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ADOLESCENT SLEEP: COMORBID PROBLEMS AND BEHAVIORAL TREATMENT OF INSOMNIA

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Adolescent sleep: comorbid problems and behavioral treatment of insomnia

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SAMMANFATTNING

Bakgrund

Sömnproblem, särskilt insomni, är vanligt hos ungdomar och ofta förknippat med andra problem, såsom ångest, depression och kronisk smärta. Trots att det finns effektiva psykologiska behanlingar för vuxna med insomni så saknas vetenskapligt underlag för ungdomar. Kognitiv beteendeterapi för insomni (KBT-I) skulle kunna vara en genomförbart och effektivt sätt att behandla insomni hos ungdomar och även kunna påverka samsjukliga tillstånd.

Syfte och metod

Huvudsyftet med denna avhandling var att utveckla och utvärdera effekten av KBT-I för ungdomar och att studera samband mellan insomni och samsjukliga problem. Effekten av kognitiva- och beteendeinterventioner utvärderades genom en systematisk genomgång och meta-analys av befintliga behandlingsstudier inom området. Efter utveckling av ett behandlingsprotokoll utvärderades genomförbarhet (bl.a. antalet avhopp och patientnöjdhet) och preliminär effektivitet (förändring av insomnisymptom, sömn och samsjukliga problem) av behandlingen i en svensk kontext i två format och två kliniska miljöer; dels som face-to-face behandling inom den öppna specialistvården (barn- och ungdomspsykiatri samt smärtbehandling), dels som internetförmedlad behandling inom en digital specialenhet. Relationen mellan sömnproblem och andra problem undersöktes genom en tvärsnittsstudie.

Resultat

Resultatet av meta-analysen visade att kognitiva och beteendeinriktade interventioner är effektiva för behandling av insomni hos ungdomar. De två pilotstudierna visade att KBT-I är genomförbar inom svensk sjukvård, både som face-to-face behandling och som internetförmedlad behandling. Den stora majoriteten deltagare avslutade behandlingen och rapporterade nöjdhet. Deltagarna rapporterade minskade insomnisymptom och förbättrad sömn, samt minskade samsjukliga tillstånd. Gällande relationen mellan sömn, andra problem och funktionsnivå rapporterade ungdomar med sömnproblem i högre grad symptom på exekutiva svårigheter, inåtvänd emotionell problematik samt skol- och sömnrelaterad ångest och funktionsnedsättning än sina jämnåriga.

Slutsats

KBT-I för ungdomar är en genomförbar behandling i svensk sjukvård, både i reguljär vård och som internetbehandling och visar på goda preliminära effekter för insomnisymptom, sömn och samsjukliga tillstånd. Resultaten är lovande och bör följas upp i större randomiserade kontrollerade studier som förhoppningsvis kan ligga till grund för utvecklingen av riktlinjer för effektiv behandling av sömnproblem hos ungdomar.

ABSTRACT

Background

Sleep problems, especially insomnia, are common in adolescents and are often associated with other problems, such as anxiety, depression and chronic pain. Even though there are effective psychological treatments for adults with insomnia, the scientific basis for adolescents is weak. Cognitive behavioral therapy for insomnia (CBT-I) could be a feasible and efficient way to treat insomnia in adolescents and could also affect comorbid conditions.

Aims and methods

The main aim of this thesis was to evaluate the effect of CBT-I in adolescents, the feasibility and preliminary efficacy of the intervention and to investigate the relationship between disturbed sleep and co-morbid conditions. The effect of cognitive and behavioral interventions was evaluated through a systematic review and meta-analysis of existing treatment studies. Feasibility and preliminary efficacy of CBT-I in a Swedish context were evaluated in two different formats and two clinical environments; as a face-to-face treatment in specialist care (child- and adolescent psychiatry and a pain clinic) and as an internet-delivered treatment within a digital special unit. Specifically, feasibility (treatment retention and patient satisfaction), change in insomnia symptoms, sleep and comorbid symptoms following treatment were evaluated. The relationship between disturbed sleep and other problems was investigated through a cross-sectional study in which young people were asked to answer questions about sleep, mood and daytime function.

Results

Results showed that CBT-I was an effective treatment and that it was feasible in the context of Swedish healthcare, both as a face-to-face and internet-delivered intervention. The vast majority of participants completed the treatments and reported overall satisfaction. Participants in both treatment formats reported decreased insomnia symptoms and improved sleep, as well as decreased comorbid symptoms. Regarding the relationship between sleep and other problems and functions, the results showed that young people with disordered sleep to a greater extent reported impaired executive functioning, internal emotional distress and sleep- and school related worry and dysfunction.

Conclusion

CBT-I for adolescents is a feasible treatment, both in regular care and as internet-delivered treatment program in Swedish healthcare and shows good preliminary effects for insomnia symptoms, sleep and co-morbid conditions. Disturbed sleep is associated with lower executive functioning, internal emotional distress and worry and dysfunction related to school and sleep. These results are promising, but controlled studies with rigorous study designs are needed to confirm the findings.

LIST OF SCIENTIFIC PAPERS

I. Åslund, L., Arnberg, F., Kanstrup, M., Lekander, M. (2018). Cognitive and Behavioral Interventions to Improve Sleep in School-Age Children and Adolescents: A Systematic Review and Meta-Analysis. *Journal of Clinical Sleep Medicine*, 14(11), 1937-1947.

II. Åslund, L., Lekander, M., Wicksell, R., Henje, E., Jernelöv,S. (2020). Cognitive-behavioral therapy for insomnia in adolescents with comorbid psychiatric disorders: a clinical pilot study. *Clinical Child Psychology and Psychiatry*. 25(4), 958-971.

III. Åslund, L., Järnelöv, S., Henje, E., Wicksell, R., Vigerland, S., Serlachius, E., Lekander, M. *Internet-delivered cognitive-behavioral therapy for adolescent insomnia: feasibility and preliminary efficacy*. Unpublished manuscript.

IV. Åslund, L., Andreasson, A., Lekander, M., Henje, E., Dennhag, I. *Disturbed sleep and patterns of psychiatric symptoms and function in a school-based sample of adolescents*. Unpublished manuscript.

