From THE DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

GUIDED INTERNET-BASED TREATMENT FOR INSOMNIA AND DEPRESSION

Kerstin Blom

Karolinska
Institutet

Stockholm 2016

Cover image: Maja Björk Lindahl

GUIDED INTERNET-BASED TREATMENT FOR INSOMNIA AND DEPRESSION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Kerstin Blom

Principal Supervisor:
Dr. Viktor Kaldo
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatry Research

Co-supervisor(s):
Dr. Susanna Jernelöv
Karolinska Institutet
Department of Clinical Neuroscience
Section of Psychology

Professor Nils Lindefors
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatry Research

Opponent:
Professor Bjørn Bjorvatn
Bergen University
Department of Global Public Health and
Primary Care
Bergen, Norge

Examination Board:
Dr. Gunilla Berglund
Stockholm University
Department of Psychology

Professor Marie Åsberg
Karolinska Institutet
Department of Clinical Sciences
Danderyd Hospital

Dr. Jan-Erik Broman
Uppsala University
Department of Neuroscience

In loving memory of Hans T. Blom – father, jazzman, psychologist, role model.

ABSTRACT

Background. Insomnia and depression are two of the most prevalent and costly disorders, and comorbidity between the two is common. Treatment of insomnia, other than pharmacological, is often overlooked in spite of the existence of effective psychological treatments. When insomnia is comorbid with depression, treatment of depression is usually prioritized, but not quite sufficient. The insomnia treatment with the strongest evidence is Cognitive Behavioral Therapy for insomnia (CBT-i). Due to a lack of trained CBT-i-therapists, therapist-guided Internet-based CBT-i (ICBT-i) has emerged as an alternative to face-to-face treatments.

Aims. To challenge the treatment paradigm for comorbid insomnia and depression by comparing ICBT-i to ICBT-d (Internet-based CBT for depression) (Study I). To strengthen the evidence for ICBT-i by comparing ICBT-i to face-to-face treatment (Study II) and by doing a 3-year follow-up of a previous trial (Study III). To investigate qualitative aspects of Study I (Study IV).

Studies. Four studies were done: Study I, a randomized controlled trial (RCT, n=43) comparing ICBT-i to ICBT-d in a sample with comorbid insomnia and depression. Study II, a non-inferiority RCT (n=48) comparing ICBT-i to group-delivered CBT-i in a sample with insomnia and various comorbidities, including mild to moderate depression. Study III, a 3-year follow-up of an RCT (n=148) comparing ICBT-i to an active control treatment. Study IV, a qualitative study investigating facilitating and hindering factors in participants' work with the treatments in Study I.

Results. Study I: ICBT-i turned out to be overall more beneficial than ICBT-d for patients with both insomnia and depression regarding e.g. effects on insomnia severity (effects on depression were similar) and reduction of sleep medication use. Study II: ICBT-i turned out to be highly effective and non-inferior to group-delivered CBT-i regarding insomnia severity, both directly after treatment and after six months. Study III: The 3-year follow-up of ICBT-i showed that the large effect on insomnia severity observed directly after treatment was maintained over time, and led to reduced consumption of sleep medication and other insomnia treatments compared to participants in the active control group. Both studies II and III showed that ICBT-i also reduced depressive symptom severity significantly. Study IV: The qualitative analyses showed that ICBT-i was easier to work with, and more positively regarded than ICBT-d, according to the participants. Multiple comorbidities were more hindering in ICBT-d than in ICBT-i.

Conclusions. ICBT-i is effective in reducing insomnia severity, also in patients with comorbid disorders, and that the effects are maintained over time. ICBT-i can lead to reduced sleep medication use and decreased depressive symptoms. The findings for comorbid insomnia and depression indicate that insomnia needs to be prioritized for evidence-based treatment, also when it is comorbid with depression.

LIST OF SCIENTIFIC PAPERS

I. Internet treatment addressing either insomnia or depression, for patients with both diagnoses – a randomized trial

II. Internet- vs. group-delivered cognitive behavior therapy for insomnia: a randomized controlled non-inferiority trial

III. Three-year follow-up of insomnia and hypnotics after controlled Internet treatment for insomnia

IV. Facilitating and hindering factors in Internet-based treatment for insomnia and depression

CONTENTS

LIST OF ABBREVIATIONS

CBT	Cognitive behavioral therapy
CBT-d	Cognitive behavioral therapy for depression
CBT-i	Cognitive behavioral therapy for insomnia
ECT	Electroconvulsive therapy
FU12	Twelve months follow-up
FU36	Thirty-six months follow-up
FU6	Six months follow-up
GP	General practitioner, i.e. physician in primary care
ICBT	Therapist-guided Internet-based cognitive behavioral therapy
ICBT-d	Therapist-guided Internet-based cognitive behavioral therapy for depression
ICBT-i	Therapist-guided Internet-based cognitive behavioral therapy for insomnia
ISI	Insomnia severity index
MADRS-S	Self-rated Montgomery Åsberg depression rating scale
Post	Measuring point at treatment end
Pre	Measuring point at treatment start
RCT	Randomized controlled trial
SE	Sleep efficiency
SOL	Sleep onset latency
TIB	Time in bed
TST	Total sleep time
TWT	Total wake time

1 INTRODUCTION

Insomnia and depression are two of the most common health complaints worldwide, entailing enormous suffering and large costs for society. This thesis presents clinical research aiming at increasing the knowledge about treatments for insomnia with and without comorbid depression.

1.1 CHARACTERISTICS OF INSOMNIA

The most commonly used criteria of insomnia disorder are specified in the Diagnostic and Statistical Manual of Mental Disorders, DSM. In our studies, we have used the research criteria for insomnia (Edinger et al., 2004), which are almost identical to the criteria in the new DSM-5, released in 2013 (American Psychiatric Association, 2013). In DSM-5, insomnia disorder is characterized by difficulties in initiating or in maintaining sleep, in spite of adequate opportunity for sleep, leading to lowered daytime functioning with regard to social, occupational, educational, behavioral, or other important areas of functioning. These characteristics must have been be present for at least three nights per week, for at least three months, to constitute persistent insomnia disorder, which is what has been studied in this thesis. Having these symptoms for one to three months constitutes episodic insomnia disorder. The previous DSM-edition, DSM-IV (American Psychiatric Association, 2000), distinguished between primary and secondary insomnia, where secondary insomnia was assumed to be caused by some other disorder. The new edition, DSM-5, recognizes that insomnia is often a precursor to, or comorbid with other disorders, and the terms primary and secondary are therefore no longer used.

Prevalence studies of insomnia employ various methods and criteria, and subsequently get varying results. In a large study, 25,579 adult subjects from seven European countries were interviewed (Ohayon and Reynolds, 2009). They found that 9.8% fulfilled the criteria for insomnia disorder as defined in DSM-IV. On the other hand, 37% complained of too short sleep, too light sleep or a global sleep dissatisfaction, and 34.5% reported having at least one of the main insomnia symptoms (difficulties initiating or maintaining sleep) for at least 3 nights per week. Another finding was that 60% of the subjects fulfilling insomnia criteria had had their sleeping problems for more than five years. The results of this thorough study are complicated by the fact that the distinction between primary and secondary insomnia was still in use. Similar results have been reported in other studies (Morin et al., 2006b, Ohayon and Bader, 2010, SBU, 2010, Ancoli-Israel and Roth, 1999), some criticizing the fact that the insomnia criteria do not seem to quite capture the actual prevalence of burdening sleep problems of insomnia type. Insomnia disorder and insomnia symptoms are approximately 1.5-2 times as prevalent among women as among men (Morin et al., 2006b, Ohayon and Reynolds, 2009, Ohayon and Bader, 2010, SBU, 2010). When left untreated, insomnia is often more or less chronic, as is reported both in epidemiological studies (Hohagen et al., 1994, Ohayon and Reynolds, 2009, Mallon et al., 2000, Ford and Kamerow, 1989) and in the reporting of number of years with insomnia in randomized controlled trials (RCT) (Edinger et al., 2001, Morin et al., 2009, Jernelöv et al., 2012).

Insomnia is related to a decreased quality of life, in some regards more so than e.g. congestive heart failure and depression (Walsh, 2004, Leger et al., 2001, Morin and Gramling, 1989). One study in Canada found that the annual cost to society per individual with insomnia disorder was around 3 400 Euros in 2009, and for individuals with insomnia symptoms, 950 Euros. Productivity loss constituted 76% of total direct and indirect costs (Daley et al., 2009). In Sweden, total annual direct and indirect costs related to sleep problems has been estimated at 325 million Euros (2008) (SBU, 2010).

1.2   CHARACTERISTICS OF DEPRESSION

The cardinal symptoms of major depressive disorder (depression) are low mood and a loss of interest or pleasure in daily activities. In addition to at least one of these symptoms, three to four of the following symptoms (making a total of at least five symptoms) must have been present for most of the day for at least two weeks: weight change or change in appetite; change in sleep; change in activity; fatigue or energy loss; feelings of guilt or worthlessness; concentration difficulties; suicidal ideation. In order to get the diagnosis, these symptoms must result in impaired social, occupational or educational function (American Psychiatric Association, 2013). These criteria are similar in DSM-IV and DSM-5. Depression is not as chronic in its nature as insomnia, but instead recurrence is common. Life time prevalence of depression was in a large American study reported to be 16.2% , 12-month prevalence was 6.6% (Kessler et al., 2003) and in a previous study, one month prevalence was 4.9% (Blazer et al., 1994). Other studies claim life-time prevalence to be a lot higher, i.e. the Lundby Study, reporting the probability of having a first depressive episode before the age of 70 to be 27% for men and 45% for women (Rorsman et al., 1990). As with insomnia, depression is approximately 1.5-2 times more common in women than men (Kessler et al., 2003, Rorsman et al., 1990).

Quality of life is highly affected by depression, especially in the social role domain (Kessler et al., 2003). Societal costs of depression in the USA were estimated to be 83 billion USD (app. 74 billion Euros) in 2000, of which 62% were work-place related. In Sweden, more than ten percent of the social security payments for sick leave were attributed to depression in 2009 (including various types, e.g. depressive episode, major depression and chronic depression, but not bipolar disorder) which puts it at the top of the list of diagnoses, followed by the costs for back pain (7%) (Försäkringskassan, 2011).

1.3   COMORBIDITY OF INSOMNIA AND DEPRESSION

People with health problems report insomnia to a higher degree than an otherwise healthy population (Kim et al., 2000, Ford and Kamerow, 1989). A study in Norway, yet unpublished but presented at a conference, investigated prevalence of insomnia among 1,346 subjects in the waiting rooms of primary care clinics. They found that insomnia disorder was present for 47.4% using DSM-5 criteria, while 55.8% reported sleep problems, 18% much or very much problems (Bjorvatn, 2015). Comorbidity of insomnia and depression is very common, and mood disturbance, sleep problems, fatigue and concentration problems – typical symptoms of

insomnia - are criteria of depression. Granted, the depression criteria "sleep problems" also encompasses hypersomnia, but insomnia is the dominating sleep problem (Ford and Kamerow, 1989). Reports on the number of people with depression that have comorbid insomnia vary from around 40% to 90 %, depending on definitions and criteria used, and around 15% to 25% of insomniacs have depression (Ford and Kamerow, 1989, Thase, 1999, Mellinger et al., 1985).

Comorbid insomnia has traditionally been seen as a symptom of other psychiatric disorders (hence the term "secondary insomnia" in DSM-IV, abandoned in DSM-5) which has had implications for the treatments studied and provided. Several factors indicated, prior to the start of this thesis project, that insomnia should not be seen as secondary to depression: Insomnia is often present before the depression (Eaton et al., 1995, Breslau et al., 1996, Livingston et al., 1993); Treating depression does not necessarily lead to remission from insomnia (Hauri et al., 1974, Carney et al., 2007); Treating insomnia decreases depressive symptoms (Fava et al., 2006, Manber et al., 2008); Insomnia is a risk factor for developing depression (Ford and Kamerow, 1989, Eaton et al., 1995, Breslau et al., 1996, Livingston et al., 1993, Baglioni et al., 2011); Residual insomnia predicts relapse into depression (Perlis et al., 1997, Reynolds et al., 1997, Dombrovski et al., 2008); Insomnia can delay recovery from depression (Kennedy et al., 1991, Pigeon et al., 2008); Insomnia without comorbidity exists, and is associated with first-onset of depression (Weissman et al., 1997, Ellis et al., 2014).

