Linköping University Medical Dissertation No. 1776

Insomnia Symptoms in Chronic Pain

– Clinical presentation, risk and treatment

Tobias Wiklund

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Clinical presentation, risk and treatment

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Linköping 2021

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Till Anna, vår förstfödda.

Waking up is a jump, a skydive from the dream.

Tomas Tranströmer

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ABSTRACT

In recent years, chronic and recurrent pain have gained interest as distinct conditions interacting both with peripheral and central parts of the nervous system as well as with the immune system. The risk of getting affected by abnormal pain modulation i.e., chronic pain is not equally distributed in the population and the search for risk factors is therefore of interest. One potential risk factor for chronic pain is insomnia symptoms i.e., difficulties falling asleep or maintaining sleep. In turn, insomnia symptoms are overrepresented in persons with chronic pain. Common current pain treatments lead to limited improvement of insomnia symptoms calling for treatments specifically directed to improve sleep. The overall aim of this thesis is therefore to investigate the distribution of insomnia severity in patients seeking specialized care for chronic pain, to investigate the role of insomnia severity as a risk factor for spreading of pre-existing pain, and to evaluate potential treatments for insomnia symptoms comorbid to chronic pain.

Study I highlighted the high prevalence rates of insomnia symptoms in patients with chronic pain conditions. Roughly, insomnia was six times more common in our sample compared to the general population. We also showed that there were weak connections between insomnia symptoms and other variables (primarily psychological symptoms and pain intensity). In **Study II** physical exercise was more efficacious than Acceptance and Commitment Therapy-based stress management and the active control group in reducing insomnia symptoms and pain intensity short term. Improvements in physical exercise were largely maintained after twelve months but pain intensity had then also declined in the control group. No improvements in the Acceptance and Commitment Therapy-based stress management remain significant when an intention to treat principles were applied. In **Study III**, a dose-dependent increase in risk for spreading of pain was confirmed in subjects reporting moderate and severe insomnia symptoms. Though, there was no increase in the risk of pain spreading in subjects reporting sub-threshold insomnia symptoms (according to Insomnia Severity Index). In **Study IV** patients in the Internet-delivered Cognitive Behavioral Therapy for insomnia group, showed a more rapid improvement in insomnia symptoms than patients in the internet-delivered applied relaxation. The effect of Cognitive Behavioral Therapy for insomnia had declined slightly after six months and the Applied Relaxation group had continued to improve, leading to a comparable outcome on the Insomnia Severity Index at six-month follow-up.

In conclusion, insomnia symptoms are common in patients seeking specialized pain care. High levels of insomnia symptoms increase the risk of spreading of pre-existing pain and this in a dose-dependent manner. Physical exercise has significant, but not clinically meaningful effects on pain intensity and insomnia symptoms. Internet-delivered Cognitive Behavioral Therapy for insomnia leads to a more rapid reduction of insomnia symptoms compared to applied relaxation, although long-term effects are uncertain.

SVENSK SAMMANFATTNING

Under senare år har kronisk och återkommande smärta uppmärksamats som egna tillstånd som interagerar med både perifera och centrala delar av nervsystemet samt immunsystemet. Risken för att bli påverkad av avvikande smärtmodulering dvs långvarig/kronisk smärta är inte jämnt fördelad i befolkningen och forskningen om riskfaktorer är därför av stor vikt. En potentiell riskfaktor för kronisk smärta är insomnisymptom, det vill säga svårigheter att somna på kvällen, eller att upprätthålla sömnen under natten. Insomnisymptom är i sin tur överrepresenterade hos personer med kronisk smärta. Sedvanliga smärtbehandlingar leder endast till begränsade förbättringar av sömnen vilket understryker behovet av behandlingar som är inriktade på att förbättra sömnen. Det övergripande syftet med denna avhandling är därför att undersöka fördelningen av insomnisymptom hos patienter som söker specialiserad vård för kronisk smärta, att undersöka insomnisymptom som riskfaktor för spridning av befintliga smärttillstånd och att utvärdera potentiella behandlingar för sömnproblem hos patienter med kronisk smärta.