CONTENTS

LIST OF ABBREVIATIONS

Bip	“Barninternetprojektet” (The child internet project)
CAMHS	Child and adolescent mental health services
CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
DSPD	Delayed Sleep Phase Disorder
EEG	Electroencephalography
ICBT	Internet-delivered cognitive behavioral therapy
ICBT-I	Internet-delivered cognitive behavioral therapy for insomnia
MDD	Major Depressive Disorder
PROMIS	Patient reported outcome measurement information system
RCT	Randomized controlled trial
REM	Rapid eye movement
SWD	Sleep wake diary

1 INTRODUCTION

Sleep problems are common in adolescence [1] and associated with increased psychiatric symptoms and dysfunctions [2]. Access to evidence-based treatment for insomnia disorder in adolescence is limited, even though cognitive behavior therapy for insomnia (CBT-I) is effective in adults [3-6], with positive effects not only on insomnia symptoms and sleep parameters but also on comorbid psychiatric disorders [7].

As a clinical psychologist, working in child- and adolescent psychiatry, my colleagues and I noted that many of the adolescents in treatment for depression and anxiety disorders also suffered from insomnia disorder. However, the sleep problem was rarely treated using psychological interventions and treatment guidelines were missing. Instead, sleep problems were approached with a range of pharmacological therapies, or just left untreated. It also seemed as if adolescents with comorbid insomnia presented more severe psychiatric symptoms, and that the sleep deprivation affected their possibilities for successful treatment. I therefore started a journey with the goal to develop and evaluate a CBT-I manual in order to meet these needs.

The present thesis thus aims to answer some of the questions regarding the use of CBT-I, the recommended treatment for adult insomnia, in adolescents. First, we aimed to investigate the current evidence base for CBT-I in older children and adolescents. Following this, a treatment program for adolescent CBT-I was developed and evaluated in two Swedish clinical settings and in two modalities: as a face-to-face intervention and an internet-delivered program. We wanted to evaluate the feasibility of the intervention, as well as preliminary efficacy of sleep and insomnia. Furthermore, we were interested in possible transfer effects on other symptoms, even though these were not specifically addressed in treatment. Finally, to deepen the understanding of how sleep and other problems coexist, the relationship between disturbed sleep and specific symptoms and dysfunctions was evaluated. We believe that this knowledge will be of use when developing the future treatment programs for adolescent insomnia.

2 BACKGROUND

2.1 DEVELOPMENTAL PERSPECTIVES ON SLEEP

Sleep patterns change as a normal part of development. Going from childhood to adolescence, a decline in slow wave sleep occurs that seems related to a decline in synaptic density[8]. REM (rapid eye movement) sleep increase during this period, but decrease moving forward into adulthood [9]. Total sleep time decrease from childhood to adolescence, a change which may partly be related to environmental factors rather than maturation as only noticeable in recordings on school days [9].

2.2 SLEEP DISORDERS IN ADOLESCENCE

2.2.1 Insomnia disorder: diagnostic features and prevalence

Insomnia is the most common of the so called sleep-wake disorders [10]. It is characterized by difficulties initiating and/or maintaining sleep with associated loss in daytime function. Insomnia is defined in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) as difficulties falling asleep, staying asleep, and/or suffering from early awakenings for at least three nights/week over at least three months with associated clinically significant loss of function [11]. Insomnia is diagnosed using subjective criteria, i.e. patient-reported complaints about both sleep and related daytime symptoms such as fatigue, mood disturbances or inattention. Regarding disordered sleep in adolescence, the prevalence of individuals who fulfil criteria for insomnia disorder is about 10%, and “at least some” insomnia symptoms are reported by more than 33% [1].

2.2.2 Other sleep disorders in adolescence

Apart from insomnia disorder, the risk of developing delayed sleep phase disorder (DSPD) increase in adolescence [12]. DSPD is defined as normal sleep with delayed timing, leading to daytime sleepiness and loss of function [11], with negative consequences for psychiatric health and school performance [13].

2.3 CONSEQUENCES OF DISRUPTED SLEEP ON COMORBID PROBLEMS

Sleep loss affects cognitive and affective functioning. In adolescence, risk behaviors (e.g., violent and criminal activity, suicidality) are associated with late bedtimes [14] and when disturbed sleep results in sleepiness, there is an association with impaired executive functions [15] and an increase in irritability, inattention, and lack of motivation [16]. Lack of sleep has a negative impact on emotional reactivity and control over emotional behaviour [17].

Among psychiatric disorders in childhood, the most common ones occurring together with insomnia are anxiety disorders and major depression disorder (MDD) [18]. In school-aged

children and adolescents, almost 80% of females and 70% of males with MDD report symptoms of disordered sleep [2]. During this period (late childhood to early adolescence), the risk of developing anxiety and sleep problems is elevated [19], with 90% of children with anxiety disorders also reporting sleep related problems [20]. In adolescence, more than half of individuals diagnosed with insomnia disorder also fulfil criteria for a comorbid psychiatric disorder [21]. In adolescent patients with chronic pain, one study reported that 60% suffer from sleep disorders that affect daytime functioning [22].

2.4 ASSESSMENT OF SLEEP AND INSOMNIA SYMPTOMS

Insomnia disorder is diagnosed using subjective indicators of sleep quality [11] and the individual's perception of the problem are considered important for diagnoses [23]. However, objective measures of sleep (e.g., actigraphy or electroencephalography (EEG)) are desirable as a complement to subjective measures [24] as they do not completely overlap [25]. Daytime sleepiness is a sensitive indicator of insufficient sleep (as measured by EEG) [26] and could provide complementary information on sleep quality. Several subjective and objective sleep parameters are relevant for the understanding of an individual's sleep quality [24, 25], e.g., sleep efficiency (quota of time sleeping/time spent in bed), sleep onset latency (duration from bedtime until the onset of sleep), wake after sleep onset (frequency and/or duration of nightly awakenings) and total sleep time (duration of sleep). The key indicators of good sleep quality in adults, and adolescents are proposed to be similar (sleep efficiency >85%, sleep onset latency<30 min, wake after sleep onset<20 min and night awakenings<2) [27]. However, what could indicate poor sleep quality differs slightly between age groups. In adolescents, wake after sleep onset>50 min and ≥ 3 night awakenings indicate poor sleep quality, as compared to wake after sleep onset>40min and night awakenings≥4 in adults [27]. It is thus important to consider these differences when assessing clinically meaningful change in the evaluation of treatment effects. Regarding subjective measures of sleep, *sleep wake diaries* (SWD) are frequently used in both adults and adolescents and is considered gold standard in subjective sleep assessment [28]. Participants answer a number of questions in the morning regarding their sleep the previous night and data on sleep onset latency, wake after sleep onset, total sleep time and sleep efficiency can be calculated. This can be used to evaluate treatment effects in research, but also as part of cognitive behavioral therapy for insomnia, in which sleep times are calculated and adjusted for participants' each week. In adolescence, at least five weekday nights of sleep entry are recommended to study sleep patterns [29]. *Questionnaires* can also be used to collect subjective sleep data, where quality and pattern of sleep is assessed in different domains (e.g., sleep onset latency and total sleep time). Regarding objective measures of sleep parameters, *actigraphy*, a wrist-based instrument that measures movement, is a well-used tool to measure objective sleep in all ages [30, 31]. *Polysomnography,* i.e., the registration of an individual's brain activity, eye movements and tonus, is more accurate than actigraphy due to the different typ of data used together to determine whether a person is asleep or awake. To date, no randomized controlled