1.4 TREATMENTS

Both insomnia and depression are usually treated with medication or psychological treatments, or both. For very severe and treatment resistant depression, electroconvulsive therapy (ECT) is also used. The current state of evidence for insomnia treatments is that sleep medication and psychological treatment, in the form of behavior therapy or cognitive behavior therapy (CBT), are equally effective in the short term, but that CBT is more effective in the long term (Riemann and Perlis, 2009, Morin et al., 2009). Several meta-analyses have concluded that CBT for insomnia (CBT-i) is effective compared to control conditions (Okajima et al., 2014, Mitchell et al., 2012). Very few previous RCTs of insomnia have done long-term follow-up of their participants after more than a few months, but the follow-up data that exist show that CBT-i effects are maintained over time. A follow-up period of three to six months is common, a few had done a one year follow-up and only one study had done a two-year follow-up prior the start of this project (Morin et al., 1999). This was the case both for face-to-face CBT-i (Mitchell et al., 2012) and different types of self-help CBT-i (Cheng and Dizon, 2012).

For depression, many types of psychological treatments that are structured and delivered with quality, have been proven effective, including CBT for depression (CBT-d) (Cuijpers et al., 2011, Butler et al., 2006, Cuijpers et al., 2013a). The effects of psychological treatments for mild to moderate depression were, in a large meta-analysis, found to be similar to those of pharmacological treatments. Another meta-analysis found that if pharmacological treatment was discontinued, patients that had received acute-phase CBT were less likely to relapse into depression (Cuijpers et al., 2013b). A combination of psychotherapy and antidepressants has been found superior to only one of the treatments (Cuijpers et al., 2011, Cuijpers et al., 2013a).

A Swedish study by the National Board of Health and Welfare of treatment of depression in three counties in 2006, showed that in Skåne County (population 1.85 million in 2006), 6.3% had retrieved antidepressant medication from a pharmacy, most of them without a depression diagnosis, according to medical records. Of those with a depression diagnosis - approximately 2% in the studied counties - 80-90% were treated with antidepressant medication, 6% with ECT and 0-15% had received some form of psychotherapy (Socialstyrelsen, 2009). These figures can be seen as somewhat problematic, considering that adherence to pharmacological treatment is poorer (Cuijpers et al., 2011, Cuijpers et al., 2013b) and that a majority of patients prefer psychological treatments (McHugh et al., 2013, Kwan et al., 2010), which may affect outcomes (Swift and Callahan, 2009).

A few clinical trials had, at the time of planning this thesis, looked in to the comorbidity of insomnia and depression. One study compared a combined treatment with antidepressants plus CBT-i, to antidepressants only. The combined treatment had better results both for depression (remission rate 61.5% vs. 33.3%) and insomnia (remission rate 50% vs. 7%) (Manber et al., 2008). Another study, comparing treatment with only antidepressants to treatment with both antidepressants and sleep medication, had similar results (Fava et al., 2006).

1.4.1 Treatment guidelines and their implications

The Swedish recommendations for health care, provided by the national Board of Health and Welfare (Socialstyrelsen), recommend guided Internet-based CBT (ICBT) as the first choice for mild depression. For moderate depression, CBT or antidepressant medication is the recommended first choice (Socialstyrelsen, 2010). The Board of Health and Welfare provides no guidelines for treatment of insomnia. In Great Britain, the National Institute for Health and Care Excellence (NICE) guidelines for treatment of depression recommend a stepped care approach, with the first choice for mild to moderate depression being so called low-intensity interventions (e.g. ICBT, physical exercise), the second step being high-intensity psychotherapy (group or individual), medication or combined treatments. NICE provides no guidelines for treatment of insomnia, but mentions that patients with sleep problems in depression should be given advise on sleep hygiene (regular sleep hours; avoid excess eating, drinking alcohol or smoking before sleep; creating proper sleep environment; do physical exercise). A final example is the American Psychiatric Association (APA), also providing guidelines for treatment of depression but not insomnia (American Psychiatric Association, 2010). While NICE and the Swedish Board of Health and Welfare do not recommend antidepressant medication for mild depression due to poor risk-benefit ratio, APA recommends antidepressant medication for mild to moderate depression. APA suggests psychotherapy "in the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, a co-occurring axis II disorder, treatment availability, or— most important— patient preference" (p. 18). The APA guideline mentions treatment of insomnia only in relation to insomnia being a side-effect to antidepressant medication, even though they include brief information that sleep problems are a predictor of depression.

I have not found any data sources directly showing that insomnia is underdiagnosed and undertreated, even though there seems to be a consensus regarding this in the insomnia research community. However, these health care guidelines are an indication of the way insomnia is and has been viewed within health care – as secondary and thus not prioritized for focused, evidence-based treatment. At the same time, sleep medication is being prescribed in large quantities: a report on insomnia published by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), states that 750 000 Swedes were prescribed sleep medication in 2008 (SBU, 2010). That is around 8% of the population. Ninety percent of these also had prescriptions for other medication - 30% antidepressants and 30% pain medication. Most of these sleep medications (82%) were prescribed by general practitioners (GPs) in the Swedish primary care.

The SBU also reports on a questionnaire sent to 600 GPs about sleep problems, answered by 58.7%. The results showed that almost all GPs agreed that insomnia needs to be taken seriously, and as many as 32% claimed they referred patients to CBT often (8%) or sometimes (24%). The type of CBT provided or the qualifications of the therapist are not reported. This report raises some questions: what were the attitudes towards treatment of insomnia among the 41.3% of GPs who did not answer the questionnaire, and what was the quality of the CBT that the patients were referred to? Access to CBT therapists is scarce (Larsson et al., 2010), and was so even more in 2008, and expertise in CBT for insomnia is even more uncommon. Interestingly, 95% of the GPs in the questionnaire study reported prescribing sleep medication, yet 31% agreed with the statement that "sleep medication is more harmful to the health than poor sleep is".

This, perhaps, is a testament to a situation where CBT-i is not sufficiently available within the health care system.

1.4.2 Content of Cognitive Behavioral Therapy for insomnia, CBT-i

CBT-i is not a strictly defined treatment, but there is a consensus about the main components usually included. These are: education about sleep and the treatment rational, sleep hygiene, sleep restriction, stimulus control and cognitive reappraisal. Many treatments also include techniques for relaxation (Morin and Espie, 2003).

The components considered most powerful in insomnia treatment are sleep restriction and stimulus control. Stimulus control is about not doing anything but sleep (and have sex) in bed, getting out of bed after 20-30 minutes without sleep, spending some time up and then going to bed again to try to sleep. Details in the instructions vary, but the rational is that the bed should be associated with sleep only. Sleep restriction entails restricting time in bed by staying in bed only for as many hours as you have slept, on average, during a previous baseline week. When the total sleep time is more than 85% of the time in bed (i.e. a sleep efficiency of 85%), the time of going to bed is set to 15 minutes earlier than the previous week. The time in bed is thus increased weekly 15 minutes at the time, until a sufficient sleep time is reached. Time of getting up should be kept constant. The rational of sleep restriction is to stabilize the sleep/wake

rhythm, create a sleep pressure that will increase the likelihood of deep, continuous sleep and, probably, function as exposure to fears about the consequences of poor sleep. An alternative to sleep restriction, though less researched, is sleep compression, or scheduled sleep. Sleep compression means that your time in bed should be set to as many hours as you wish to sleep, with a constant time for getting out of bed. If sleep efficiency is less than 80-90%, the sleep window is reduced by 15 minutes at the time, by going to bed 15 minutes later, until sleep efficiency is 80-90%. The sleep window can then be increased again if needed, in the same way as in sleep restriction. Other components that are sometimes included in CBT-i are stress management, relaxation and mindfulness.

1.4.3 Content of Cognitive Behavioral Therapy for depression, CBT-d

The content of CBT-d seems to vary between manuals, probably more so than CBT-i. Some emphasize the behavioral aspects more, while others more or less equal CBT to Cognitive Therapy. These are the main components used in the treatments we have studied ourselves, and they are likely to encompass what is most commonly used: education about depression and the treatment rational, behavioral activation and cognitive reappraisal. Behavioral activation is about increasing the amount of positively reinforced activities (such as positive interaction with others, cultural experiences, eating good food, being in nature), managing negatively reinforced, but important activities (could be for example cleaning, working, taking care of others) and reducing avoidance behaviors (e.g. excessive TV-watching and Internet-surfing). Lately, emphasis on stabilizing the circadian rhythm by keeping stable sleep/wake hours and getting daylight has increased. Cognitive reappraisal is mainly focused on decreasing rumination, i.e. negative brooding. CBT-d will also sometimes include components on how to handle anxiety and poor sleep.

1.4.4 Internet-based treatments

Due to a lack of CBT-trained psychotherapists, different forms of delivery have been developed and studied. First, bibliotherapy and telephone therapy emerged (Cuijpers, 1997, Mimeault and Morin, 1999, Jernelöv et al., 2012), but during the past ten years Internet-based therapies have dominated the self-help research. The treatments studied vary in many ways, e.g. content, level of interactivity, level of automation and therapist support.

The first study of Internet-based CBT-i was Swedish (Ström et al., 2004) and used limited therapist support via email. The treatment group had large attrition of 44%, i.e. the percentage of randomized participants lost at the assessment, and even though the analyses were based on completers only, effects sizes were modest and not superior to the waitlist group. Suzuki et al. had similar attrition rates and completer results in a later study (Suzuki et al., 2008). Ritterband et al. introduced a compensation of 100 USD for completing the post-assessments in a study of an unguided Internet-based CBT-i, did intent-to-treat analyses, and achieved both minimal attrition (4.5%) and large effects sizes and remission rates compared to waitlist control. Subsequent studies of Internet-based CBT-i, reported after the start of this doctoral project (not including the studies in this thesis) have continued to report promising results in different

populations and with different levels and types of support (Ritterband et al., 2012, van Straten et al., 2013, Espie et al., 2012, Ho et al., 2014, Thiart et al., 2015). Attrition has continued to be an issue in all studies that have not, like Ritterband et al. in both their studies, compensated for completion of post-assessments.

The first study on Internet-based CBT-d was an American, unguided treatment which seems to have had an emphasis on cognitive reappraisal, rather than behavioral activation. Participants received a small compensation for each completed assessment (5 USD), but attrition was high (34-47% at different assessments) and effects small and not superior to the control group (Clarke et al., 2002). Since then, a large number of studies have been carried out on Internet-based CBT-d, targeting different populations and using different types and levels of support, generating varying effect sizes (Hedman et al., 2012).

In summary, both completely unguided and therapist-guided Internet-based treatments for insomnia and depression have been found effective (Cheng and Dizon, 2012, Ho et al., 2015, Zachariae et al., 2016, Andersson and Cuijpers, 2009, Hedman et al., 2013b). Thus far, therapist-guided treatments generally have generated better effects than unguided (Spek et al., 2007, Andrews et al., 2010, Zachariae et al., 2016).

In this thesis we will refer to therapist-guided Internet-based CBT as ICBT. ICBT for insomnia is called ICBT-i, and ICBT for depression is called ICBT-d.

1.5 RESEARCH QUESTIONS

The evidence for ICBT-i is strong, but before this doctoral project started, several research questions still needed answers. Also, the comorbidity between insomnia and depression was in need of more clinical research, to help clinicians with treatment choices. Research questions targeted in this thesis are:

- How does ICBT-i compare to face-to-face CBT-i?
- What are the long term effects of ICBT-i?
- Can treatment of insomnia in a non-depressed sample affect depression levels in the long term?
- Is CBT-i a better treatment than CBT-d for persons with comorbid insomnia and depression?

2 THE EMPIRICAL STUDIES

2.1 AIM

The overall aims of this thesis were:

- to challenge the treatment paradigm for comorbid insomnia and depression, which is to primarily treat the depression, by comparing ICBT-i to ICBT-d in this patient group
- to strengthen the evidence for ICBT-i by comparing ICBT-i to face-to-face treatment, and by doing a 3-year follow-up.

2.2 METHODS

This section will describe the parts of the methods that were shared by Studies I-IV.

2.2.1 Participants

The participants in Study I-IV were all recruited via advertisements in media, newspaper articles, websites and social media. No direct referrals from other health professionals were done, though some participants would have heard about a study from a health professional. All studies were directed at Swedish speaking adults with regular access to a computer and the Internet. All participants were diagnosed with Insomnia disorder as defined in the research criteria by Edinger (Edinger et al., 2004). These criteria correspond to the criteria described in DSM-5 of 2013 (American Psychiatric Association, 2013). Comorbidities were allowed, with the exception of diagnoses that were contraindicative to state-of-the-art Insomnia treatment (bipolar disorder, narcolepsy and sleep apnea), as well as conditions urgently requiring other treatments, e.g. suicidality. Persons in jobs with night shift were excluded from the studies.