Studie I lyfte fram den höga förekomsten av insomnisymptom hos patienter med kroniska smärta. Insomnisymptom var ungefär sex gånger vanligare i vårt stickprov jämfört med befolkningen i stort. Vi visade också att det fanns relativt svaga samband mellan insomnisymptom och andra variabler (främst psykologiska symtom och smärtintensitet). I **studie II** var fysisk träning mer effektiv än acceptansbaserad stresshantering och den aktiva kontrollgruppen för att minska insomnisymptom och smärtintensitet på kort sikt. Förbättringarna av fysisk träning kvarstod i stor utsträckning efter tolv månader, men smärtintensiteten hade då också minskat i kontrollgruppen. Inga effekter av den acceptansbaserade stresshanteringen var signifikanta när data från samtliga deltagare togs med i analyserna. I **studie III** bekräftades ett dos-responsförhållande mellan insomnisymptom och risk för smärtspridning hos personer som skattade måttliga till svåra insomnisymtom. Däremot förelåg det ingen ökad risk för smärtspridning hos patienter som skattade lätt förhöjda nivåer av insomnisymptom. I **studie IV** uppvisade patienter som fått internetadministrerad kognitiv beteendeterapi för insomni en snabbare förbättring av insomnisymptom jämfört med patienter som fick internetlevererad tillämpad avslappning. Effekten av kognitiv beteendeterapi för insomni hade minskat något efter sex månader och avslappningsgruppen hade fortsatt att förbättras, vilket ledde till likvärdiga resultat vid sexmånadersuppföljningen.

Sammanfattningsvis är insomnisymptom vanliga hos patienter som söker specialiserad smärtvård. Höga nivåer av insomnisymptom ökar risken för spridning av befintlig smärta och detta på ett dosberoende sätt. Fysisk träning har signifikanta, men inte kliniskt betydelsefulla, effekter på smärtintensitet och insomnisymptom. Internetadministrerad kognitiv beteendeterapi för insomni leder till en snabbare minskning av insomnisymptom jämfört med tillämpad avslappning, även om långtidseffekterna är oklara.

LIST OF PAPERS

The present thesis is based on the following studies, which hereafter will be referred to by their Roman numerals.

- I. Alföldi, P., Wiklund, T., & Gerdle, B. (2014). Comorbid insomnia in patients with chronic pain: a study based on the Swedish quality registry for pain rehabilitation (SQRP). *Disability and rehabilitation*, 36(20), 1661-1669.
- II. Wiklund, T., Linton, S. J., Alföldi, P., & Gerdle, B. (2018). Is sleep disturbance in patients with chronic pain affected by physical exercise or ACT-based stress management? – A randomized controlled study. *BMC musculoskeletal disorders*, 19(1), 111.
- III. Wiklund, T., Gerdle, B., Linton, S. J., Dragioti, E., & Larsson, B. (2020). Insomnia is a risk factor for spreading of chronic pain: A Swedish longitudinal population study (SwePain). *European Journal of Pain*, 24(7), 1348-1356.
- IV. Wiklund, T., Molander, P., Lindner, P., Andersson, G., Gerdle, B., & Dragioti, E. Internet-delivered cognitive behavioral therapy for insomnia comorbid with chronic pain – a randomized controlled trial. (Submitted)

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
ACT	Acceptance and Commitment Therapy
ACT-bsm	Acceptance and Commitment Therapy-based stress management
AR	Applied Relaxation
CBTi	Cognitive Behavioral Therapy for Insomnia
CNS	Central Nervous System
CON	Control Condition
CWP	Chronic Widespread Pain
DSM-5	Diagnostic and Statistical Manual of mental disorders, fifth edition
EEG	Electroencephalography
EMA	Early Morning Awakenings
EQ-5D	EuroQol 5 Dimensions
FACTA	Fysisk träning, Acceptance and Commitment Therapy & Aktiv kontrollgrupp (Physical exercises, Acceptance and Commitment Therapy & Active control group)
FFI	Fatal Familiar Insomnia
GAD-7	Generalised Anxiety Disorder 7-item scale
GLM	Generalized Linear Model
GWBS	General Well-Being Schedule
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety
HADS-D	Hospital Anxiety and Depression Scale – Depression
IASP	International Association for the Study of Pain
ICBT-i	Internet delivered Cognitive Behavioral Therapy for Insomnia
IMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ISI	Insomnia Severity Index
ITT	Intention-To-Treat
LMM	Linear Mixed Model
MPI	Multidimensional Pain Inventory
NREM	Non-Rapid Eye Movement
NRS	Numeric Rating Scale
OPLS	Orthogonal Partial Least Square