trial on the effect of adolescent CBT-I has used polysomnography, perhaps due to a combination of cost and feasibility issues. *Insomnia symptoms* are often measured with questionnaires, designed to capture symptoms of disturbed sleep but also daytime fatigue and psychological distress regarding symptoms.

2.5 TREATING INSOMNIA DISORDER

2.5.1 Cognitive behavioral therapy

Cognitive behavioural therapy for insomnia refers to using a standardized protocol that aims to improve the participants' sleep by targeting both cognitive and behavioral components of the disorder [32]. CBT-I techniques for both adults and adolescents include the promotion of behavioral change through the use of sleep restriction and stimulus control [33] as well as cognitive techniques and relaxation. The intervention can be of different length but the minimum number of sessions found most effective in adult CBT-I is four [34]. The intervention can be delivered in multiple forms such as face-to-face individual meetings or in small groups, via an Internet platform, through a self-help book or as a school-based sleep education programs for children and/or adolescents.

CBT-I is recommended as first-line treatment for chronic insomnia in adults [35] and several meta-analyses show positive effects of CBT-I on sleep parameters [3-6], irrespective of the mode of delivery [36-38]. Research on e.g., group CBT-I has shown moderate to large effect sizes for several sleep parameters with positive effects retained over time [3]. Although CBT-I targets sleep, transfer effects on co-morbid anxiety and depression have been shown [7]. Results from a study on adults with insomnia and co-current depression indicates that CBT-I improves symptoms of both insomnia and depression, but that the opposite is not necessarily true [39].

In adolescents, robust information on the effects of cognitive and behavioral sleep interventions for insomnia is lacking. A systematic review and meta-analysis on pediatric insomnia showed small to large effect sizes for sleep onset latency, wake after sleep onset and sleep efficiency [40]. However, the evidence for adolescents were weak due to a lack of studies. A meta-analyses on within-group differences of CBT-I for adolescents found statistically significant effects on total sleep time, sleep onset latency and wake after sleep onset at post-treatment as well as on daytime sleepiness and comorbid anxiety [41]. However, due to a lack of randomized controlled trials, between-group effects were not estimated.

Internet-delivered CBT for insomnia (ICBT-I) is founded on the same principles as face-to-face CBT, but is offered through an online platform. Positive effects of adult ICBT-I are seen on sleep parameters [42], insomnia symptoms and comorbid anxiety [43]. In adolescents, studies are scarce, but between-group effects have been noted on sleep parameters, both in objective and subjective measures [44]. Studies on ICBT for children with other disorders than insomnia (e.g., chronic pain and anxiety disorders) have shown good efficacy and

acceptability [45], further emphasizing the benefit of establishing evidence based treatments for adolescent insomnia in an online format.

2.5.2 Pharmacological interventions

In adults, a pharmacological intervention (e.g., benzodiazepines, antidepressants) can be offered for short-term treatment (≤4 weeks) if CBT-I is not effective enough or not available [35]. In adolescence, controlled studies on the of pharmacological interventions (e.g., benzodiazepines) for insomnia disorder [46] are scarce. Some studies on the use of melatonin have shown improved sleep quality in children with co-morbid disorders [47] and problems associated with DSPD in adolescents [48]. However, the effectiveness and potential side effects of melatonin in adolescents have to be evaluated in future randomized controlled trials.

3 OBJECTIVE AND RESEARCH QUESTIONS

3.1 OVERALL OBJECTIVE

The overall objective of this thesis was to examine the feasibility and effects of CBT-I in adolescents. This includes the examination of existing empirical support, as well as an investigation of the feasibility and preliminary efficacy of a novel intervention provided in a Swedish context, both delivered face-to-face and via Internet. In addition, the relation between disturbed sleep and patterns of comorbid symptoms and functioning was examined.

3.2 SPECIFIC RESEARCH QUESTIONS

This encompasses four specific research questions, which are presented below:

3.2.1 Does CBT-I lead to better sleep and less insomnia symptoms?

In Study I, the effects on cognitive- and behavioral interventions on insomnia among school children and adolescents were examined through a systematic review and meta-analysis of published studies. In study II and III, efficacy of CBT-I was examined in two pilot studies. It was hypothesized that CBT-I would lead to improvements in sleep and insomnia symptom severity that would be larger for the intervention groups than for the control groups (between-group effects in Study I) and that sleep and insomnia symptoms would improve from pre- to post treatment (within-group effects in Study II and III).

3.2.2 Is CBT-I a feasible treatment in regular clinical setting delivered face-to-face or via Internet?

In study II and III, the feasibility of CBT-I was examined both in regular clinical care (Child and adolescent mental health services (CAMHS)) as a face-to-face treatment and as an internet-delivered intervention in a specialized digital care unit. It was hypothesized that both CBT-I and ICBT-I would be feasible treatments.

3.2.3 Does CBT-I lead to less comorbid symptoms?

In study I, the effect of CBT-I on daytime sleepiness was evaluated. In study II and III, the preliminary efficacy of CBT-I on comorbid symptoms (psychiatric symptoms, pain and functional ability) was examined. It was hypothesized that CBT-I would lead to improvements in all comorbid symptoms and functioning following treatment.

3.2.4 What are the relations between disturbed sleep and comorbid symptoms?

In study IV, the relation between disturbed sleep and comorbid symptoms (psychiatric symptoms, pain) and functional ability were assessed. It was hypothesized that adolescents with disturbed sleep would report more comorbid symptoms. This study used an explorative approach to examine if specific symptoms were related to disturbed sleep.