2.2.2 Procedure of the Internet-based treatments

The treatments described in this thesis were delivered on the same technical platform, developed and used at the Internet Psychiatry Clinic, part of the public health care in Stockholm County, Sweden. ICBT is built up by modules and accessed on a secure web site, which only the participant and their therapist can access. The treatment modules are text-based. Added to this were interactive components, such as behavioral assignments (e.g. activity scheduling and sleep restriction), questions to answer on theory, worksheets to be filled out, and for the insomnia treatment a sleep diary. In the case of studies I and III, the insomnia treatment text was sent to the participants on the form of a book (Jernelöv, 2007), while the internet part of the treatment consisted of the sleep diary, reading instructions for the book, summary of the text, weekly assignments, work sheets and communication with the therapist.

The participants were expected to complete approximately one module per week on average. Each module ended with the participant sending in a home-work report via a secure messaging system. The therapist received the message, then reviewed answers, work sheets and sleep diary (ICBT-i only), gave written feedback the following week day, and then gave the participant access to the next module. The participants also had the possibility to send messages

with e.g. questions to their therapist and these messages were also answered the following week day.

The therapist had access to data from weekly online symptom severity assessments with Insomnia Severity Index (ISI) (Morin and Espie, 2003), and the self-rated version of the Montgomery Åsberg Depression Rating Scale (MADRS-S) (Montgomery and Åsberg, 1979), which allow monitoring of the participant's progress. The system flagged the therapist if a participant scored 4 or more points on the suicide ideation item in MADRS-S (item 9), implying the participant had thoughts about suicide. The therapist then followed a standard procedure for assessment of suicidal ideation, which starts with a structured telephone interview. If a participant was inactive for seven days, the therapist would send a personalized mobile phone text message, often accompanied by a message on the web-page, encouraging the participant to get in touch and continue treatment. If this did not lead to resumed activity, a phone call was made. If the participant could not be reached, eventually a letter would be sent.

2.2.3 Content of ICBT-i

The insomnia treatments in these studies were based on a self-help manual previously published in a book (Jernelöv, 2007), which has been tested in a randomized clinical trial (Jernelöv et al., 2012). The main focus of the treatments was on sleep restriction and stimulus control, which were emphasized throughout the treatments. The other strategies and techniques in the manual were introduced as a sort of "smorgasbord", where the participants could choose to work with the strategy they found most relevant (see Table 1).

Table 1. Content of ICBT-i

Component	Description
Psychoeduction about sleep	The function of sleep, sleep patterns, normal sleep range, age differences, models of disturbed sleep, insomnia characteristics
Sleep hygiene	Habits and environmental factors that may affect sleep, e.g. bedroom factors (dark and cool, no TV or computer) and lifestyle factors (caffeine, alcohol, physical exercise, stress)
Sleep restriction	Restricting time in bed and getting up at a fixed time, in order to increase sleep pressure and stabilize circadian rhythm. Could also function as exposure to fears about being very sleepy during the day. Initially, time in bed should equal average hours of sleep in the week before treatment start. When sleep time is 80-90% of time in bed, for one week, bed time can be set to 15 minutes earlier, until the desired number of hours of sleep is reached.
Stimulus control	Associating bed with sleep, by only using the bed for sleep (and sex), and not lying awake for more than 20-30 minutes before getting up and staying up for a while. When stimulus control is practiced without sleep restrictions, instructions on bed times are usually included, either recommending fixed time for getting up, or both bed time and time for getting up.

Cognitive reappraisal	Identifying and reappraising negative thoughts about sleep. Challenging misconceptions about sleep, such as the consequences of poor sleep and the individual's need for sleep.
Optional components	Importance of daylight and daytime activity (such as physical exercise), relaxation techniques, visualization, going-to-bed-routines, acceptance training, focus training/mindfulness, sleep compression as an alternative for those refusing to do sleep restriction
Relapse prevention	Summarizing the treatment, making a plan for sleep times and other strategies for the near future, how to handle relapse.

2.2.4 Content of ICBT-d

The depression treatment used in Study I was the same as the one used in regular treatment at the Internet Psychiatry Clinic, except that the module on how to handle sleep problems was removed (see Table 2). The treatment has been tried in a randomized controlled trial (RCT) (Andersson et al., 2005) and its effectiveness has later been evaluated (Hedman et al., 2013b).

Table 2. Content of ICBT-d

Component	Description
Psychoeducation about depression	Characteristics of depression, impact of cognitions and behaviors on depression
Behavioral activation	Increasing positively reinforced activities (e.g. social interaction, enjoyable activities), decreasing avoidance behaviors (e.g. excessive TV-watching), handling long term beneficial, but negatively reinforced activities (e.g. duties such as work, cleaning, taking care of others)
Cognitive reappraisal	Registering and challenging negative thoughts, through analyzing and questioning their validity, and through behavioral experiments.
Anxiety and worry	Psychoeducation about anxiety and the fight-or-flight response, scheduled worrying.
Relapse prevention	Summarizing treatment, making a plan for the near future, handling relapse.

2.2.5 Outcome measures

These measure have been used in all studies.

Insomnia. Insomnia severity was measured with ISI, developed by Charles Morin (Morin, 1993, Morin and Espie, 2003). The psychometric properties of ISI are adequate and it is sensitive to change (Bastien et al., 2001), also when web-based (Thorndike et al., 2011) and across different cultures (Chen et al., 2015). ISI has seven items that are scored 0-4 points covering: problems initiating sleep, problems with waking up during the night and early awakenings, level of

satisfaction with sleep, daytime impairment, effect on quality of life and worry about sleep. More points indicate more severe insomnia.

Depression. Depression severity was measured with MADRS-S, which is a much used, validated instrument for measuring and detecting changes in the severity of depression (Montgomery and Åsberg, 1979, Svanborg and Åsberg, 1994). MADRS-S has nine items that are scored 0-6 points covering: mood, worry, sleep, appetite, ability to concentrate, take initiative and engage oneself emotionally, feelings of guilt and suicidal ideation. More points indicate more severe depression

Sleep diary. The sleep diary used in these studies ask participants to register times of going to bed, falling asleep, waking up during the night, morning awakening and getting out of bed. From these data we can calculate time in bed (TIB), sleep onset latency (SOL), total wake time (TWT), total sleep time (TST=TIB-TWT) and sleep efficiency (SE=TST/TIB). The participants were also asked to register some other phenomena such as level of daytime activity, mood, daytime napping and use of sleep medication.

Diagnostic assessments. The diagnosing of insomnia was done in interviews, using the ISI combined with questions on opportunity for sleep, daytime dysfunction, frequency of sleep problems and insomnia duration. The diagnosing of depression was done in interviews using either the depression section of the Structured Clinical Interview for DSM-IV-TR (SCID-I) (First et al., 1999) or the Mini-International Neuropsychiatric Interview M.I.N.I. (Sheehan et al., 1998).

2.2.6 Ethical considerations

All RCTs in this thesis were approved by the regional ethics review board in Stockholm or Linköping.

Participation was voluntary, only the participants themselves could apply for participation, and they could leave the study at any time. A potential negative side of a treatment is if you get treatment for a condition you do not have, or if some other condition should have been prioritized for treatment. This was handled through thorough assessments, face-to-face or via telephone, of both psychiatric and somatic conditions. The assessments were performed or supervised by licenced psychologists and physicians with expertise in the areas assessed.

The risk of negative side-effects from a psychological treatment is fairly small compared to more invasive treatments. The most demanding component in our treatments is probably sleep restriction. Doing sleep restriction usually implies increased daytime sleepiness in the beginning, since sleep deprivation is an assumed mechanism to improve sleep. Potential side-effects were very little studied when this project was planned, but since then attention to side-effects and adverse events have increased. One study indicated that daytime sleepiness and temporarily impaired cognitive performance can occur (Kyle et al., 2014). All methods in the treatments provided in our studies were optional, and the participants decided what they wanted to try and for how long. Also, they were informed that doing sleep restriction could lead to

increased sleepiness, and were advised against e.g. driving and operating dangerous machines if this occurred.

Another ethical consideration is the risk that patients do not seek other treatments that they might need. This risk is reduced both by the thorough assessments and by the weekly symptom measurements, as well as the therapist support available in all treatments (except the control treatment in study III). Participants were not told not to seek other treatments during the study period. When suicide ideation was indicated by MADRS-S item 9, action was taken the same day as the instrument was filled out.

There is always a risk that poor outcome of a psychological treatment could lead to a feeling of hopelessness and failure, which might lead to an overall lowered belief in psychological treatments. We tried to minimize this risk by helping participants with referrals or recommendations to other treatments when this was deemed necessary. Doing live post-treatment assessments was an important part of this effort.

2.3   STUDY I

2.3.1   Aim and hypothesis

The aim of this study was to compare ICBT-i to ICBT-d for participants diagnosed with both insomnia and depression. We wanted to evaluate effects on insomnia and depression severity, as well as the participants' self-rated need for, and intention to seek other treatments for insomnia and depression after the study treatment ended.

The hypothesis was that ICBT-i would be more beneficial than ICBT-d, in that effects on insomnia were expected to be better and effects on depression were expected to be similar. Participants in ICBT-d were expected to express more need for further treatment after the treatment in this trial.

2.3.2   Methods

Participants in this RCT were 43 adults with insomnia disorder and major depression, 53% were women and 53% had attended higher education (college/university). Sixty-three percent used sleep medication at baseline, and 30% used antidepressant medication. MADRS-S and ISI scores indicated moderate insomnia and depression levels at baseline, on average (MADRS-S = 25.0; ISI = 21.3). Fifty-one percent had an average total sleep time of less than six hours.

Screening was done online using web-based instruments and questionnaires, followed by structured telephone interviews. Face-to-face assessments were done both before and after treatment by physicians or psychiatrists at the Internet Psychiatry Clinic. Participants were randomized between ICBT-i or ICBT-d, and the treatment lasted for nine weeks. Six- and twelve-month assessments were done using online sleep diary, questionnaires and telephone interviews.

2.3.3 Results

Analysis with hierarchical mixed modeling showed that ICBT-i was significantly more effective than ICBT-d in reducing insomnia severity during treatment ($p = 0.05$), and equally effective in reducing depression severity (see Figures 1 and 2). The group differences in insomnia severity were maintained during the twelve months follow-up period. Within group Cohen's *d* effect sizes from pre-treatment assessment to 12-month assessment were for ISI 1.84 (ICBT-i) vs. 0.95 (ICBT-d) and for MADRS-S 1.12 (ICBT-i) vs. 0.94 (ICBT-d).

Insomnia and depression diagnostics were done in the face-to-face posttreatment assessments. In the ICBT-i group 57% (12 out of 21) no longer had insomnia, compared to 19% (3 out of 16) in the ICBT-d group, which is a significant difference ($p < 0.05$). There was no significant difference between groups regarding remission from depression: 37% (7 out of 19) were in remission from depression in the ICBT-i group and 21% (4 out of 19) in the ICBT-d group.