PCA	Principal Component Analysis
PCS	Pain Catastrophizing Scale
PDI	Pain Disability Index
PLS	Partial Least Square
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized Controlled Trial
REM	Rapid Eye Movement (R or formerly)
SF36	Short Form Health Survey
SIMCA	Soft Independent Modelling by Class Analogy
SOL	Sleep Onset Latency
SoV	Sömn och Värk-studien (Sleep and Pain-study)
SQRP	Swedish Quality Registry for Pain rehabilitation
SWA	Slow-Wave Activity
TST	Total Sleep Time
VAS	Visual Analog Scale
VIP	Variables Influence on Projection
WASO	Waketime After Sleep Onset

INTRODUCTION

Pain

Pain is usually categorized with respect to intensity, duration, spread, and persistence. The International Association for the Study of Pain (IASP) revised its definition in 2020 as follows:

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

(Raja et al., 2020)

In the notes following, they also state that pain is a personal experience, that there is always biological, psychological, and social aspects of pain, that pain is distinct from nociception, that pain usually serves an adaptive role but that it can impair functioning, and that pain is a learned concept, etc (Raja et al., 2020). Over the last decades there has been a shift in how the scientific society looks at pain. Going from considering chronic pain as merely a symptom of disease, to reconsider it as a disease (or diseases) in its own right. Hence, in 2004 the European Pain Federation stated:

“Pain is a major healthcare problem worldwide. Although acute pain may reasonably be considered a symptom of disease or injury, chronic and recurrent pain is a specific healthcare problem, a disease in its own right.”

(EFIC., 2004)

Pain intensity

Measuring pain goes with great challenges. Its subjective nature and the absence of reliable objective measures omits the scientific society to patient-reported outcomes. Numeric rating scales (NRS) are commonly used and considered to be the *gold standard measurement* of pain intensity (Safikhani et al., 2018). Although several other factors have been proposed and scientifically evaluated concerning their impact on daily function and perceived health, pain intensity remains central (Bromley Milton et al., 2013).

Pain duration

The distinction between acute and chronic pain is essential. IASP classifies pain as chronic if it lasts for more than three months (Treede et al., 2019). A time limit of six months is also frequently used in the literature (Breivik et al., 2006) while others argue for a definition based on expected healing time for the underlying condition. Regardless of the definition used, chronic pain is highly prevalent, and most sufferers have had their pain condition for several years (Breivik et al., 2006). For instance, 19 % of the adult European population report severe chronic pain ($\geq$ NRS 5, lasting > 6 months). Irrespective of pain intensity the prevalence of chronic pain is higher according to Swedish studies 31-54% (Bergman et al., 2001, Gerdle et al., 2004). There is considerable variance in prevalence rates between studies and that is, at least in part, due to inconsistent definitions of chronic pain.

Persistent or recurrent pain

Chronic pain can occur in different forms and vary over time. IASP (Treede et al., 2019) lists three different types of temporal characteristics: continuous, episodic recurrent, and continuous with pain attacks. In the former, pain is always present. The second is characterized by recurrent pain attacks with pain-free intervals whilst the latter means recurrent pain attacks as exacerbations of underlying continuous pain. Though, all three are considered to be parts of the concept of chronic pain.

Spread of pain

The spatial distribution of pain on the body varies considerably from different pain conditions and injuries. In some cases, the spread of pain corresponds well with the associated tissue damage. In other cases, as in fibromyalgia and chronic widespread pain (CWP), widespread pain is the hallmark of the conditions itself (Wolfe et al., 1990). Pain conditions that debut in a limited area can develop into conditions with more extensive pain distribution over time (Graven-Nielsen and Arendt-Nielsen, 2010, Viniol et al., 2015). This process has been linked to several risk factors such as depression, female sex, age, and a family history of pain. Interestingly, already reporting several pain sites is a risk factor for further spreading (Larsson et al., 2012). Further, *years with chronic pain* also constitute a risk factor for spreading of pain (Viniol et al., 2015). Therefore, spreading of pain can be seen as a continuum where fibromyalgia and CWP constitute the worst endpoint. This is known as the *pain transition hypothesis*.

Besides the few studies performed evaluating the spreading of pre-existing pain, there are several population-based studies on the risk of developing CWP and fibromyalgia in general (also including the pain-free part of the population). A recent review by Creed (2020) describes an array of risk factors also including

sleep disorders, low education, musculoskeletal disorders, and other medical disorders.