4 THE STUDIES

4.1 STUDY I: EFFECTS OF CBT-I

4.1.1 Aims

The aim of Study I was to examine the effect of cognitive and behavioral sleep interventions from randomized controlled trials in school-age children and adolescents.

4.1.2 Methods

A systematic literature review and meta-analysis was conducted. The primary outcomes combined objective (actigraphy) and self-reported (sleep-wake diaries, questionnaires) measures of sleep onset latency, wake after sleep onset and total sleep time. Secondary outcome was daytime sleepiness. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool for randomized controlled trials (RCTs) [49]. The groups (interventions; control) were compared at post-intervention and at short-term follow up (<8 weeks).

4.1.3 Results

Six RCT's were identified and included in the study (n = 528; mean age = 14.6 years; female = 63%). Regarding interventions, the mean number of treatment sessions was 6.2 (range 4-10 sessions). Six sleep intervention components, all classic components in CBT-I, were identified across the six studies. Quality ratings pointed to a high risk of bias due to study heterogeneity and lack of reporting. Regarding sleep results at post intervention, sleep onset latency decreased in the intervention group compared to controls as measured by both diaries (-9.31 minutes) and actigraphy (-19.48 minutes). Effect sizes ranged from small to large. No effect was seen on subjective total sleep time after intervention when comparing the groups, but when measured with actigraphy, an effect favouring the intervention group was observed (+11.49 minutes). No effect was observed for wake after sleep onset or daytime sleepiness. Short-term follow-up data (n=4 studies) indicated maintained positive effects on sleep onset latency and the effects in wake after sleep onset were now statistically significant. No effect on total sleep time was indicated at follow-up.

4.2 STUDY II: PRELIMINARY EFFICACY OF CBT-I

4.2.1 The insomnia treatment program: ySNOOZE®

The treatment program for youth insomnia, called ySNOOZE®, is a CBT-I program for adolescents with insomnia disorder. We developed the ySNOOZE® manual from manualized treatments for adults [35]. The manual was adapted to adolescents by reducing the amount of educational information and increasing the behavioral components of the intervention. The program consists of six weekly face-to-face individual sessions with a therapist, following a pre-set structure and fixed time frames with homework for participants between the sessions. In session 1, participants are introduced to CBT-I and receive psychoeducational information about sleep and sleep disorders. The participant's own sleep problem is assessed using functional analysis. Participants are also encouraged to set goals. In session 2, sleep restriction is introduced and adjusted weekly based on calculated sleep efficiency from sleep-wake diary registrations kept by participants throughout the treatment. This session also introduces the participant to stimulus control. Session 3-6 teaches participants about avoidance and problem-solving skills to overcome obstacles related to applying the sleep restriction. Participants also learn about stress management techniques (e.g., relaxation, breathing). Finally, participants work on identifying and preventing possible setbacks in treatment gains.

Figure 1. Example of homework from the ySNOOZE® program.

4.2.2 Aims

The aim of Study II was to evaluate changes in insomnia, sleep, and comorbid symptoms following ySNOOZE® in adolescents with comorbid psychiatric disorders and chronic pain and to assess acceptability of the program in a Swedish adolescent CAMHS and pain clinic setting.

4.2.3 Methods

Study II was an uncontrolled clinical pilot study (ClinicalTrials.gov Identifier: NCT 04136483). Participants (*n*=23, 78% female, mean age 15.5 years) with insomnia disorder were recruited from three adolescent psychiatry outpatient clinics and one pediatric pain clinic. All participants received CBT-I as described above. Assessments of self-reported insomnia symptoms and sleep parameters (sleep onset latency, wake after sleep onset, total sleep time and sleep efficiency) were collected, together with self-assessments of depression, anxiety, functional disability and pain intensity, at pre- and post- intervention at 3 months follow-up. Paired sample t-tests (intent-to-treat) were used to assess whether changes from pre to post treatment were statistically significant. Missing data at post-treatment were imputated. Due to a large amount of missing data at follow-up, data from this time-point are reported for descriptive purposes.

4.2.4 Results

For insomnia symptoms, statistically significant improvements were seen from pre- to post assessment (-7.2 points, large effect size). This change was considered clinically significant. For sleep parameters, a significant change was seen in sleep onset latency (-63.1 minutes, large effect size), wake after sleep onset (-10.1 minutes, small effect size), total sleep time (+21.9 minutes, small effect size) and sleep efficiency (+10%, medium effect size)) as well as for depression (medium effect size) and anxiety (small effect size). Only eight participants (35% of the original sample) reported follow-up data, with maintained improvements for all measures. Regarding treatment acceptability, 18 of the 23 participants (78%) finished all sessions and all drop-out from treatment occurred during the first three sessions.

4.3 STUDY III: FEASIBILITY AND PRELIMINARY EFFICACY OF ICBT-I

4.3.1 The iSNOOZE© programme

The iSNOOZE© programme (also called BiP Sleep) is an ICBT program for adolescents with insomnia disorder, developed from the ySNOOZE® program evaluated in Study II. iSNOOZE© is web-based and consists of six modules. The treatment duration is six weeks long and participants work with one module each week. iSNOOZE© consists of text, images and a few short videos. In module 1, participants are given information about sleep and sleep disorders, and are encouraged to set treatment goals. In module 2, sleep restriction is introduced, as well as stimulus control. In modules 2-5, participants work with identifying behaviors of avoidance, problem solving and strategies for dealing with worry (e.g., through relaxation). Module 6 deals with relapse prevention and how to maintain treatment gains. Therapist support is provided approximately three times per week, mainly through messages and feedback on homework. The main role of the therapist is to encourage the participant to work on the program, use the sleep-wake diary daily on a daily basis and to answer questions. The therapist adjusts the sleep restriction schedule on a weekly-basis and provides feedback on the participant's sleep during the past week.