Posttreatment, participants in ICBT-i used less sleep medication ($p < 0.05$) than participants in ICBT-d: 12 out of 13 participants in ICBT-i stopped using sleep medication vs. 6 out of 12 in ICBT-d. Participants in ICBT-i had significantly less self-rated need for further insomnia treatment ($p < 0.001$) while the need for depression treatment was similar in both groups.
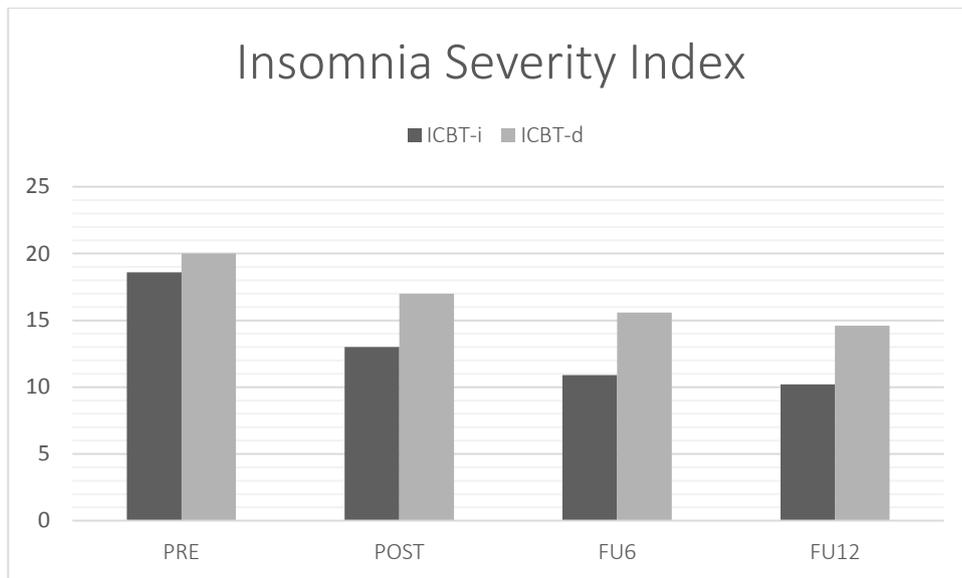
Figure 1. Change in insomnia severity – comparison between treatments, observed means.
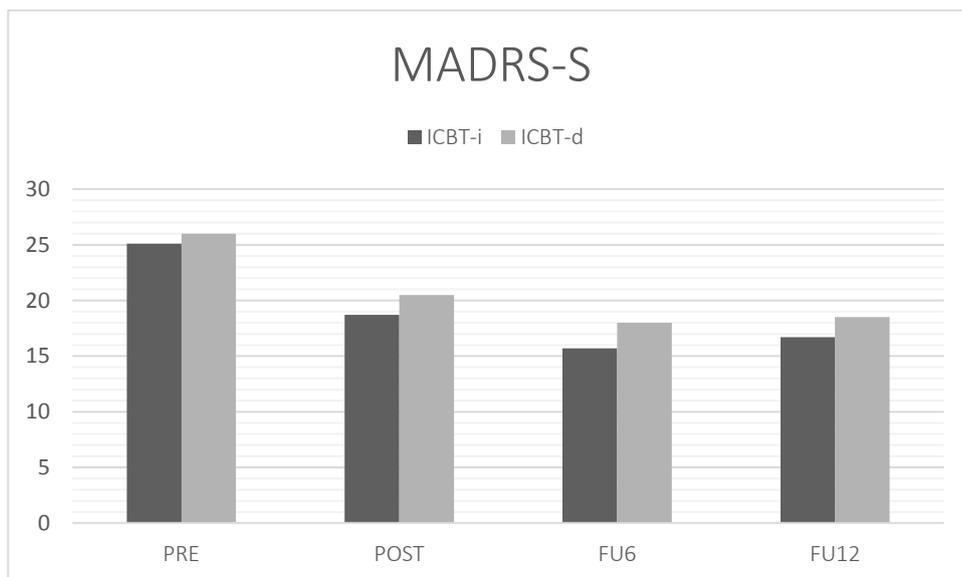
Figure 2. Change in depression severity – comparison between treatments, observed means.

Fig. 1 and 2: ISI,Insomnia Severity Index, mean values; MADRS-S,Montgomery Åsberg Depression Rating Scale – Self rating, mean values; PRE, post-treatment; POST, directly after treatment, FU6, 6-month follow-up, FU12, 12-month follow-up; ICBT-i, Group receiving internet-based cognitive behavior therapy for insomnia; ICBT-d, Group receiving internet-based cognitive behavior therapy for depression

2.3.4 Conclusions

The results indicate that CBT-i is an important treatment for patients suffering from both insomnia and depression. Overall, ICBT-i was found to be more effective than ICBT-d. The participants had more severe insomnia and depression at baseline than is common in studies of insomnia or depression, and ended up with on average mild depression in both groups, indicating that more powerful treatments are needed. The results support the notion that insomnia, when comorbid with depression, is not merely a symptom of, or secondary to depression. Instead both problems need to be addressed with evidence-based treatments.

2.4 STUDY II

2.4.1 Aim and hypothesis

The aim of Study II was to compare ICBT-i with face-to-face treatment, in the form of group-delivered CBT-i, GCBT in a randomized controlled trial. Primary outcome was insomnia severity, secondary outcomes were sleep diary data, sleep medication use and depression severity.

The hypothesis was that ICBT-i would not be inferior to GCBT.

2.4.2 Methods

Participants in this RCT were 48 adults diagnosed with insomnia, 65% were women and 50% had attended higher education (college/university). Sixty-three percent used sleep medication at baseline. ISI and MADRS-S scores indicated moderate insomnia and mild depression levels on average at baseline (ISI = 18.5; MADRS-S = 13.9).

This non-inferiority study was done in collaboration with Linköping University and set in Östergötland County. Screening was done online using web-based instruments and questionnaires, followed by structured telephone interviews and face-to-face assessments by master students of psychology, supervised by an experienced psychologist. Participants were randomized between ICBT-i or GCBT, and the treatment lasted for eight weeks. Six-month follow-up assessments were done using online sleep diary, questionnaires and telephone interviews.

The group therapy was provided in weekly two hour-sessions, using the same content as the ICBT-i modules. Therapists were one psychology student at master level plus one supervising licensed psychologist.

2.4.3 Results

Both treatment groups reached significant improvements and large effect sizes for ISI (within groups Cohen's *d*: ICBT-i post = 1.8, 6-months follow-up = 2.1; GCBT post = 2.1, 6-month follow-up = 2.2) (see Figure 3). The confidence interval of the difference between groups on ISI post-treatment and at the 6-month follow-up indicated non-inferiority of ICBT-i compared to GCBT. At post-treatment, two thirds of patients in both groups were considered responders

using the criteria that the reduction of ISI should be more than 7 points. Using diagnostic criteria, 63% (ICBT) and 75% (GCBT) were in remission.

Sleep diary data effect sizes were: Sleep Efficiency pre-post: 1.78 (GCBT) and 1.61 (ICBT-i); Sleep Latency pre-post: 1.31(GCBT) and 1.1 (ICBT-i); Total Sleep Time pre-post: 0.48 (GCBT) and 0.14 (ICBT-i). Sleep medication use decreased in both groups: from 16 to 3 users in GCBT and from 14 to 6 users in ICBT-i. Depression severity was significantly reduced in both groups, effect sizes in MADRS-S pre-post were 0.89 (GCBT) and 0.69 (ICBT-i).
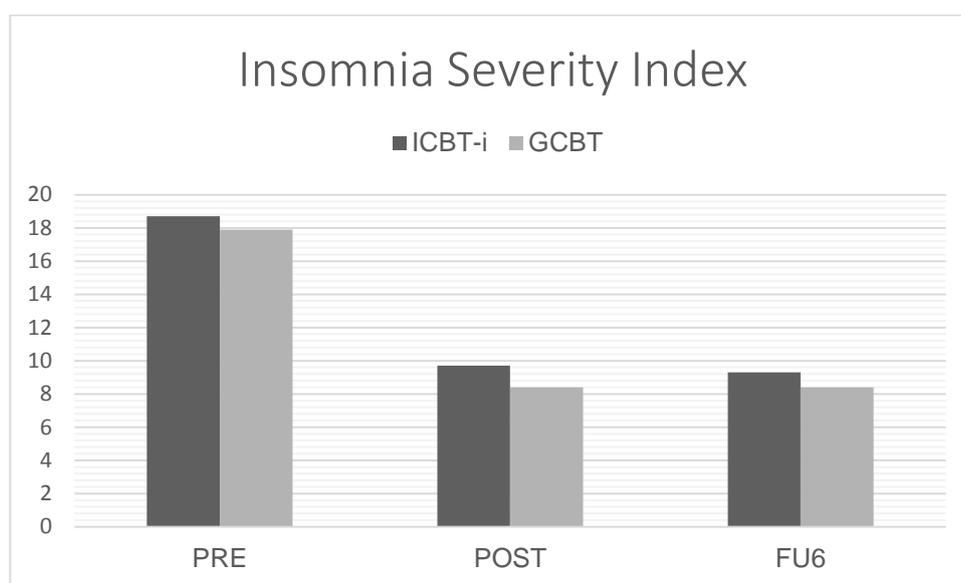
Figure 3. Outcome on Insomnia Severity Index (observed data) from pre-treatment to 6 months follow-up. ICBT, Internet-delivered cognitive behavioral therapy; GCBT, group-delivered cognitive behavioral therapy; PRE, post-treatment; POST, after treatment; FU6, 6-month follow-up.

2.4.4 Conclusions

Both ICBT-i and group-delivered CBT were efficacious in this study. The effect sizes were comparatively large for insomnia severity and small to very large for sleep diary data and depressive symptoms. Both treatments compared well to other studies of CBT-i delivered in groups or via the Internet. The results indicate that ICBT-i was not inferior to GCBT. The results of this study are in line with previous research on ICBT and strengthen the evidence for guided ICBT-i for insomnia as a viable treatment alternative.

2.5 STUDY III

2.5.1 Aim and hypothesis

This study was a long-term follow up of a previously reported randomized controlled trial (Kaldo et al., 2015). The aim was to do a three year follow-up, comparing ICBT-i to an active control treatment regarding insomnia symptoms and sleep medication use. Effects on depressive symptoms have not been reported in the article included in this thesis, but will be reported here.

The hypothesis was that the effects of ICBT-i would be maintained and that ICBT-ctrl would have used more other treatments during the follow-up period.

2.5.2 Methods

Participants were 148 adults with insomnia, 78% were women and 74% had attended higher education (college/university). Participants diagnosed with major depression were excluded from this study and included in Study I. Forty-seven percent used sleep medication at baseline. ISI and MADRS-S pretreatment scores indicated moderate insomnia and mild depression levels on average (ISI = 16.6; MADRS-S = 12.6).

Recruitment and screening were done jointly with Study I, using web-based instruments and questionnaires, followed by structured telephone interviews. Recruitment was national and therefore no face-to-face assessments were done. Participants were randomized between ICBT-i or the active control treatment (ICBT-ctrl). The treatments lasted for eight weeks. Six- and 12-month assessments were done using online sleep diary, questionnaires and telephone interviews. The 36-month assessment reported in Study III used online questionnaires and telephone interviews.

The active control treatment consisted of psychoeducation about sleep, sleep hygiene and limited versions of relaxation training, stress management and mindfulness, as well as a sleep diary. Thus ICBT-ctrl encompassed components expected to have some effect on insomnia, but not the components considered most effective – sleep restriction and stimulus control. ICBT-ctrl had a discussion forum but no therapist support, other than the possibility to get technical assistance. Therapists in ICBT-i were psychology students at master level supervised by a licensed psychologist.

2.5.3 Results

In the previously reported post- 6-month and 12-month follow-ups, we found that ICBT-i was more effective than ICBT-ctrl posttreatment and at the 6-month follow-up. Between-groups effect size (Cohen's *d*) on ISI was large posttreatment, 0.85. At the 12-month follow-up, however, the control group had reached similar results as the ICBT-i group. The large pre-post improvements in insomnia severity of the ICBT-i group were maintained during the long term follow-up, and the difference between groups was non-significant (see Figure 4). The within-group effect sizes from pre-treatment to the 36-month follow-up were 1.6 (ICBT-i) and 1.7 (ICBT-ctrl), and 74% of the interviewed participants no longer had insomnia diagnosis after 36 months. A possible explanation to the improvements in ICBT-ctrl could be that they used significantly more sleep medication (p = 0.01) and underwent significantly more other insomnia treatments (p < 0.001) during the follow-up period. Depressive symptoms were significantly improved in both groups.
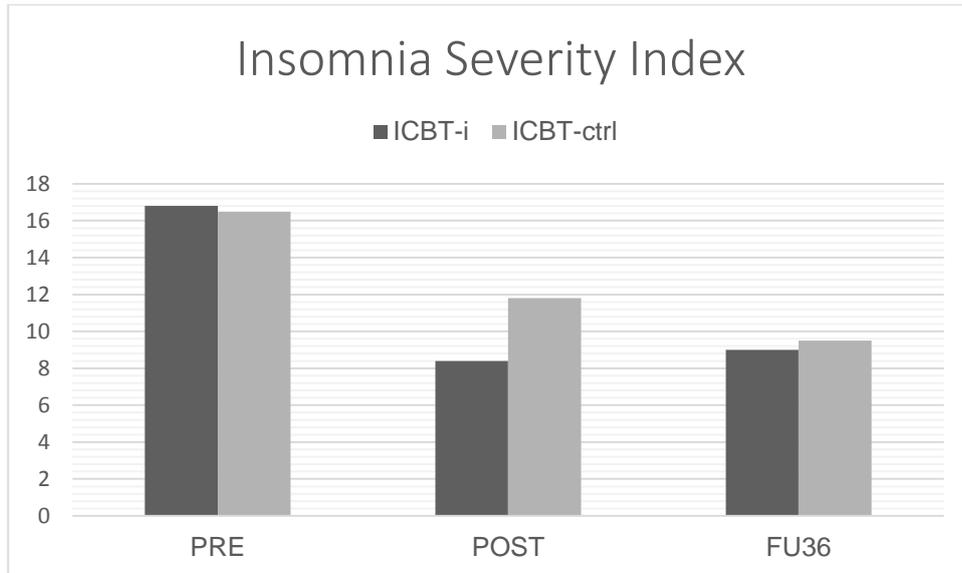
Figure 4. Mean Insomnia Severity Index values at the pretreatment (PRE), post-treatment (POST) and 36-month (FU36) follow-up assessments. ICBT-i, treatment, ICBT-ctrl, active control treatment.