Neurobiological alterations in chronic pain conditions

Increased pain sensitivity i.e., lower pain thresholds have been confirmed in local, regional, and wide-spread pain conditions (Graven-Nielsen and Arendt-Nielsen, 2010). Patients present allodynia (experiencing pain when exposed to usually non-noxious stimuli) and hyperalgesia (experiencing more pain when exposed to noxious stimuli). The mechanisms underlying these phenomena are called central and peripheral sensitization. Sensitization has been linked to inflammatory processes both peripherally, affecting nociceptors, and centrally, affecting the spinal cord (Ji et al., 2018). Further, extensive afferent input (peripheral) can contribute to central alterations and thereby worsen and maintain a pain condition.

Animal studies have shown that incoming pain/ nociceptive signals can be modulated by the brain itself (Heinricher, 2016). This process is known as top-down regulation and in humans, this process is affected by psychological phenomena such as mood, attention, stress, and executive control. In acute pain, pain is generally facilitated by suppression of a group of “OFF-cells” in the rostral ventromedial medulla, in combination with activation of “ON-cells”. When interacting normally, these groups of cells balance over time in a homeostatic manner. However, this balance is somehow disturbed in chronic pain conditions, causing an uncontrolled activation of ON-cells.

In fibromyalgia, brain imaging studies have demonstrated structural as well as functional alterations (Cagnie et al., 2014). That is atrophy of gray matter (primary in anterior cingulate cortex and prefrontal cortex), increased reactions to noxious stimuli in the pain matrix (see below), and decreased connectivity related to top-down pain modulation. However, there seem to be significant differences in pain processing between chronic pain conditions with signs of central sensitization such as fibromyalgia and whiplash-associated disorders, and local pain conditions such as low-back pain and shoulder myalgia (Nijs et al., 2012). Patients with local pain conditions are more similar to healthy controls in terms of pain processing and their response to physical exercise.

Although much focus has been put on central alterations there is a growing body of evidence for peripheral tissue changes in local as well as widespread pain conditions (Gerdle et al., 2014). The milieu surrounding the nociceptor can have either an analgesic or sensitizing impact on nociception. Peripheral factors may drive central alterations by continuous afferent input, but the interrelationship between central and peripheral factors is still unknown.

Pain neuromatrix?

Pain is not solely nociception reaching the somatosensory cortex. The neuromatrix theory presented by Melzack integrates affective and cognitive aspects to the perception of pain (Melzack, 1999). He proposes a plastic network that is not only affected by former pain, but also by psychological aspects such as fear, stress, and depression. Further, the model also includes motivational factors as well as pain behaviors. These factors affect the brain's ability to filter, select and modulate inputs. The theory empathies that the neuromatrix is a functional network, in contrast to older views that assumed a neuroanatomical "pain center". Nevertheless, Melzack mentions somatosensory, limbic, and thalamocortical components as central for the ability to discriminate, localize, and evaluate the pain experience. Incoming pain signaling is also modulated in the dorsal horns where it can be either inhibited or amplified.

Although this theory has been widely accepted and applied in the field of pain research, there is reasonable doubt whether this is a pain-specific network or not. Iannetti and Mouraux (2010) argue that the neuro-signature, reported in numerous brain imaging studies of pain, is not specific to nociception. The identified pattern is rather the reflection of a neural network sensitive to salient stimuli, regardless of modality (e.g., visual or auditive). The ability to identify salient information in the noise from incoming stimuli, and to recognize the unexpected, is essential for survival. Thus, the observed high correlations between painful stimuli and the activation of these networks are rather the expression of the salient nature of pain due to its highly important protective function.

Biopsychosocial model

Besides the biological and psychological aspects mentioned above, the biopsychosocial model also includes social (and economic) dimensions. The model includes both causes and consequences as well as the interaction between biological, psychological, and social factors (Gatchel et al., 2007). For instance, a recent review on low-back pain (Karran et al., 2020) identified social determinants of health. The most frequently reported were occupational factors (positions and tasks), level of education, socioeconomic status, and sex/gender. However, these factors are defined as strikingly different in the reviewed studies and there is considerable overlap between the categories. This overlap has shown that the number of significant determinants drops when controlling for the other factors is mentioned. Female sex was also mentioned in the review of risk factors for spreading of pain by Larsson et al. (2012), together with a family history of pain. These two are illustrative examples of risk factors that carry both biological, psychological, and social dimensions.