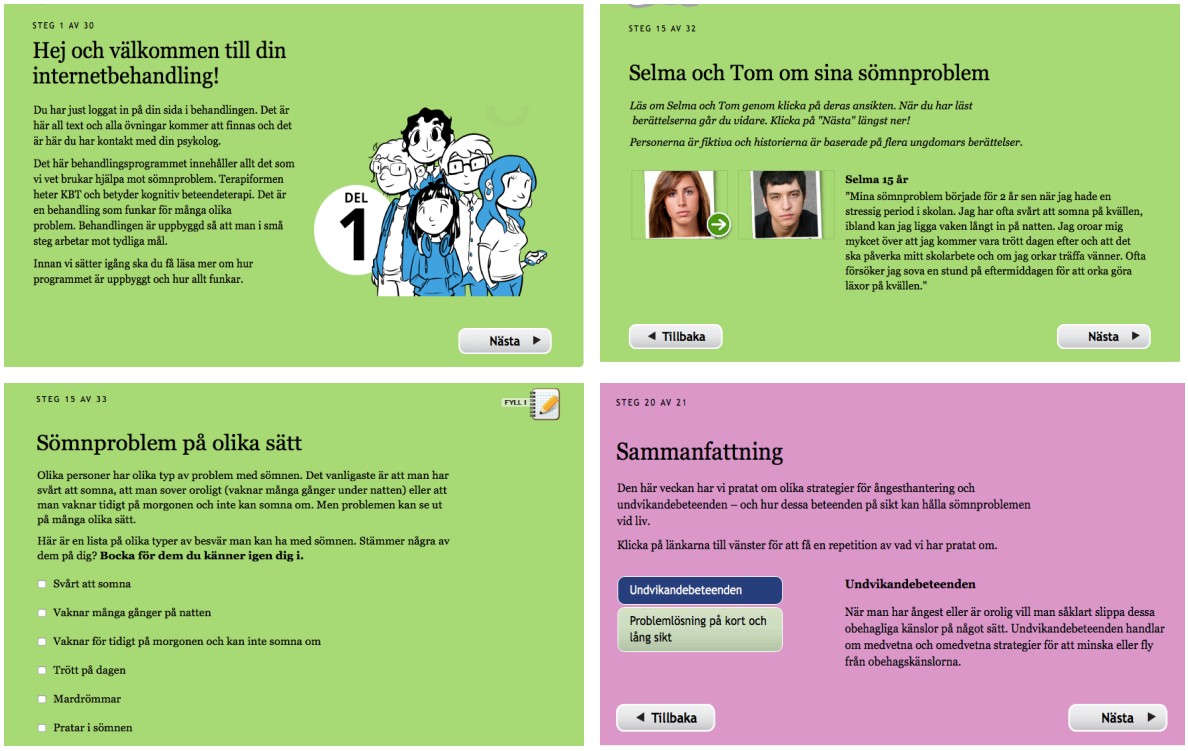

Figure 2. Screenshots from the iSNOOZE© programme.

4.3.2 Aims

The main aim of Study III was to evaluate feasibility and preliminary efficacy of iSNOOZE© on insomnia, sleep and comorbid symptoms in adolescents.

4.3.3 Methods

Study III was an uncontrolled feasibility pilot trial (ClinicalTrials.gov Identifier: NCT 04616157). Participants (n=27, 78% female, mean age 15.2 years) with insomnia disorder were recruited through primary clinics, school health care and newspaper advertisement. All participants received ICBT-I (as described above). Assessment of feasibility data, together with self-reported insomnia symptoms, sleep measures (sleep onset latency, wake after sleep onset, total sleep time, sleep efficiency), depression, anxiety and daytime function were collected before and after the interventions. Paired samples t-tests were performed (intent-to-treat) to assess whether changes from pre- to post-treatment were statistically significant. Multiple imputations were used for missing data.

4.3.4 Results

Regarding adherence to treatment, 23 of 27 participants (85%) were considered treatment completers. Participants reported overall good treatment credibility and satisfaction following the intervention. For measures of preliminary treatment efficacy, improvements in insomnia symptoms were statistically significant (-8.4 points, medium effect size). The change was considered clinically significant. For sleep parameters, significant improvements were seen for sleep onset latency (-36.4 minutes, small effect size), wake after sleep onset (-19.7 minutes, small effect size) and sleep efficiency (10%, small effect size). Changes in depression were also statistically significant (small effect size).

4.4 STUDY IV: RELATION BETWEEN DISTURBED SLEEP, SYMPTOMS AND FUNCTIONAL ABILITY

4.4.1 Aims

The aim of Study IV was to explore relationships between levels of psychiatric symptoms and functional ability in adolescents with and without self-reported disturbed sleep in a school-based Swedish sample.

4.4.2 Methods

Study IV was a cross-sectional study. Data collected from a school-based sample of Swedish adolescents in order to develop new instruments for screening of mental illness was analyzed with regards to sleep problems, psychiatric symptoms and functional ability. Participants (n=618, 62% female, mean age 15.7 years) answered the PROMIS pediatric measures for fatigue, anxiety, depression, pain interference, anger, physical activity and peer and family relationships. Respondents were categorized as having "disturbed sleep" or not depending on their answers to two sleep-related questions that were part of a larger data collection. Logistic regression analyses were then performed to examine differences between the two groups (disturbed sleep vs. non-disturbed sleep) in terms of psychiatric symptoms and functional ability.

4.4.3 Results

Based on the sleep-related questions, 23% (n=142) of respondents were classified as having "disturbed sleep". This group reported significantly higher levels of symptoms (fatigue, anxiety, depression, anger and pain interference) and lower functional ability (physical activity, peer- and family relationships) compared with respondents reporting non-disturbed sleep. Also, disturbed sleep was associated with a symptom pattern in PROMIS outcomes suggesting impaired executive functioning, internal emotional distress, sleep- and school related worry and dysfunction.

Table 1. Demographic data for Study I-IV and main pre-post treatment results (insomnia symptoms and sleep parameters (from sleep-wake diaries and actigraphy)) from Study I-III.

		Study I	Study II	Study III	Study IV
N		528	23	27	618
Mean age		14.6	15.5	15.2	15.7
Sex, female (%)		63	78	78	62
ISI-a		n/a	-7.2*	-8.4*	
SOL (min)	SWD Act	-9.3* -19.5*	-63.1*	-36.4*	
WASO (min)	SWD Act	-9.9 -1.2	-10.1*	-19.7*	
TST (min)	SWD Act	3.4 11.5*	21.9*	20.3	
SE	SWD	n/a	0.1*	0.1*	

Note. n/a= Not applicable; ISI-a=Insomnia Severity Index- adolescent version; SWD=Sleep-wake diary; Act=Actigraphy; SOL=Sleep onset latency; WASO= Wake after sleep onset; TST=Total sleep time; SE=Sleep efficiency. For Study I, only results for the intervention groups are presented. * Indicates a statistically significant change between the groups (for Study I) or between pre- and post assessments (for Study II and III).