2.5.4 Conclusions

The three-year follow-up in this study is the longest follow-up period of CBT for insomnia thus far. The results show that the large pretreatment to posttreatment improvements on ISI in the ICBT-i group were maintained throughout the follow-up period, as were the improvements on MADRS-S. After three years, ICBT-ctrl had reached the same low levels of insomnia symptoms as ICBT-i, but participants in ICBT-ctrl used significantly more other insomnia treatments and sleep medication during the follow-up period compared with ICBT-i.

2.6 STUDY IV

2.6.1 Aim

Study IV was a qualitative study based on the results and participants of Study I. This patient group seemed more burdened by symptoms and reached less satisfactory results than in many other studies of insomnia, where comorbidity with depression was not an inclusion criteria. The aim of Study IV was therefore to investigate hindering and facilitating factors for the participants' work with ICBT. This was done through a qualitative interview study with additional quantitative and semi-qualitative analyses. This study was not hypothesis driven.

2.6.2 Methods

At the time of the 6-month follow-up, qualitative telephone interviews were done with all participants that could be reached. Thirty-five out of 43 possible interviews were done and recorded. The interviews started with the question "How did you think the treatment went?". The participants were asked to choose between the alternatives very well, rather well, rather

badly or very badly. The second question was: "Why do you think it went [*well/badly*]?". The interview was thereafter free to follow whatever the participant brought up, trying to stay with open questions to allow for variation in the participants view of the treatment. The recorded and then transcribed interviews were analyzed with a grounded theory approach. During the interview analysis, several themes were identified for further analyses using other types of data – quantitative data from instruments and questionnaires, and semi-qualitative data from the treatments themselves, i.e. the content of homework assignments and communication between therapist and participant.

2.6.3 Results

The analyses resulted in 738 coded sentences, which were condensed into 47 categories corresponding to the main message of the sentences. These 47 categories were grouped into 11 themes: Problems with ICBT content, Stressful demanding treatment, Hindered by insomnia/depression symptoms, Hindered by illness in general, Negative towards treatment, Positive towards treatment, Active with treatment components, Inactive with treatment components, Acceptance of diagnose-related problems, Facilitating other and Hindering other. Four of these themes were deemed of particular interest and further analyzed with quantitative and semi-qualitative methods: Opinions about the treatment and therapist support, Motivation and adherence, Hindering comorbidities and Acceptance. Statistical analyses were chosen depending on the research question raised, mainly correlations, Chi-square testing and t-tests.

Three hypotheses for future research emerged from the analyses:

1. A combination of CBT for insomnia and CBT for depression, with emphasis on CBT for insomnia, is more effective than only one of the treatments, for patients with comorbid insomnia and depression.
2. Additional, or a different type of therapist support will increase outcomes for patients with more comorbidities.
3. Acceptance of sleep problems, and/or negative emotions and cognitions in general, is a mechanism of change in CBT-i.

2.6.4 Conclusions

The analyses indicated that participants in ICBT-i were more positive about their treatment than participants in ICBT-d. Having several comorbid conditions was perceived as hindering in the work with the treatment, and more so in ICBT-d than in ICBT-i. Usage of treatment components was positively associated with better outcome in both groups, and acceptance of sleep problems and of negative emotions and cognitions, was positively associated with outcome in ICBT-i.

2.7 SUMMARY OF RESULTS

The mean values, standard deviation and effect sizes of ISI and MADRS-S in study I-III are summarized in Table 3. MADRS-S for Study III has not been reported previously.

Table 3. Summary of Means, SD and effect sizes for ISI and MADRS-S. Observed data.

Study	Measure	Group	Pre M (SD)	Post M (SD)	FU6 M (SD)	FU12 M (SD)	FU36 M (SD)	Effect size within group (Cohen's *d*)			
								Pre-Post	Pre-FU6	Pre-FU12	Pre-FU36
I	ISI	ICBT-i	18.6 (4.0)	13.0 (6.4)	10.9 (5.9)	10.2 (5.0)		1.06	1.54	1.84	
		ICBT-d	20.0 (4.1)	17.0 (7.0)	15.6 (6.7)	14.6 (7.3)		0.54	0.81	0.95	
	MADRS-S	ICBT-i	25.1 (5.9)	18.7 (11.4)	15.7 (8.6)	16.7 (9.2)		0.74	1.30	1.12	
		ICBT-d	26.0 (6.9)	20.5 (9.8)	18.0 (7.1)	18.5 (9.1)		0.66	1.14	0.94	
II	ISI	ICBT-i	18.7 (4.4)	9.7 (5.3)	9.3 (4.8)			1.81	2.08		
		GCBT	17.9 (3.9)	8.4 (4.9)	8.4 (4.9)			2.13	2.17		
	MADRS-S	ICBT-i	12.5 (7.5)	7.7 (6.1)	7.7 (6.7)			0.69	0.83		
		GCBT	14.1 (5.7)	8.4 (6.9)	9.6 (7.2)			0.89	0.70		
III	ISI	ICBT-i	16.8 (3.8)	8.3 (4.1)	9.5 (5.4)	8.9 (4.1)	9.0 (4.9)	2.07	1.71	1.95	1.58
		ICBT-ctrl	16.5 (3.8)	11.8 (4.4)	11.5 (5.1)	9.6 (4.8)	9.5 (4.7)	1.09	1.22	1.50	1.67
	MADRS-S[a]	ICBT-i	12.6 (5.6)	7.8 (3.5)	10.0 (4.8)	8.6 (4.2)	8.6 (6.0)	1.05	0.48	0.59	0.70
		ICBT-ctrl	12.7 (6.0)	11.2 (5.4)	10.2 (5.3)	9.5 (5.2)	8.3 (5.5)	0.26	0.43	0.59	0.81

ISI, Insomnia Severity Index; MADRS-S, Montgomery Åsberg Depression Rating Scale – Self rating; ICBT-i, Group receiving internet-based cognitive behavior therapy for insomnia; ICBT-d, Group receiving internet-based cognitive behavior therapy for depression; GCBT, Group receiving group therapy, ICBT-ctrl, active control treatment; Pre, Before treatment; Post, After treatment; FU6, 6-month follow-up; FU12, 12-month follow-up; FU36, 36-month follow-up; M, Mean; SD, standard deviation;
[a] MADRS-S data for Study III is not previously reported

3 DISCUSSION

3.1 PRIMARY FINDINGS

The aim of this doctoral project was to strengthen the evidence for ICBT-i by comparing it to face-to-face treatment and study long term effects. We also wanted to challenge the current view of insomnia as a secondary disorder by looking at effects of ICBT-i on depressive symptoms, and specifically target the treatment of comorbid insomnia and depression.

ICBT-i compared well with, and was non-inferior to a highly effective face-to-face CBT-i delivered in groups. The decrease in insomnia symptoms were maintained for three years after ICBT-i, and consumption of sleep medication and other insomnia health care was decreased, compared to an active control treatment. ICBT-i reduced depression symptoms in samples with and without comorbid depression. When comparing ICBT-i to ICBT-d for patients with both insomnia and depression, and following up over one year, ICBT-i was found more effective – the decrease in depression symptom levels was similar in both treatments, but the decrease in insomnia symptom levels was higher in ICBT-i. Qualitative findings from this study suggest that patients in ICBT-i were more positive about their treatment and less hindered by comorbidities in their work with the treatment. Acceptance of sleep problems and negative emotions and cognitions could be a mediator of insomnia treatment effects.

3.1.1 Effects on insomnia symptoms

In all three RCTs in this thesis, the effects of ICBT-i on insomnia symptom severity have been large to very large. Benchmarking against other studies we see that the effect sizes found in our studies were as large as, or larger than the previous RCTs with the highest effects (Ritterband et al., 2009, Ritterband et al., 2012, Lancee et al., 2012). Study I, having participants with both insomnia and major depression, overall had more modest effects than the other studies, but they were still comparable to other large-effects studies. Looking at remission from insomnia diagnosis, the results are equally encouraging. Using diagnostic criteria, 57% in Study I (posttreatment), 75% in Study II (FU6) and 74% in Study III (FU36) were in remission from insomnia after ICBT-i. The sleep diary data in our studies have been consistent with the ISI-results in terms of treatment effects (sleep diary data was not part of Study III, the long-term follow-up, but it was part of the original report of that study (Kaldo et al., 2015)). Unlike most previous studies, our studies have not excluded participants with comorbidities, other than when they were contraindicative of our treatments, which further strengthens the evidence that this type of ICBT-i is a viable treatment option for insomnia.

Since the publication of Study II, one more non-inferiority study of ICBT-i has been published, although non-inferiority statistics were not applied (Lancee et al., 2015). This study found individual CBT-i to be more effective than ICBT-i. The intervention and therapist support of their ICBT-i appears to have been very similar to that in Study II, except that less total therapist time was spent on patients in the Dutch study (90 vs. 184 minutes/patient). The patients with more depressive symptoms had lower adherence and more attrition in ICBT-i than in the individual therapy. A previous study has indicated that patients with more depressive

symptoms benefit more from therapist support (Lancee et al., 2014), suggesting that the less intensive support in the Dutch study could be a partial explanation as to why the Dutch ICBT-i was less effective than the ICBT-i in Study II. The individual therapy was delivered by an expert in CBT-i, which is likely to have boosted the effects. However, given that it presently is very difficult to get any type of CBT-i, in any country, it does not seem realistic that individual therapy will be an available option for the majority of insomniacs any time soon, if ever. Further comparisons of ICBT-i to individual CBT-i is therefore probably not the most pressing research need.

Sleep diary data are not emphasized in this thesis, although sleep diaries have been part of all studies up to the 12-month assessment. The reason is that insomnia is defined as a subjective disorder measured well by ISI – insomnia is not the same as sleep deprivation, which needs to be measured with sleep diary data or objective measures. Also, research indicates that insomniacs receiving CBT-i tend to underestimate the sleep diary parameters pretreatment, while this discrepancy is reduced (or even turned into overestimation) posttreatment, making sleep diary data less indicative of treatment effects (Lund et al., 2013). Interestingly, this shift in sleep time perception could be mediated by an increase in sleep depth.

3.1.2 Effects on depressive symptoms

The effects of ICBT-i on depression symptom severity were large in Study I, comparable to those of ICBT-d, and medium to large in Studies II and III. Many other insomnia studies that have measured depressive symptoms, have found similar results (Lancee et al., 2013, Manber et al., 2008, Ashworth et al., 2015, Christensen et al., 2016). Norell-Clarke et al. recently compared CBT-i to Relaxation Training in a sample with insomnia comorbid with major depression or subthreshold depression. They found that CBT-i was effective in reducing depression symptoms both patient categories (Norell-Clarke et al., 2015). In another study researchers added CBT-i or a placebo intervention to a treatment with antidepressant medication for patients with comorbid insomnia and depression, and found that adding CBT-i improved remission rates for both insomnia and depression quite dramatically compared to placebo (Manber et al., 2008). It is also known, that insomnia often precedes and is an important risk factor for development of depression (Ford and Kamerow, 1989, Breslau et al., 1996, Baglioni et al., 2011). Thus, it should perhaps not be a surprise that a comparison of ICBT-i and ICBT-d head-to-head in treating comorbid insomnia and depression, such as in Study I, turned out in favor of ICBT-i. Still, reactions to this study have included expressions of surprise even among experienced insomnia researchers: *"...their report asks us the once unthinkable question: Can depression be effectively treated by treating insomnia alone? [...] Surprisingly, this study showed that an internet-based intervention for insomnia was more effective than an internet-based depression treatment for treating both insomnia and depression symptoms among individuals suffering from both conditions."* (Editorial in SLEEP 38, p. 267; Edinger, 2015). The slightly provocative design of Study I, courtesy of Dr. Viktor Kaldo, was well suited for ICBT, since ICBT minimizes deviations from manual content and facilitates analysis of treatment adherence, as is done in Study IV.