Categorizing pain by mechanistic descriptors

Besides the above-mentioned categories based on pain characteristics, pain can be categorized by known or probable origin (2020). Today, three different mechanisms are predominant. *Nociceptive pain* has its origin in “*actual or threatened damage to non-neural tissue and is due to the activation of nociceptors*”. The term *non-neural tissue* contrasts nociceptive pain from *neuropathic pain* which refers to pain that is “*caused by a lesion or disease of the somatosensory nervous system*”. Neuropathic pain can be peripheral (e.g., pain after surgery or trauma) or central (e.g., after stroke or damage to the spinal cord).

The latest addition to this terminology is *nociplastic pain*. Nociplastic pain is pain due to “*altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain*”. It is characterized by increased pain sensitivity and spreading of pain to larger areas. Although theoretically separated, the clinical presentation can include a combination of these pain mechanisms (Gerdle et al., 2020, Kosek et al., 2016).

Sleep

Over millions of years, life on earth has developed based on the shift between day and night i.e. light and darkness (Dvornyk et al., 2003). Circadian clock genes - i.e., parts of the genome that regulates day and night variation of the vital functions - are present already in procaryotes. The regulation of sleep in humans is a complex interaction between internal processes and the external environment (Deboer, 2020). The ability to adapt to changes in living conditions is essential while these vital processes have to be stable enough to be maintained over time. However, the ability to adapt comes with the risk of maladaptation and the risk to develop several sleep disorders.

Sleep stages

Based on polysomnography (PSG), according to the American Academy of Sleep Medicine (AASM) updated scoring manual, sleep can be divided into different stages (Malhotra and Avidan, 2014). First, there is rapid eye movement (R or formerly REM) sleep and non-rapid eye movement (NREM) sleep. REM sleep is characterized by wake-like electroencephalography (EEG) -pattern but with active motor inhibition and rapid eye movements behind closed eyelids. Further, NREM can be divided into three sub-categories; N1, N2, and N3.

Normally, N1 is the first sleep stage in the transition from wakefulness to sleep and it is also referred to as *light sleep*. Physiologically, the heart rate becomes

regular, blood pressure falls, and breathing is shallow. The person asleep is easy to wake and might deny sleeping at all.

N2, or *intermediate sleep*, constitutes the main part of sleep, in adults. EEG is characterized by so-called *K complexes* and *sleep spindles*. As N2 proceeds, the sleeper becomes harder and harder to wake up. Also, there is a decrease in blood pressure, brain metabolism, gastrointestinal secretions, and cardiac activity.

N3, also known as *deep sleep* or *slow-wave sleep*, typically dominates the first half of night sleep. This is the most relaxed and refreshing sleep stage where the peak in the release of growth hormone occurs. As the name suggests, the EEG has recognizable high-amplitude slow waves, reflecting synchronized firing of neurons. Thresholds for awakening are massive and waking up can take several minutes, so-called *sleep inertia*.

Over the last decades, the concept of *local sleep* has enhanced the understanding of how the brain sleeps. Both human and animal studies (Krueger et al., 2019) show a distinct connection between the amount (and magnitude) of NREM sleep like electric activity in neuroanatomical structures engaged in tasks performed before sleep. This illustrates a bottom-up process where local sleep is initiated based on the need for recovery in the area in question.

The necessity of sleep

It is common knowledge that humans sleep approximately one-third of their lifespan and the related question is why? Current literature is evident that there are multiple answers to that question and some of the answers are still not known. One aspect that has gained attention in recent years is that the brain needs to clear out metabolic by-products in order to maintain its health and functions (Xie et al., 2013). It has been shown in mice that the interstitial space of the cortex increases by 60 % during sleep, resulting in an increased convective exchange of cerebrospinal fluid and clearance of β -amyloid, a protein involved in Alzheimer's disease. Levels of tau (a protein also involved in Alzheimer's disease) in mice's interstitial fluid follow the sleep-wake cycle and levels of tau in cerebrospinal fluid are increased by sleep deprivation in humans (Holth et al., 2019).