5 DISCUSSION

5.1 EFFECT AND EFFICACY OF CBT-I FOR ADOLESCENT INSOMNIA DISORDER

STUDY I, II AND III

5.1.1 Sleep measures

Results from the meta-analysis (Study I [50]) showed that the treatment effect of cognitive and behavior interventions for insomnia disorder in school-children and adolescents were significantly larger for several sleep measures (sleep onset latency, total sleep time) in the intervention groups compared to the control groups, with small to large effect sizes. This is in line with previous findings regarding in-group comparisons for adolescent CBT-I [41]. In study II [51], examining preliminary efficacy of CBT-I in a Swedish adolescent CAMHS and pain clinic setting, all changes in sleep parameters (sleep onset latency, wake after sleep onset, total sleep time, sleep efficiency) were significant (effect sizes ranged from small to medium), giving preliminary support to the use of CBT-I in an adolescent clinical population with comorbid disorders. Study III (Åslund et al, manuscript in preparation) showed similar results as Study I and II, with preliminary indications that internet-delivered CBT-I could also be suited for this age group to improve sleep. Effect sizes were in the medium range. Regarding clinical significance, the change in sleep parameters differed between the studies. In both Study II and III, average sleep onset latency at post-treatment was above cut-off for what is considered relevant for the indication of insomnia disorder (>31 minutes) [52]. Average sleep efficiency after intervention in Study II was just below what indicates good sleep in adolescents and above in Study III (>85 minutes) [27]. To summarize, the current studies support the notion of significant positive changes in sleep parameters following CBT-I in an adolescent population.

5.1.2 Insomnia symptoms

Both Study II and Study III showed significant reductions of insomnia symptom severity between pre- and post-treatment with medium to large effect sizes following CBT-I. This is in line with previous studies on adolescents receiving face-to-face and internet-delivered CBT-I [44]. For both studies, changes in symptoms corresponded to what is considered as a clinically significant improvement in adults [53]. Thus, although tentatively, these studies support the idea that insomnia symptoms in adolescents can be reduced following a CBT-I intervention.

5.1.3 Methodological considerations

The studies included in the systematic review (Study I) were considered heterogeneous regarding participants, protocols and interventions, and the risk of bias was thus considered

high. As the quality of the results of a meta-analysis are dependent on the quality of the included studies, issues related to bias, transparency and heterogeneity should be addressed in future studies. Notably, using active control treatments could lower the bias associated with blinding (i.e., keeping participants unaware of the assigned treatment) in psychological treatment research. Study II and III both examined different formats of the same treatment program (six sessions/modules of CBT-I for adolescents between 13-17 years) with similar study protocols. Even though the study protocol did not intend for results from the two studies to be compared, a future randomized controlled trial could permit such comparison.

A general methodological consideration regarding intervention trials is the difficulty to choose outcome measures in order for meaningful comparisons with other trials. In Study I, trials using common outcome measures for sleep parameters (total sleep time, sleep onset latency, sleep efficiency) were included. Regarding sleep parameters, most studies in research on CBT-I use these outcome measures, collected by both subjective (sleep-wake diaries) and objective (actigraphy) assessments. For Study III, objective measures of sleep were collected, and will be analyzed and reported as a complement to their subjective counterparts. For insomnia symptoms, different trials tend to use different questionnaires, often dependent of the preference of the research group. In study II and III, Insomnia Severity Index (ISI-a) was used to evaluate insomnia symptom severity. ISI-a is currently being evaluated in Swedish adolescent psychiatry (Jansson-Fröjmark et al, manuscript in preparation). A consensus on which outcome measure to use for adolescent insomnia symptoms, and at what time-points, would allow for easier comparisons between trials. Meanwhile, comparisons using different outcome measures can be performed using cut-offs for clinical significance for each measure, rather than raw scores of changes in symptoms.

Study II and Study III were both clinical pilot studies without control conditions, and with small sample sizes (n=23 and 27, respectively). The results concerning efficacy on insomnia and sleep should therefore be considered as preliminary. Nonetheless, the preliminary evaluations of efficacy are encouraging, meaning that CBT-I for adolescent insomnia are well suited for larger controlled trials, also in clinical populations.

Because attrition was relatively high in both Study II and III, and that imputations were used, the internal validity is reduced, and results need to be interpreted with caution. Drop-out and attrition are not uncommon in clinical studies on CBT. As a result of learnings achieved from the attrition that occurred in Study II, Study III used digital questionnaires only as a way to facilitate for participants. However, the effect of this on attrition was limited.

Both Study I and Study II include short-term follow-up assessments (ranging from 4-12 weeks post-intervention). However, long-term follow up assessments are necessary to better understand the treatment effectiveness of CBT-I in a larger perspective, and our preliminary conclusions do thus only apply to a shorter time-span. More studies with long-term follow-ups of treatments effects of CBT-I in adolescents are needed.

5.2 FEASIBILITY OF CBT-I FOR ADOLESCENT INSOMNIA DISORDER

Study II and III

5.2.1 Adherence to treatment

Both Study II and III examined adherence to treatment by investigating drop-out during CBT-I. The proportion of participants who attended all sessions/modules were 78% in Study II and 59% in Study III. This is similar to what has been shown in previous studies on CBT-I in adolescents with comorbid physical problems [54]. A collaborative project with Uppsala Region (that is not part of this thesis) on adolescent ICBT-I showed similar study retention (Zetterqvist et al, accepted). Participants were considered treatment completers if they completed ≥ 4 of the 6 modules, which was obtained by 100% (Study II) and 85% (Study II) of participants respectively. Drop-out or non-adherence to CBT-I is not uncommon among adults [55], possibly due to the sleep restriction component that can be perceived as aversive and negatively impact performance [56]. Using the internet-format to deliver treatment could permit treatment retention for some participants, but for others, the lack of a physically present therapist may be critical to pursue long-term treatment goals. Overall, the present results suggest that adolescence adhere to CBT-I in various formats, but the question for whom CBT-I is suited at this age is still unanswered.

5.2.2 Therapist and participant treatment activity

During the six treatment weeks, therapists in Study III spent 26 minutes less on average on each participant per week, as compared to therapists in Study II (i.e., 19 minutes vs. 45 minutes). This suggests that ICBT-I might be a more time-efficient way to deliver treatment than face-to-face CBT-I. Regarding participant activity, participants spent approximately 2,5 hours logged in to the platform in Study III.