Many types of structured depression treatments, delivered with quality, have been shown efficacious (Cuijpers et al., 2011). ICBT-i is a highly structured treatment, and it targets many areas believed to be important in depression, besides improving sleep, such as stabilizing the circadian rhythm, increasing daytime activity and reducing stress. For insomnia, on the other hand, the mechanisms of action seem to be more specific than for depression, why it is to be expected that the effects on insomnia severity would not be as large in ICBT-d as in ICBT-i.

While having large effects on depression, ICBT-i did not seem to be a sufficient treatment of depression when comorbid with insomnia. The participants in Study I started on unusually high depression levels, compared to other CBT-studies of depression (Andersson et al., 2005, Hedman et al., 2013b), and ended up with mild depression, on average. It was clear to the therapists that doing ICBT was hard for many of these patients. Study IV confirmed this clinical impression in the interviews done at the time of the six-month follow-up. However, participants in ICBT-i expressed some factors that were more beneficial in ICBT-i than in ICBT-d: they were overall more positive and less negative about their treatment, and comorbidities other than insomnia and depression seemed less hindering in this treatment. A speculation is that ICBT-i is easier to adhere to than ICBT-d, possibly by being more specific and having relatively simple instructions for the main components, though they are often hard to execute. Interestingly, participants in ICBT-i expressed that acceptance of their sleep problems had been helpful, and indeed measures of both insomnia acceptance and acceptance of general negative emotions and cognitions were positively associated with treatment effect in ICBT-i. More research is needed to further investigate the relationship between insomnia and depression, and their treatments.

3.1.3 Long term effects of ICBT-i

The studies in this thesis employ follow-up periods of six months (Study II), twelve months (Study I) and 36 months (Study III). A 36-month follow-up has been done for Study I as well, but has not yet been published. All studies show that treatment effects were stable over time. In Study I and II effects increased after the treatment end, while they were largest directly at posttreatment in Study III. The long-term findings are consistent with other studies with shorter follow-up periods (Zachariae et al., 2016, Mitchell et al., 2012). In Study III, the interpretation of the 36-month results were made more complicated by the fact that the control group, after twelve and 36 months, also had improved to a degree where the effects on both insomnia and depressive symptoms were similar to those of ICBT-i. One interpretation of this could be that insomnia subsides with time. This does, however, not seem likely, given the chronic nature of insomnia disorder, evident both in epidemiological studies (Ohayon and Reynolds, 2009) and in RCTs reporting number of years with insomnia, which is typically around ten years, on average (Jernelöv et al., 2012, Kaldo et al., 2015, Morin et al., 2009, Edinger et al., 2001). Also, studies with waitlist controls report small effects for the control groups (Ho et al., 2015, Morin et al., 2006a). The effects for the control treatment in Study III likely had several other reasons: that the treatment itself was moderately effective, that ICBT-ctrl used more additional treatments for insomnia during the follow-up period and, perhaps most importantly, used more sleep medication.

3.1.4 Sleep medication

Both in Study I and Study III, participants receiving ICBT-i reduced their sleep medication use compared to the control treatments, and in Study II, sleep medication use decreased dramatically in both treatment arms. This outcome is not always reported in RCTs of insomnia, but has by many been noted as an important area of research due to the problems associated with sleep medication, which are mainly the lack of studies of long-term use, the side effects, patient preferences for psychological treatment and that effects do not last after tapering of the medication (Riemann and Perlis, 2009, Toner et al., 2000, Morin et al., 1999, Vincent and Lionberg, 2001).

In relation to sleep medication use and comorbid depression, it might be worth mentioning that researchers in Norway showed that the use of hypnotics was associated with subsequent development of depression and anxiety (Neckelmann et al., 2007). These results should, however, be viewed with caution, since the sleep medication used at the first assessment was benzodiazepines, which was what was available at the time. At the second assessment, more modern, so called "z-drugs" (zolpidem, zopiclone and zaleplon) were the most common sleep medications, but the authors do not report if or when benzodiazepine users had moved on to "z-drugs" between assessments.

An impressive, four-arm study by Morin et al. of a sample with insomnia disorder, found a slight superiority long-term (six months) of a combination treatment (CBT-i plus zolpidem) compared to CBT-i only, where sleep medication use was terminated after six weeks while CBT-i continued monthly for another six months (Morin et al., 2009). It would be interesting to replicate this study with a sample with insomnia and depression, to see what the effects would be of an initial, short-term, carefully managed, nightly and stable sleep medication dose, to be phased out during treatment. This might make the employment of strenuous CBT-i-interventions a little easier and improve outcomes for this patient group.

In summary, more research on the topic of sleep medication is warranted, but ICBT-i is clearly promising as a way of reducing sleep medication use.

3.2 ATTRITION

Attrition is usually defined as the percentage of randomized participants from which one has not obtained follow-up measures, at a given assessment. This is the definition used in Studies I-IV. Being able to analyze the data of participants with poor outcomes, as well as of participants who have dropped out of treatment, is of the essence.

Attrition on primary measures has been relatively low in Studies I-III, especially the post-assessment attrition: 2-4% in Study I, 2% in Study II and 10% in Study III. Long-term follow-up assessments tend to result in more attrition, and do so also in Studies I-III, though it is still comparatively low. The latest meta-analysis of ICBT-i reports an average attrition of 24.7% in 11 studies: $12.5 - 42.9\%$ for all studies except the two previously mentioned that compensated participants with 100 USD for completing post-assessment, which had an attrition of 0 and

4.4% at the post-assessment (Zachariae et al., 2016). Interestingly, the two latter studies also had the largest effect sizes of the studies in this meta-analysis, even though they did not have any therapist-guidance (Ritterband et al., 2012, Ritterband et al., 2009). This is likely an indication as to the importance of a planned follow-up after treatment – one can suspect that the participants in these two studies made an effort to adhere to the treatment, because they knew someone would take an interest in, and ask them about how they did (since they wanted the 100 USD).

So why can we report less attrition than most other ICBT-i studies, even though we did not compensate participants in any way for completing assessments? One reason could be the focus on qualified therapist support, perhaps creating a sense of duty among participants. This hypothesis is supported by the fact that the un-guided control group in Study III had more attrition than the therapist-guided group, at all assessments. Another explanation could be that our research team follows a long tradition of perseverance, and countless engaged researchers and students make calls, send text messages and mail participants with a very positive energy (known as "the friendly leech-approach"), until all retrievable data is retrieved. Another reason why attrition is kept rather low is that the primary outcome data is collected both via the Internet and in telephone interviews, since not all participants complete both. This way one type of data can be replaced with the other using an imputation algorithm, based on regression analysis of a lot of previous assessments where Internet- and telephone-data were collected within one week. This method has been described in a previous article (Hedman et al., 2013a).

However, if the willingness to adhere to treatment and complete assessments found in the studies by Ritterband et al. (Ritterband et al., 2012, Ritterband et al., 2009) can be generalized to a substantial portion of insomniacs, paying participants 100 USD in lieu of therapist guidance and chasing assessment data, would most certainly be cost-effective to society.

3.3 ADVERSE EVENTS

The reporting of adverse events during psychological treatments is increasing in frequency, and measures are being refined (Rozental et al., 2014). When this project started, little was done in this area. Still, measures of adverse events were included in the studies in this thesis, albeit in a qualitative and non-standardized way, since there were no standards available. Participants were, in posttreatment interviews, asked the question "Did the treatment lead to any negative consequences?". If they answered yes, they were asked to elaborate. This answers were recorded and later reviewed for each participant as part of the analyses, and have been reported in the articles in this thesis.

The question about negative consequences were answered in the affirmative by 18% in Study I, 19% in Study II and 24% in Study III (reported in the original article (Kaldo et al., 2015)). This may seem like a large proportion of the participants, but in order to interpret these figures one must look at the nature of the complaints. The adverse events can roughly be divided into two groups:

Direct negative consequences from doing sleep restriction or stimulus control, e.g. being sleepy, getting headaches, having to stop driving due to sleepiness, concentration problems, unwanted changes of habits (e.g. not being "allowed" to watch TV in bed) and even one minor traffic accident. These events are temporary and in many cases seen by the participant as acceptable means to an end. Becoming sleepy, for example, is after all the point of sleep restriction, and is supposedly what leads to better sleep.

Increased stress and worry. Working with the treatment can be stressful both in terms of having to perform, and in terms of increased focus on the sleep problems. Participants complained about being stressed by the technical platform and having difficulties with the treatment content, and some experienced a lack of time. Not being able to keep up with what participants perceive is expected of them, could result in feelings of guilt and hopelessness.

Kyle et al. did an interesting study on negative effects of sleep restriction, and found that subjective sleepiness increased and objective cognitive performance (psychomotor vigilance tasks) decreased in the acute phases of sleep restriction, but had returned to baseline values at the three-month follow-up (Kyle et al., 2014). As mentioned in section 3.1.1, previous studies have reported that a person's perceived sleep time pretreatment, recorded in a sleep diary, is longer than the objective sleep time, recorded with polysomnography (Lund et al., 2013). Setting the sleep window according to the sleep diary thus implies, that most participants will, in the beginning of doing sleep restriction, get even less objective sleep than at baseline, which could at least partially explain the negative effects.

In our studies, participants were informed that sleepiness may increase during sleep restriction, and that e.g. driving or operating sensitive machinery may have to be avoided. However, the study by Kyle et al., and our own recordings of adverse events, indicate that we may need to be more specific and directive regarding risks in the acute phases of sleep restriction, and perhaps, overall, better manage the expectations of the patients. Performance-related stress could be managed by making the treatment content more flexible in its scope, or flexible in a way that is easier for participants to understand and make use of.

3.4   LIMITATIONS

The limitations of each study are discussed in their respective article. There are, however, some limitations that the studies have in common that will be discussed here.

The generalizability of the results of clinical trials is always a topic of interest. We now that ICBT-i is an effective treatment, but for whom? Are the results generalizable to the entire insomnia disorder population? We have seen, in these and other studies, that large effects can be obtained also in a sample with comorbidity with other psychiatric and somatic disorders. The percentage of men and women in our studies are similar to those found in prevalence studies. The education levels among our participants is, however, a little higher than among the Swedish population: 55% in our studies have attended higher education, compared to 40% in Sweden (Statistics Sweden, 2015). This does not necessarily mean that the treatment would be ineffective for a less educated sample, but it does indicate that our studies attract more highly

educated people. Only people who can read and write Swedish have been included, which excludes e.g. newly arrived immigrants and refugees, who may be in dire need of insomnia treatment.

Perhaps the biggest difference between the participants in our studies and the whole insomnia population, is that they actively sought Internet-based treatment (though many of our participants may have preferred other modes of delivery, had they been available). This means that generalizability to, for example, patients in primary care is limited. Since more than half of the patients in primary care are likely to suffer from insomnia (Bjorvatn, 2015), and will usually only get pharmacological treatment (SBU, 2010), this is an important group to treat, and we cannot be sure that ICBT-i will be suitable for them.

3.5 SUGGESTIONS FOR FUTURE RESEARCH

Several areas of interest for future research have emerged from the studies in this thesis:

- Can CBT-i prevent depression? This is a strong hypothesis, and attempts have been made at answering this question, but so far studies have been too few and too limited to draw any confident conclusions about prevention.
- Is ICBT-i a cost-effective treatment? We need to look at savings in societal costs, including health care expenses and work productivity losses, and compare this to costs of delivering treatment.
- Does the level of therapist support matter, and if it does, for whom? Our research group is doing an RCT looking at the effects of individualized extra support for patients at risk of not succeeding with the treatment. The results will further the knowledge in this area.
- Is a combination treatment, combining CBT-i and CBT-d, more effective than either treatment for patients with both insomnia and major depression? Our group is doing an RCT comparing a combination ICBT to regular depression treatment, hoping to contribute to this area.
- Is ICBT-i effective for patients in primary care with insomnia? We need to capture difficulties and possibilities in how to best help this large, comorbid patient group.
- Can blended treatment, i.e. a combination of ICBT-i and other forms of delivery such as individual-, group-, or telephone-delivered therapy, enhance outcomes for patients who do not benefit sufficiently from ICBT-i? The burdened group with comorbid depressions seems likely to require some kind of blended treatment.
- How can ICBT-d be improved? Study IV indicated that ICBT-d was more difficult to work with than ICBT-i. Perhaps we can learn from ICBT-i and improve ICBT-d accordingly. The Internet Psychiatry Clinic has recently made some changes to ICBT-d provided in regular care, and some of the changes are inspired by the findings in Study I and IV. This treatment has not been tried in an RCT, though its effectiveness is being monitored.

