the past 30 days.

The trial also had around 20 % participants lost to follow up, which is similar to other trials (167), but which obviously hampers the possibilities to draw firm conclusions.

6 CONCLUSIONS

The main conclusions of the thesis are the following:

- Treatment for alcohol dependence is seen as an issue for the health care services.
- Shame and stigma impose important barriers to seeking treatment.
- The knowledge of health consequences associated with alcohol and treatment for alcohol dependence were limited.
- Knowledge of treatment was limited to traditional forms of treatment. However, these forms of treatments often stood in sharp contrast to preferred treatments among non-treatment seekers.
- Treatment for alcohol dependence in primary care was non-inferior to specialist care at 12 month follow up. The results were statistically inconclusive at six month follow up, and sub analyses suggested that severity of dependence was an important factor for outcome in different settings.
- The main reduction of alcohol use occurred between baseline and six month follow up, and the effects were sustained at 12 month follow up.
- Treatment in primary care with the 15-method is a promising approach.

From these results, five strategies are suggested to reach a larger proportion of individuals with alcohol dependence with treatment and decrease the current treatment gap:

- Reduce stigma.
- Organize health care in an attractive way.
- Offer controlled drinking as a treatment goal.
- Improve health literacy regarding alcohol use, health, alcohol dependence and treatment.
- Try new ways to increase dissemination of alcohol interventions in primary care.

7 SVENSKSPRÅKIG SAMMANFATTNING

I Sverige uppskattas 4 % av den vuxna befolkningen uppfylla kriterierna för alkoholberoende. Dock söker endast en minoritet, cirka en av fem, av dessa vård. Liknande uppskattningar görs internationellt.

Det övergripande syftet med avhandlingen var att studera hur fler individer med alkoholberoende kan nås med behandling.

I studie I var syftet att undersöka vilken typ av behandling för alkoholproblem, och hos vilken vårdgivare, som personer i den allmänna befolkningen föredrar. Även skäl till att inte söka vård undersöktes. I en tvärsnittsstudie inkluderades ett representativt urval av 9005 individer ur den vuxna befolkningen i åldrarna 16 till 80 år. Resultaten visade att en majoritet föredrog behandling för alkoholproblem inom hälso- och sjukvården, medan endast 5 % föredrog socialtjänsten. Stödgrupper, psykologisk behandling och behandlingshem föredrogs i störst utsträckning. Skam var det vanligaste skälet till att inte söka behandling.

I studie II var syftet att beskriva hur individer med alkoholberoende uppfattar behandling för alkoholproblem och deras skäl för att söka och inte söka behandling. 32 deltagare i åldrarna 18-62 år med alkoholberoende rekryterades via ett marknadsundersökningsföretag. Data samlades in via fokusgrupper och individuella intervjuer. Resultaten visade att skam och stigma var viktiga hinder till att söka behandling. Andra hinder var; föreställningen att behandling innebar att acceptera en målsättning av helnykterhet resten av sitt liv, låg kunskap om hälsokonsekvenser av alkohol samt låg kunskap om behandling. Psykologisk behandling var den typ av behandling som flest föredrog.

I studie III studerades effekter av behandling för alkoholberoende inom primärvård. 288 vuxna med alkoholberoende randomiserades antingen till behandling i primärvård enligt 15-metoden, en kort behandling som anpassats för generalistmiljöer, eller till specialiserad beroendevård. Hypotesen var att behandling i primärvård var lika effektiv som specialistvård. Vid uppföljningen efter sex månader var resultaten på det primära utfallsmåttet, veckokonsumtion av alkohol, statistiskt inkonklusivt. Behandling i specialistvård var dock inte mer effektiv än behandling i primärvård. Subgruppsanalyser visade att primärvårdsbehandling var lika effektiv som specialistbehandling för deltagare med låg till måttlig grad av beroende, medan den mindre gruppen deltagare med hög grad av beroende hade reducerat sin alkoholkonsumtion mer efter specialistvård.

I studie IV undersöktes långtidseffekter av behandling för alkoholberoende inom primärvård, samt mönster i förändring av alkoholkonsumtionen. Studien baserades på uppföljningen vid 12 månader av deltagarna i studie III. Resultaten bekräftar att primärvårdsbehandling var lika effektiv som specialistbehandling avseende veckokonsumtion av alkohol. Resultaten av de sekundära utfallsmåtten följer samma mönster – en minskning från baslinje till uppföljning, men inga skillnader mellan primärvård och specialistvård, undantaget nöjdhet med behandlingen, där deltagare som randomiserats till specialistvård var mer nöjda med behandlingen. Analyserna av mönster av förändring visade att den huvudsakliga minskningen av konsumtion skedde under de första sex månaderna och vidmakthölls till uppföljningen vid 12 månader.

Sammanfattningsvis uppfattades behandling för alkoholberoende som en uppgift för hälso- och sjukvården. Skam och stigma var viktiga hinder till att söka behandling. Kunskapen om hälsokonsekvenser av alkohol samt behandling för alkoholberoende var begränsad. Vanliga föreställningar om behandling stod i skarp kontrast till de önskemål som individer med alkoholberoende hade på behandling. Behandling för alkoholberoende i primärvård med 15-metoden framstår som lovande då effekterna är likvärdiga med specialistvårdens, behandlingen lät sig genomföras inom ordinarie behandlingsrutiner i primärvården och krävde inte mer än en dags utbildning för deltagande allmänläkare.

Slutligen, utifrån resultaten av delstudierna, föreslås fem strategier för att nå fler individer med alkoholberoende med behandling:

- reducera stigma
- erbjuda attraktiv behandling
- erbjud kontrollerat drickande som behandlingsmål
- öka kunskapen om hälsokonsekvenser av alkohol samt öka kunskapen om behandling för alkoholberoende
- nya metoder för ökad implementering av alkoholinterventioner i primärvården

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