5.2.3 Treatment satisfaction

In Study III, almost 80% of participants reported “good” or “excellent” satisfaction with the overall treatment. As the design in Study II did not have feasibility as primary aim, treatment satisfaction was not assessed. In retrospect, measures of feasibility, such as treatment satisfaction and expectation, would have provided important information on how to adapt the treatment to an online format.

5.2.4 Methodological considerations

In Study III, the design was focused on the evaluation of acceptability and preliminary efficacy. The inclusion of additional outcome measures, e.g., demand for the program or possible integration of a program into an existing clinical infrastructure, could have added valuable information for the preparation of an RCT [57]. However, Study III provided

important information to plan for the next step in the evaluation of ICBT-I in a Swedish adolescent setting. Study II did not have feasibility as primary aim, but still provided valuable insights that permitted the step from face-to-face treatment into a digital intervention. The problem of blinding in psychological treatment studies is also applicable to CBT-I, and when having an uncontrolled design, factors such as social desirability could have affected e.g., ratings of treatment satisfaction. Using active controls, receiving an equal number of sessions/modules with educational information about sleep and sleep disorders, but lacking the behavioral intervention components, could be valuable in future RCTs to minimize the risk of bias.

5.3 REDUCTION OF COMORBID PROBLEMS FOLLOWING CBT-I STUDY II AND III

5.3.1 Depression and anxiety

Study II showed that adolescent with insomnia who undergo CBT-I show a reduction in self-reported comorbid symptoms of depression and anxiety, with small to medium effect sizes. In study III, this was the case for depression (small effect size) but not for anxiety. Previous studies in adults have shown reductions in comorbid psychiatric symptoms following ICBT-I [7] and the current results, although preliminary, seem to point in the same direction. Results from a study on adults with concurring depression and insomnia show that these patients could possibly benefit more from CBT-I than CBT for depression, as they tend to show reduced symptoms of both insomnia and depression following CBT-I, while the opposite was not necessarily true [39]. Regarding clinical significance, the level of comorbid symptoms differed between the participants in Study II and III. In Study II, pre-treatment levels of psychiatric symptoms were above cut-of for depression [58] and anxiety [59] and even though the reduction of symptoms of depression and anxiety was statistically significant, the post-treatment levels were still above cut-off. In Study III, participants reported pre-treatment scores of comorbid psychiatric symptoms that were below clinical levels for both depression and anxiety [60]. To summarize, it seems that symptom levels of depression and anxiety can be reduced following CBT-I in adolescents, even though these disorders are not specifically addressed in treatment.

5.3.2 Sleepiness, functional ability and pain

For daytime sleepiness, no significant between-group effect (Study I) or within-group effect (Study III) was observed. These results are contradictory to those of a previous meta-analysis on adolescent CBT-I where a significant reduction in sleepiness with moderate effect size was reported [41]. Regarding clinical significance, mean pre-treatment score of sleepiness in Study III corresponded to “low sleepiness”, perhaps not permitting a substantial change due to a floor-effect. For functional disability, neither Study II nor Study III reported improvements following intervention. Although insomnia symptoms have been related to

functional disability in adolescents [22], no studies on adolescent CBT-I have included general function as an outcome measure. In future studies, more in-depth examination of the relation between insomnia and daytime function would add to the understanding of how disturbed sleep affect general functioning in adolescence. For pain intensity, Study II showed no difference in current pain intensity following the intervention. Although not targeted in CBT-I, pain can be reduced following CBT-I in adults, with a small effect size [3].

5.3.3 Methodological considerations

As for preliminary efficacy on insomnia and sleep parameters, the designs of Study II and III (uncontrolled pilot studies) do not permit any firm conclusions regarding treatment effects on comorbid problems and future research should include larger RCTs to validate the results seen in these studies.

In Study II, participants fulfilled criteria for at least one comorbid disorder (the most common being MDD and anxiety disorders) and on average 3.8 comorbid disorders. In study III, only 37% of participants fulfilled criteria for any comorbid diagnoses and for those who did, the average number of comorbid diagnoses was 1.6 (the most common being generalized anxiety disorder and specific phobia). As noted above regarding pre-treatment scores, the participants in Study III reported less severe symptoms than those in Study II with regards to psychiatric symptoms. Interestingly, the two populations were rather similar regarding insomnia symptoms, both for pre-treatment scores and mean reduction score (see Table 1). It thus seems that a reduction of insomnia symptoms following CBT-I occur irrespectively of the weight of comorbid symptoms or diagnoses. However, results on preliminary efficacy might only be generalizable to the specific sample and not necessarily applicable in all adolescent populations. It could be that the independence required for ICBT-I is not suitable for a CAMHS-population, perhaps in need of more therapist support.

The lack of long-term follow-up also affects the preliminary conclusion possible regarding efficacy of comorbid psychiatric symptoms. In this regard, RCTs with long-term follow-ups should also include measures of comorbid psychiatric symptoms.

5.4 RELATION BETWEEN DISTURBED SLEEP, OTHER PROBLEMS AND FUNCTIONAL ABILITY

STUDY IV

5.4.1 Relation to anxiety, depression and anger

Study IV showed that adolescents with self-reported symptoms of disturbed sleep report significantly higher levels of anxiety, depression and anger than those with not reporting disturbed sleep (moderate effect sizes). This is in line with previous reports on the relation between disrupted sleep and other problems, such as mood disorders and anger [61]. Regarding anxiety, disturbed sleep seemed more related to worry at bedtime and in school

than to generalized anxiety. For depression, adolescents with disturbed sleep reported internal emotional distress (e.g., feeling sad) rather than high levels of stress and feeling of loss of control. Reported symptoms of anger were internalized rather than displaying, or wanting to display, overt aggressive behaviors. To summarize, it would seem that adolescents with disturbed sleep in the present sample to a higher extent than their better-sleeping peers report internalized symptoms, and that these symptoms are related to school and specifically to sleep.

5.4.2 Relation to pain, fatigue and functional ability

Results from Study IV showed that adolescents reporting sleep disturbances displayed significantly higher levels of pain interference compared to adolescents without sleep problems, with a moderate effect size. This is line with a previous report of insomnia as a mediator between pain and functional disability in adolescents [22]. A relationship between p sleep restriction and increased pain experience is shown in experimental studies [62]. Study IV also showed a relation between disturbed sleep and fatigue (large effect size) as well as physical activity, peer- and family relationships (small effect sizes). Regarding pain interference, school attendance and sleep quality seemed related to disturbed sleep, rather than physical exercise and use of medication.