- Can sleep compression be a viable alternative to sleep restriction in terms of effects and adverse events? Sleep restriction is hard to execute and sleep compression is probably less aversive, but assumed to be less effective. Our research group is presently starting a study directly comparing the two interventions.
- What are the major mechanisms of change in CBT-i? CBT-i consists of many interventions. Dissemination studies have been done, but very little is known about the mechanisms of change. Acceptance is a candidate mechanism that emerged in Study IV, but more established theories about mechanisms of change also remain to be investigated experimentally.
- Can sleep medication combined with ICBT-i reduce the adverse effects that make employment of sleep restriction so hard? This should be tried for patients with comorbid insomnia and depression and focus on, besides effects on insomnia and depression, adverse events and side effects.

4 CONCLUSIONS

The overall aim of this project was to challenge the treatment paradigm for, and perception of comorbid insomnia and depression, and to strengthen the evidence for ICBT-i.

Study I, while being a fairly small study in terms of participants, was fruitful when it came to putting forward insomnia as a disorder that requires proper treatment. The evidence indicating that CBT-i is a powerful, though not quite sufficient, treatment of depression for patients with both diagnoses was strengthened. This study highlights the importance of providing evidence-based treatment for insomnia also when it is comorbid with other disorders, specifically with major depression.

We produced the first report of ICBT-i compared to face-to-face treatment, and the first long-term follow-up of a controlled Internet-based insomnia treatment longer than one year. Both these studies were sought-after missing pieces in the evidence puzzle of ICBT-i, and regarding the long-term follow-up, of CBT-i using any mode of delivery. Studies II and III do strengthen the evidence for ICBT-i and CBT-i, also for patients with comorbidities. The finding in Study IV, that ICBT-i was easier to work with, and a more positive experience than ICBT-d, speaks in favor of ICBT-i. It also indicates that there is probably room for improvement of the depression treatment.

Given the fact that CBT-i is virtually unavailable to insomniacs in Sweden and elsewhere, it seems to me that if we can provide treatment via the Internet to those who seek this, we will reach a large proportion of insomniacs. Hopefully, dissemination of ICBT-i will increase the pressure on public health organizations to start providing other types of CBT-i at a large scale, to those who prefer or require this.

5 ACKNOWLEDGEMENTS

6 REFERENCES

AMERICAN PSYCHIATRIC ASSOCIATION, A. 2000. DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. *In:* ASSOCIATION, A. P. (ed.).

AMERICAN PSYCHIATRIC ASSOCIATION, A. 2010. Practice Guideline for the Treatment of Patients With Major Depressive Disorder.

AMERICAN PSYCHIATRIC ASSOCIATION, A. 2013. *Diagnostic and statistical manual of mental disorders (DSM-5®)*, American Psychiatric Pub.

ANCOLI-ISRAEL, S. & ROTH, T. 1999. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. *Sleep,* 22**,** S347-53.

ANDERSSON, G., BERGSTRÖM, J., HOLLÄNDARE, F., CARLBRING, P., KALDO, V. & EKSELIUS, L. 2005. Internet-based self-help for depression: randomised controlled trial. *The British journal of psychiatry : the journal of mental science,* 187**,** 456-61.

ANDERSSON, G. & CUIJPERS, P. 2009. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cognitive behaviour therapy,* 38**,** 196-205.

ANDREWS, G., CUIJPERS, P., CRASKE, M. G., MCEVOY, P. & TITOV, N. 2010. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One,* 5**,** e13196.

ASHWORTH, D. K., SLETTEN, T. L., JUNGE, M., SIMPSON, K., CLARKE, D., CUNNINGTON, D. & RAJARATNAM, S. M. 2015. A randomized controlled trial of cognitive behavioral therapy for insomnia: an effective treatment for comorbid insomnia and depression. *J Couns Psychol,* 62**,** 115-23.

BAGLIONI, C., BATTAGLIESE, G., FEIGE, B., SPIEGELHALDER, K., NISSEN, C., VODERHOLZER, U., LOMBARDO, C. & RIEMANN, D. 2011. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of affective disorders,* 135**,** 10-9.

BASTIEN, C. H., VALLIERES, A. & MORIN, C. M. 2001. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine,* 2**,** 297-307.

BJORVATN, B. M., E; FLO, E; MILDESTVEDT, T 2015. High prevalence of insomnia, self-reported sleep problems, and hypnotic use in patients visiting their general practitioner. *Nordic Sleep Conference.* Göteborg, Sweden.

BLAZER, D. G., KESSLER, R. C. & MCGONAGLE, K. A. 1994. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Age (years),* 15**,** 24-7.

BRESLAU, N., ROTH, T., ROSENTHAL, L. & ANDRESKI, P. 1996. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry,* 39**,** 411-8.

BUTLER, A. C., CHAPMAN, J. E., FORMAN, E. M. & BECK, A. T. 2006. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clinical psychology review,* 26**,** 17-31.

CARNEY, C. E., SEGAL, Z. V., EDINGER, J. D. & KRYSTAL, A. D. 2007. A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *The Journal of clinical psychiatry,* 68**,** 254-60.

CHEN, P. Y., YANG, C. M. & MORIN, C. M. 2015. Validating the cross-cultural factor structure and invariance property of the Insomnia Severity Index: evidence based on ordinal EFA and CFA. *Sleep Med,* 16**,** 598-603.

CHENG, S. K. & DIZON, J. 2012. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. *Psychother Psychosom,* 81**,** 206-16.

CHRISTENSEN, H., BATTERHAM, P. J., GOSLING, J. A., RITTERBAND, L. M., GRIFFITHS, K. M., THORNDIKE, F. P., GLOZIER, N., O'DEA, B., HICKIE, I. B. & MACKINNON, A. J. 2016. Effectiveness of an online insomnia program (SHUTi) for prevention of depressive episodes (the GoodNight Study): a randomised controlled trial. *The Lancet Psychiatry,* 3**,** 333-341.

CLARKE, G., REID, E., EUBANKS, D., O'CONNOR, E., DEBAR, L. L., KELLEHER, C., LYNCH, F. & NUNLEY, S. 2002. Overcoming depression on the Internet (ODIN): a randomized controlled trial of an Internet depression skills intervention program. *Journal of medical Internet research,* 4**,** e14.

CUIJPERS, P. 1997. Bibliotherapy in unipolar depression: a meta-analysis. *Journal of behavior therapy and experimental psychiatry,* 28**,** 139-147.

CUIJPERS, P., ANDERSSON, G., DONKER, T. & VAN STRATEN, A. 2011. Psychological treatment of depression: results of a series of meta-analyses. *Nord J Psychiatry,* 65**,** 354-64.

CUIJPERS, P., BERKING, M., ANDERSSON, G., QUIGLEY, L., KLEIBOER, A. & DOBSON, K. S. 2013a. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Canadian Journal of Psychiatry,* 58**,** 376.

CUIJPERS, P., HOLLON, S. D., VAN STRATEN, A., BOCKTING, C., BERKING, M. & ANDERSSON, G. 2013b. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ open,* 3**,** e002542.

DALEY, M., MORIN, C. M., LEBLANC, M., GREGOIRE, J. P. & SAVARD, J. 2009. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep,* 32**,** 55-64.

DOMBROVSKI, A. Y., CYRANOWSKI, J. M., MULSANT, B. H., HOUCK, P. R., BUYSSE, D. J., ANDREESCU, C., THASE, M. E., MALLINGER, A. G. & FRANK, E. 2008. Which symptoms predict recurrence of depression in women treated with maintenance interpersonal psychotherapy? *Depression and anxiety,* 25**,** 1060-1066.

EATON, W. W., BADAWI, M. & MELTON, B. 1995. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. *The American journal of psychiatry,* 152**,** 967.

EDINGER, J. D. 2015. The brave new world of healthcare delivery: just where are we in our understanding of e-health methods for insomnia and depression management? *Sleep,* 38**,** 177-178.

EDINGER, J. D., BONNET, M. H., BOOTZIN, R. R., DOGHRAMJI, K., DORSEY, C. M., ESPIE, C. A., JAMIESON, A. O., MCCALL, W. V., MORIN, C. M. & STEPANSKI, E. J. 2004. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep,* 27**,** 1567-96.

EDINGER, J. D., WOHLGEMUTH, W. K., RADTKE, R. A., MARSH, G. R. & QUILLIAN, R. E. 2001. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA : the journal of the American Medical Association,* 285**,** 1856-64.

ELLIS, J. G., PERLIS, M. L., BASTIEN, C. H., GARDANI, M. & ESPIE, C. A. 2014. The natural history of insomnia: acute insomnia and first-onset depression. *Sleep,* 37**,** 97.

ESPIE, C. A., KYLE, S. D., WILLIAMS, C., ONG, J. C., DOUGLAS, N. J., HAMES, P. & BROWN, J. S. 2012. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep,* 35**,** 769-81.

FAVA, M., MCCALL, W. V., KRYSTAL, A., WESSEL, T., RUBENS, R., CARON, J., AMATO, D. & ROTH, T. 2006. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biological Psychiatry,* 59**,** 1052-1060.

FIRST, M. B., GIBBON, M., SPITZER, R. I., WILLIAMS, J. B. W. & BENJAMIN, L. S. 1999. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Swedish version)*, Pilgrim Press: Danderyd.

FORD, D. E. & KAMEROW, D. B. 1989. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA : the journal of the American Medical Association,* 262**,** 1479-84.

FÖRSÄKRINGSKASSAN 2011. Vad kostar sjukförsäkringen? Socialförsäkringsrapport 2011:4.

HAURI, P., CHERNIK, D., HAWKINS, D. & MENDELS, J. 1974. Sleep of depressed patients in remission. *Archives of General Psychiatry,* 31**,** 386.

HEDMAN, E., LJÓTSSON, B., BLOM, K., EL ALAOUI, S., KRAEPELIEN, M., RÜCK, C., ANDERSSON, G., SVANBORG, C., LINDEFORS, N. & KALDO, V. 2013a. Telephone versus internet administration of self-report measures of social anxiety, depressive symptoms, and insomnia: psychometric evaluation of a method to reduce the impact of missing data. *Journal of medical Internet research,* 15**,** e229.

HEDMAN, E., LJÓTSSON, B., KALDO, V., HESSER, H., EL ALAOUI, S., KRAEPELIEN, M., ANDERSSON, E., RÜCK, C., SVANBORG, C., ANDERSSON, G. & LINDEFORS, N. 2013b. Effectiveness of Internet-based cognitive behaviour therapy for depression in routine psychiatric care. *Journal of affective disorders*.

HEDMAN, E., LJÓTSSON, B. & LINDEFORS, N. 2012. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness. *Expert Rev Pharmacoecon Outcomes Res,* 12**,** 745-64.

HO, F. Y.-Y., CHUNG, K.-F., YEUNG, W.-F., NG, T. H.-Y. & CHENG, S. K.-W. 2014. Weekly brief phone support in self-help cognitive behavioral therapy for insomnia disorder: Relevance to adherence and efficacy. *Behaviour research and therapy,* 63**,** 147-156.

HO, F. Y., CHUNG, K. F., YEUNG, W. F., NG, T. H., KWAN, K. S., YUNG, K. P. & CHENG, S. K. 2015. Self-help cognitive-behavioral therapy for insomnia: a meta-analysis of randomized controlled trials. *Sleep Med Rev,* 19**,** 17-28.

HOHAGEN, F., KÄPPLER, C., SCHRAMM, E., RINK, K., WEYERER, S., RIEMANN, D. & BERGER, M. 1994. Prevalence of insomnia in elderly general practice attenders and the current treatment modalities. *Acta Psychiatrica Scandinavica,* 90**,** 102-108.

JERNELÖV, S., LEKANDER, M., BLOM, K., RYDH, S., LJÓTSSON, B., AXELSSON, J. & KALDO, V. 2012. Efficacy of a behavioral self-help treatment with or without therapist guidance for co-morbid and primary insomnia--a randomized controlled trial. *BMC psychiatry,* 12**,** 5.

JERNELÖV, S. 2007. *Sov gott! Råd och tekniker från KBT,* Stockholm, Wahlström & Widstrand.

KALDO, V., JERNELÖV, S., BLOM, K., LJÓTSSON, B., BRODIN, M., JÖRGENSEN, M., KRAEPELIEN, M., RÜCK, C. & LINDEFORS, N. 2015. Guided internet cognitive behavioral therapy for insomnia compared to a control treatment - A randomized trial. *Behav Res Ther,* 71**,** 90-100.