Other animal studies have shown that sleep is essential, not only for the brain but also for several vital body functions (Everson et al., 2014). After ten days of total sleep deprivation, negative effects of oxidative stress have been demonstrated in tissue forms e.g., heart, lung, liver, and gut. These changes were normalized after recovery sleep. The same group has also shown immune

suppression and bacterial growth in the gut lymphatic system as a result of sleep deprivation. (Everson and Toth, 2000). Further, studies on fruit flies have shown a gradual increase of oxidative stress in the gut, but not in other organs studied, with possible lethal outcome after ten days of total “sleep-restriction” (Vaccaro et al., 2020). Again, this effect was reversible if recovery sleep was allowed in time. Notably, flies that had been exposed to total sleep restriction for an extensive period were vulnerable to further sleep restriction over two-weeks period of recovery.

Since this kind of lethal experiments, are probably unethical in humans, the nearest data comes from natural studies of the genetically inheritable disorder *fatal familial insomnia* (FFI). The disorder affects regions of the thalamus and is characterized by the inability to initiate physiological sleep, affecting both REM and NREM (Llorens et al., 2017). FFI also disrupts other homeostatic processes such as temperature regulation, endocrine fluctuations, and cardiac activity. Typically, death occurs within a year from the onset, which usually happens during adulthood (Krasnianski et al., 2008).

Memory consolidation

Memory consolidation is the process in which information is moved from recent and labile representation to more stable storage in long-term memory (Diekelmann and Born, 2010). This takes place by re-activation of memories so that they can be integrated with pre-existing information. Encoding and retrieval of memories take place in an awake state, but consolidation seems to require sleep. Memory consolidation is achieved during all sleep stages, but declarative, procedural, and emotional memories are affected differentially depending on in what stage sleep is interrupted. REM sleep seems to be more important to the consolidation of procedural and emotional memories, whereas N3 (formerly slow-wave sleep) plays an important role in the consolidation of declarative memories. However, there is evidence suggesting that it is the interplay between N3 and REM that is most important for both declarative and non-declarative memories.

In an awake state, memories are encoded in parallel in temporary (fast-learning) and long-term (slow-learning) storage. During sleep, temporary memories are re-activated and repeated. Meanwhile, the same representations are re-activated, and integrated with pre-existing knowledge, in the long-term storage. Further, synaptic downscaling takes place during N3. This is a global decrease in neural connections, with the purpose to weed out weak connections and prevent saturation of synaptic networks, preparing the brain for new encoding during future wakefulness.

The two-factor model

Although sleep and wakefulness are influenced by several factors, the two-factor model presented by (Borbély, 1982) constitutes a useful theoretical viewpoint in behavioral sciences. The first factor is called *the homeostatic sleep factor*, *sleep propensity* or *process S*. Process S increases during wakefulness and decreases exponentially during sleep. It can be expressed by the amount of slow-wave activity (SWA) measured by electroencephalography (EEG) during the night and increasing theta activity in wakefulness (Borbely et al., 2016) and has been linked to adenosine levels in the central nervous system (CNS) (Landolt, 2008, Porkka-Heiskanen and Kalinchuk, 2011). Hence, sleep deprivation leads to an increased amount of SWA besides prolonged sleep-time.

The other factor in the model is the *circadian factor* or *process C* which is controlled by light and other *zeitgebers* (environmental time cues). Process C can be expressed by levels of melatonin in the CNS and by shifts in core body temperature over the day (approximately 24 h). When properly synchronized, both process C and process S facilitate sleep in the evening and awakening in the morning as they decline throughout the night. Although, a misalignment between process C and the external environment can result in a circadian rhythm sleep disorder such as delayed sleep phase disorder, shift work disorder, or jet lag disorder (Bjorvatn and Pallesen, 2009).

Circadian oscillations have also been demonstrated in a large variety of cell types outside the CNS (Gallego and Virshup, 2007). These oscillations are synchronized by a “central clock” i.e., the *suprachiasmatic nucleus*, which is dependent on the shift in light and darkness detected by ganglion cells in the retina of the eye. These shifts in organ-specific cells influence strictly speaking all vital functions in the human body and keep an approximate circadian pace even when detached from the central clock. This is due to an “internal clock” in every cell that is dependent on the delayed negative-feedback loop of several proteins (CLOCK, PER, CRY, and BMAL1). The “peripheral clocks” are synchronized by the “central clock” via oscillations in hormones and neurotransmitters (Palada et al., 2020).