5.4.3 Clinical implications

As the results of Study IV allow for a more in-depth understanding of how specific symptoms relate to disturbed sleep, such studies can be informative when designing future treatment programs for CBT-I in adolescents, and especially for those with comorbid disorders. As previously noted, transfer effects of CBT-I on e.g., anxiety have been noted for adults [7]. However, the results from Study IV suggest that some psychiatric symptoms might be more related to disordered sleep than others. If so, the transfer effect might only concern the symptoms where the relation to disturbed sleep is strong, meaning that other symptoms of comorbid anxiety might not be affected by the sleep intervention. One such example could be symptoms of generalized worry or stress that might remain after CBT-I, even though a change in mean anxiety symptom score show a transfer effect on comorbid symptoms. Specifically addressing anxious rumination in adolescents with co-morbid insomnia and generalized anxiety disorder might be a way to further enhance treatment effectiveness, and this might also be true for other diagnoses and symptoms.

5.4.4 Methodological considerations

As Study IV had an observational design with one assessment-point, conclusions regarding causality between disturbed sleep and symptoms or dysfunctions cannot be drawn. This is a common methodological concern in observational studies. Also, the generalizability of the present results is limited by the study populations, which is not entirely representative of he Swedish adolescent population (e.g., regarding geography and gender).

5.5 ETHICAL CONSIDERATIONS

5.5.1 Informed consent/assent

In research involving children/adolescents, informed consent is important yet complex, since the researcher need to ascertain that the adolescent fully understands what it means to participate in the research study. The children in study II, III and IV all provided written informed consent. In study II and III, informed consent was also provided by all parents/guardians, while in Study IV, this was done only for participants under the age of 15. For study II and III, separate documents for adolescents and parents/guardians were used to inform families about the study. Information was also given orally to the family prior to the decision to participate in the trial. The adolescent was encouraged to ask questions and was informed that he or she could withdraw from the trial without explaining why.

5.5.2 Assessing symptoms

As Study III involved ICBT, with no physical interaction between the participant and the therapist during the treatment, the risk of not detecting adverse events, such as a deterioration of comorbid psychiatric symptoms (e.g., depression), was enhanced as compared to in Study II, which evaluated face-to-face CBT-I. Therefore, participants were instructed to fill out additional questionnaires at the beginning of week 4 regarding depression and suicidal ideations. For inactive participants (i.e., participants who did not log in to treatment according to plan), parents/caregivers were contacted to investigate the reason for their inactivity.

5.5.3 Sleep restriction

As previously noted, the sleep restriction component of CBT-I is often perceived by participants as aversive, and sleep time often decrease in the initial phase of the treatment [63]. In Study II, all dropouts occurred during the first three sessions of treatment, supporting this notion. Decreased sleep time was also reported as concerning by parents/caregivers, both in Study II and III. For adolescents, a minimum recommended total sleep time during sleep restrictions was not suggested. However, in the current pilot studies, no participant had a total sleep time below 5 hours.

5.5.4 Research ethics

Both Study II and III have been pre-registered at ClinicalTrials.org. Pre-registration of clinical trials are important as they allow researchers to identify ongoing trials and unmet needs. The registration of outcome measures can reduce p-hacking as well as publication and outcome reporting bias. Clinical pilot studies, as Study II and III, are important as they provide information on participant recruitment rate and feasibility. Even though low power might make preliminary analyzes on treatment efficacy unreliable, such analyzes allow for an initial understanding of changes in symptoms following treatment. From an ethical point of view, this knowledge is important, as an RCT might require a large number of participants

investing time in a treatment that has not been initially tested. Another aspect to consider is the difficulties of replicability in clinical studies. Publishing a study protocol, together with pre-registration of the trial, could address this problem and facilitate replication.

5.6 FUTURE DIRECTIONS

The pilot studies of Study II and III present a promising base for future trials as CBT-I seem to be a feasible treatment for adolescents and that results on preliminary efficacy show improvements in sleep, insomnia and comorbid symptoms. As previously mentioned, RCT's with long-term follow-ups are needed to confirm the results. Ideally, such studies would include measures of comorbid disorders, and analyze the transfer effects on specific symptoms. Understanding for whom CBT-I is suitable, as has been done for ICBT for pediatric anxiety disorders (Jolstedt et al, manuscript in preparation) would also be important, and could possibly reduce drop-out rates in future trials. Regarding clinical significance of symptoms, an investigation of what changes in sleep parameters and insomnia symptoms following CBT-I in adolescents are perceived as useful for participants would aslo be important.

6 CONCLUSIONS

Although tentative, the presented studies indicate that CBT-I may be an effective treatment for adolescents with insomnia and that the intervention can improve several sleep parameters. The evaluations of preliminary efficacy show improvements in sleep, as well as reductions in insomnia symptom severity following CBT-I. These results are in line existing research on adults, further supporting the utility of CBT-I for youth. Also, CBT-I appears to be a feasible intervention, both as a face-to-face treatment program and as an internet-delivered intervention (ICBT-I), with acceptable drop-out rates in both settings. CBT-I can also result in reduced comorbid depression and anxiety, even if comorbid psychiatric disorders are not directly addressed in the treatment program. It also seems that the intervention can be used in clinical settings with patients presenting several comorbid psychiatric diagnoses with high symptom levels.

As the results suggest that disturbed sleep is associated with e.g., school-related worry and dysfunction, as well as executive functions important for learning, treating insomnia disorder might have a positive effect on school performance as well as school attendance. An explorative in-depth study of symptoms specifically related to sleep problems add important information to the understanding of the relationship between disturbed sleep and specific symptoms of comorbid problems and can lead to clinical implications when designing future treatment programs for adolescent insomnia.

In summary, this thesis provides support for CBT-I as a clinically efficacious and feasible treatment for insomnia disorders in adolescents. CBT-I is a promising choice of treatment for this age group, where untreated insomnia could lead to lifelong suffering and dysfunction. The results from the four studies of the present thesis can together with future work hopefully be of guidance when establishing clinical guidelines for the psychological treatment of insomnia in adolescents both with and without comorbid disorders.

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