KENNEDY, G. J., KELMAN, H. R. & THOMAS, C. 1991. Persistence and remission of depressive symptoms in late life. *The American journal of psychiatry,* 148**,** 174.

KESSLER, R. C., BERGLUND, P., DEMLER, O., JIN, R., KORETZ, D., MERIKANGAS, K. R., RUSH, A. J., WALTERS, E. E. & WANG, P. S. 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Jama,* 289**,** 3095-3105.

KIM, K., UCHIYAMA, M., OKAWA, M., LIU, X. & OGIHARA, R. 2000. An epidemiological study of insomnia among the Japanese general population. *Sleep,* 23**,** 41-7.

KWAN, B. M., DIMIDJIAN, S. & RIZVI, S. L. 2010. Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behaviour research and therapy,* 48**,** 799-804.

KYLE, S. D., MILLER, C. B., ROGERS, Z., SIRIWARDENA, A. N., MACMAHON, K. M. & ESPIE, C. A. 2014. Sleep restriction therapy for insomnia is associated with reduced objective total sleep time, increased daytime somnolence, and objectively impaired vigilance: implications for the clinical management of insomnia disorder. *Sleep,* 37**,** 229-37.

LANCEE, J., SORBI, M. J., EISMA, M. C., VAN STRATEN, A. & VAN DEN BOUT, J. 2014. The effect of support on internet-delivered treatment for insomnia: does baseline depression severity matter? *Behavior therapy,* 45**,** 507-516.

LANCEE, J., VAN DEN BOUT, J., VAN STRATEN, A. & SPOORMAKER, V. I. 2012. Internet-delivered or mailed self-help treatment for insomnia?: a randomized waiting-list controlled trial. *Behav Res Ther,* 50**,** 22-9.

LANCEE, J., VAN DEN BOUT, J., VAN STRATEN, A. & SPOORMAKER, V. I. 2013. Baseline depression levels do not affect efficacy of cognitive-behavioral self-help treatment for insomnia. *Depression and anxiety,* 30**,** 149-56.

LANCEE, J., VAN STRATEN, A., MORINA, N., KALDO, V. & KAMPHUIS, J. H. 2015. Guided Online or Face-to-Face Cognitive Behavioral Treatment for Insomnia? A Randomized Wait-list Controlled Trial. *Sleep*.

LARSSON, B. P., KALDO, V. & BROBERG, A. G. 2010. Theoretical orientation and therapists' attitudes to important components of therapy: a study based on the valuable elements in psychotherapy questionnaire. *Cogn Behav Ther,* 39**,** 161-72.

LEGER, D., SCHEUERMAIER, K., PHILIP, P., PAILLARD, M. & GUILLEMINAULT, C. 2001. SF-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. *Psychosomatic medicine,* 63**,** 49-55.

LIVINGSTON, G., BLIZARD, B. & MANN, A. 1993. Does sleep disturbance predict depression in elderly people? A study in inner London. *Br J Gen Pract,* 43**,** 445-448.

LUND, H. G., RYBARCZYK, B. D., PERRIN, P. B., LESZCZYSZYN, D. & STEPANSKI, E. 2013. The discrepancy between subjective and objective measures of sleep in older adults receiving CBT for comorbid insomnia. *Journal of clinical psychology,* 69**,** 1108-1120.

MALLON, L., BROMAN, J.-E. & HETTA, J. 2000. Relationship between insomnia, depression, and mortality: a 12-year follow-up of older adults in the community. *International Psychogeriatrics,* 12**,** 295-306.

MANBER, R., EDINGER, J. D., GRESS, J. L., SAN PEDRO-SALCEDO, M. G., KUO, T. F. & KALISTA, T. 2008. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep,* 31**,** 489-95.

MCHUGH, R. K., WHITTON, S. W., PECKHAM, A. D., WELGE, J. A. & OTTO, M. W. 2013. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *The Journal of clinical psychiatry,* 74**,** 1,478-602.

MELLINGER, G. D., BALTER, M. B. & UHLENHUTH, E. H. 1985. Insomnia and its treatment. Prevalence and correlates. *Arch Gen Psychiatry,* 42**,** 225-32.

MIMEAULT, V. & MORIN, C. M. 1999. Self-help treatment for insomnia: bibliotherapy with and without professional guidance. *Journal of Consulting and Clinical Psychology,* 67**,** 511.

MITCHELL, M. D., GEHRMAN, P., PERLIS, M. & UMSCHEID, C. A. 2012. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract,* 13**,** 40.

MONTGOMERY, S. A. & ÅSBERG, M. 1979. A new depression scale designed to be sensitive to change. *The British journal of psychiatry : the journal of mental science,* 134**,** 382-9.

MORIN, C. M. 1993. *Insomnia: Psychological Assessment and Management,* Guilford Press.

MORIN, C. M., BOOTZIN, R. R., BUYSSE, D. J., EDINGER, J. D., ESPIE, C. A. & LICHSTEIN, K. L. 2006a. Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). *Sleep,* 29**,** 1398-414.

MORIN, C. M., COLECCHI, C., STONE, J., SOOD, R. & BRINK, D. 1999. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA,* 281**,** 991-9.

MORIN, C. M. & ESPIE, C. A. 2003. *Insomnia: A clinician's guide to assessment and treatment,* Springer.

MORIN, C. M. & GRAMLING, S. E. 1989. Sleep patterns and aging: comparison of older adults with and without insomnia complaints. *Psychology and aging,* 4**,** 290-4.

MORIN, C. M., LEBLANC, M., DALEY, M., GREGOIRE, J. & MERETTE, C. 2006b. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep medicine,* 7**,** 123-130.

MORIN, C. M., VALLIERES, A., GUAY, B., IVERS, H., SAVARD, J., MERETTE, C., BASTIEN, C. & BAILLARGEON, L. 2009. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA,* 301**,** 2005-15.

NECKELMANN, D., MYKLETUN, A. & DAHL, A. A. 2007. Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep,* 30**,** 873-80.

NORELL-CLARKE, A., JANSSON-FRÖJMARK, M., TILLFORS, M., HOLLÄNDARE, F. & ENGSTRÖM, I. 2015. Group cognitive behavioural therapy for insomnia: Effects on sleep and depressive symptomatology in a sample with comorbidity. *Behaviour research and therapy,* 74**,** 80-93.

OHAYON, M. M. & BADER, G. 2010. Prevalence and correlates of insomnia in the Swedish population aged 19–75 years. *Sleep medicine,* 11**,** 980-986.

OHAYON, M. M. & REYNOLDS, C. F. 2009. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). *Sleep medicine,* 10**,** 952-960.

OKAJIMA, I., KOMADA, Y. & INOUE, Y. 2014. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep and biological rythms,* 9**,** 24-34.

PERLIS, M. L., GILES, D. E., BUYSSE, D. J., TU, X. & KUPFER, D. J. 1997. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *Journal of affective disorders,* 42**,** 209-12.

PIGEON, W. R., HEGEL, M., UNUTZER, J., FAN, M. Y., SATEIA, M. J., LYNESS, J. M., PHILLIPS, C. & PERLIS, M. L. 2008. Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort? *Sleep,* 31**,** 481-8.

REYNOLDS, C. R., FRANK, E., HOUCK, P. R., MAZUMDAR, S., DEW, M. A., CORNES, C., BUYSSE, D. J., BEGLEY, A. & KUPFER, D. J. 1997. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *American Journal of Psychiatry,* 154**,** 958-962.

RIEMANN, D. & PERLIS, M. L. 2009. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep medicine reviews,* 13**,** 205-14.

RITTERBAND, L. M., BAILEY, E. T., THORNDIKE, F. P., LORD, H. R., FARRELL-CARNAHAN, L. & BAUM, L. D. 2012. Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psycho-Oncology,* 21**,** 695-705.

RITTERBAND, L. M., THORNDIKE, F. P., GONDER-FREDERICK, L. A., MAGEE, J. C., BAILEY, E. T., SAYLOR, D. K. & MORIN, C. M. 2009. Efficacy of an Internet-based behavioral intervention for adults with insomnia. *Archives of general psychiatry,* 66**,** 692-8.

RORSMAN, B., GR, A., HAGNELL, O., LANKE, J., OHMAN, R., OJESJ, L. & OTTERBECK, L. 1990. A prospective study of first-incidence depression. The Lundby study, 1957-72. *The British Journal of Psychiatry,* 156**,** 336-342.

ROZENTAL, A., ANDERSSON, G., BOETTCHER, J., EBERT, D. D., CUIJPERS, P., KNAEVELSRUD, C., LJÓTSSON, B., KALDO, V., TITOV, N. & CARLBRING, P. 2014. Consensus statement on defining and measuring negative effects of Internet interventions. *Internet Interventions,* 1**,** 12-19.

SBU 2010. Behandling av sömnbesvär hos vuxna. En systematisk litteraturöversikt. Stockholm: Statens beredning för medicinsk utvärdering.

SHEEHAN, D. V., LECRUBIER, Y., SHEEHAN, K. H., AMORIM, P., JANAVS, J., WEILLER, E., HERGUETA, T., BAKER, R. & DUNBAR, G. C. 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry,* 59 Suppl 20**,** 22-33;quiz 34-57.

SOCIALSTYRELSEN 2009. Vård av patienter med depression och ångest - en nulägesrapport.

SOCIALSTYRELSEN 2010. Nationella riktlinjer för vård vid depression och ångestsyndrom 2010 – stöd för styrning och ledning.

SPEK, V., CUIJPERS, P., NYKLICEK, I., RIPER, H., KEYZER, J. & POP, V. 2007. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. *Psychological medicine,* 37**,** 319-28.

STATISTICS SWEDEN, S. 2015. Yearbook of Educational Statistics.

STRÖM, L., PETTERSSON, R. & ANDERSSON, G. 2004. Internet-based treatment for insomnia: a controlled evaluation. *J Consult Clin Psychol,* 72**,** 113-20.

SUZUKI, E., TSUCHIYA, M., HIROKAWA, K., TANIGUCHI, T., MITSUHASHI, T. & KAWAKAMI, N. 2008. Evaluation of an internet-based self-help program for better quality of sleep among Japanese workers: a randomized controlled trial. *Journal of occupational health,* 50**,** 387-399.

SVANBORG, P. & ÅSBERG, M. 1994. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta psychiatrica Scandinavica,* 89**,** 21-8.

SWIFT, J. K. & CALLAHAN, J. L. 2009. The impact of client treatment preferences on outcome: A meta-analysis. *Journal of clinical psychology,* 65**,** 368-381.

THASE, M. E. 1999. Antidepressant treatment of the depressed patient with insomnia. *The Journal of clinical psychiatry,* 60**,** 1,478-31.

THIART, H., LEHR, D., EBERT, D. D., BERKING, M. & RIPER, H. 2015. Log in and breathe out: internet-based recovery training for sleepless employees with work-related strain-results of a randomized controlled trial. *Scand J Work Environ Health,* 41**,** 164-74.

THORNDIKE, F. P., RITTERBAND, L. M., SAYLOR, D. K., MAGEE, J. C., GONDER-FREDERICK, L. A. & MORIN, C. M. 2011. Validation of the insomnia severity index as a web-based measure. *Behavioral sleep medicine,* 9**,** 216-23.

TONER, L. C., TSAMBIRAS, B. M., CATALANO, G., CATALANO, M. C. & COOPER, D. S. 2000. Central nervous system side effects associated with zolpidem treatment. *Clin Neuropharmacol,* 23**,** 54-8.

WALSH, J. K. 2004. Clinical and socioeconomic correlates of insomnia. *J Clin Psychiatry,* 65 Suppl 8**,** 13-9.

VAN STRATEN, A., EMMELKAMP, J., DE WIT, J., LANCEE, J., ANDERSSON, G., VAN SOMEREN, E. J. & CUIJPERS, P. 2013. Guided Internet-delivered cognitive behavioural treatment for insomnia: a randomized trial. *Psychological medicine***,** 1-12.

WEISSMAN, M. M., GREENWALD, S., NIÑO-MURCIA, G. & DEMENT, W. C. 1997. The morbidity of insomnia uncomplicated by psychiatric disorders. *General hospital psychiatry,* 19**,** 245-250.

VINCENT, N. & LIONBERG, C. 2001. Treatment preference and patient satisfaction in chronic insomnia. *Sleep: Journal of Sleep and Sleep Disorders Research.*

ZACHARIAE, R., LYBY, M. S., RITTERBAND, L. M. & O'TOOLE, M. S. 2016. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia–A systematic review and meta-analysis of randomized controlled trials. *Sleep medicine reviews,* 30**,** 1-10.