Insomnia disorder

As with chronic pain, it has been argued that insomnia is a disorder in its own right rather than a symptom or consequence of other mental or somatic conditions. The diagnoses of primary and secondary insomnia were displaced together with the criteria of nonrestorative sleep in the latest revision of the diagnostic and statistical manual of mental disorders (2013). Insomnia disorder is characterized by longer sleep latency, frequent and/or early morning awakenings. This despite good conditions for sleep, results in some sort of daytime

impairment such as fatigue, decreased energy, mood disturbances, impaired attention, concentration, or memory. Insomnia can be either episodic, persistent or recurrent. There is no criterion for objective sleep length and the diagnose is based on subjective dissatisfaction with sleep quality and/or duration. However, it can be adequate to separate those with normal sleep duration from those with short sleep (<6 h), since the latter group has more severe health effects (Morin et al., 2015).

Insomnia disorder is highly prevalent and international epidemiological studies estimate the prevalence in adults to about 10 % based on DSM-IV criteria (Morin et al., 2015). The same rate has been also reported in Swedish data (SBU, 2010). However, insomnia symptoms or sub-clinical sleep complaints are much more common. Percentages vary considerably depending on the criteria used. There is also a significant effect of sex, age, and level of education (Sivertsen et al., 2009).

The development of persistent insomnia can be seen as the result of predisposing, precipitating, and perpetuating factors (Spielman et al., 1987). Predisposing factors, or risk factors, can be personality traits such as neuroticism (emotional instability) or genetic/social such as a family history of insomnia. Precipitating factors, or triggers, are linked to the onset of insomnia e.g., stressful life events that result in emotional distress or onset of acute pain. Perpetuating factors, such as dysfunctional coping strategies or worry about sleep, can make insomnia disorder last even when the initial trigger no longer is present. An example of a dysfunctional coping strategy in response to is excessive daytime symptoms is napping. Napping can give temporary relief but prevent the homeostatic sleep drive from compensating properly for accumulated sleep loss during the night.

Psychological factors affecting both sleep and pain

There are findings of a reciprocal relationship between insomnia disorder and psychological factors i.e., anxiety and depression (Jansson-Fröjmark and Lindblom, 2008, Sivertsen et al., 2012). This means that longitudinal studies have shown that the presence of anxiety or depression at the first data collection increases the risk of reporting insomnia after a certain period (usually years later) in patients that did not suffer from insomnia at baseline. And, that insomnia at baseline increases the risk for onset of psychological symptoms at follow-up.

Psychological symptoms are overrepresented in chronic pain patients and cross sectional data show that levels of anxiety and depression increases as pain spreading of pain does (Gerdle et al., 2021). Psychological risk factors are linked to the onset of back and neck pain as well as the transition from acute to chronic

pain (Linton, 2000). There is a substantial literature on prognostic effect of depression, anxiety, stress/distress and overt pain behaviours. Also, catastrophizing is an aggravating factor in both depression and chronic pain (Linton et al., 2011). Further, the implementation of DSM-5 criteria for insomnia disorder (removing nonrestorative sleep as diagnostic criterium) has led to an even higher occurrence of anxiety and depression in persons suffering from insomnia disorder (Olufsen et al., 2020).

Transdiagnostic factors

The term transdiagnostic factors can refer several to several psychological processes that drive psychopathology, but also treatment. Affected sleep is part of the clinical picture and diagnostic criteria for both major depressive disorder and several anxiety disorders (Herlofson, 2014). This overlap between diagnostic criteria and the high co-occurrence, together with the involvement of insomnia in onset, relapse, and maintenance of several disorders has led to an increased interest in transdiagnostic perspectives on common mechanisms and treatment processes (Harvey, 2008). It is possible that there are common underlying causes resulting in both insomnia and other conditions. It is also possible that insomnia is a transdiagnostic factor in itself, causing or aggravating other conditions (even chronic pain) potentially through impaired emotional regulation (Harvey, 2008, Hamilton et al., 2007).

Another transdiagnostic factor is the sleep interfering effect of anxiety and stress (Dahl, 1996). Vigilance towards potential threats and shallow sleep has been an adaptive ability in the past and surely is in certain contexts today. Many people live with increased stress and anxiety without present or potential threats, making this ability to adapt rather maladaptive. Unfortunately, this leads to even worse emotional regulation.

Even though different forms of comorbid insomnia have unique precipitating factors, they can share perpetuating factors that are transdiagnostic. From this perspective it is expected that treatments targeting this perpetuating factors are effective irrespectively of their aetiology (Geiger-Brown et al., 2015).

The interaction between sleep and pain

Above I have discussed pain and sleep distinctively but now I will delve into how they affect each other. First, do patients with chronic pain conditions have abnormal sleep? The short answer is yes, most of them have. But the alterations reported in polysomnographic studies do not show any clear or diagnose-specific pattern (Bjurstrom and Irwin, 2015). Neither does self-reports measures (Lavigne et al., 2011). Rather, there were no significant differences in sleep architecture between a mixed group of chronic pain patients and pain-free

controls with chronic insomnia (Schneider-Helmert et al., 2001). The authors conclude that there is no support for the notion that insomnia symptoms in chronic pain patients are caused by night-time pain sensations, at least not in the chronic stage of insomnia that is mainly driven by perpetuating factors. To conclude, the characteristics of insomnia in chronic pain patients are essentially like insomnia disorder in general, possibly with the exception that patients with insomnia and chronic pain tend to worry less than patients with insomnia disorder alone (Tang et al., 2012b).

Given that up to 89 % of patients seeking specialized care for chronic pain also report sleep complaints (McCracken and Iverson, 2002), and that up to 50 % of people with insomnia report chronic pain (Ohayon, 2005, Taylor et al., 2007), addresses the question of which comes first, the chicken or the egg. In a review of longitudinal trials, Smith and Haythornthwaite (2004) suggest a reciprocal relationship between pain (acute and chronic) and sleeping problems. Though, this view is challenged by a more recent review by Finan et al. (2013) who conclude that sleep problems rather predict and worsen chronic pain than the other way around. Also, there is some evidence that restorative sleep predicts the resolution of chronic pain (Davies et al., 2008).

Sleep and pain perception share some fundamental aspects. Except for the circadian rhythm in sleep described above, there are circadian oscillations in pain intensity in many pain conditions (Palada et al., 2020, Bruguerolle and Labrecque, 2007) Also, several proteins and neurotransmitters involved in the regulation of sleep are highly involved in nociception. Further, there is a significant overlap between the neuroanatomical structures involved in pain perception and sleep (Harvey and Dickenson, 2010). Both conditions are also more prevalent in women (Sivertsen et al., 2009, Gerdle et al., 2004) the elderly (Finan et al., 2013, Schofield, 2018), and low-income groups (Gerdle et al., 2004, SBU, 2010).

Knowledge gap

There is extensive literature about insomnia disorder, chronic pain, and their risk factors and comorbidities. Less is known about the interrelation between these risk factors and comorbidities. Given the overlapping criteria of comorbid symptom diagnosis and the overlap of psychosocial risk factors (Karran et al., 2020) there are a problem with intercorrelation between covariates in many statistical models. Therefore, there is room for further research as well as the need for other statistical approaches to explore the relationship between insomnia symptoms, pain, and other aspects of health such as psychological and social factors.

One possible alternative can be found in the nearby field of proteomics. That body of work typically includes hundreds of variables with a varying degree of covariance. For this reason, specialized software (SIMCA) and methodology have been developed to investigate large datasets and to deal with extensive covariance between variables i.e., Principal Component Analysis (PCA) and Partial Least Square (PLS) regression. The results give clusters of variables with high intercorrelation and a hierarchy of variables that influence (Variables Influence on Projection; VIP) the Y-variable in the regression model.

The prevalence rates of insomnia symptoms in chronic pain patients vary greatly and many studies rely on single questions (yes/no) or questions about the frequency of sleep complaints. Therefore, refined methods of measuring self-measuring with a validated sleep scale such as the Insomnia Severity Index would not only standardize and validate the measurement of insomnia symptoms, but would also variegate the results and give the possibility to stage subjects by the degree of insomnia symptoms. Epidemiological studies investigating insomnia symptoms as a risk factor would also benefit from such a division, enabling the study of dose-dependent effects that would strengthen the evidence for a causal relation between insomnia symptoms and the development of chronic widespread pain.

Many studies in this field of research come up with a call for cost-effective, accessible, non-pharmacological treatment of insomnia symptoms for patients experiencing pain. Several studies have shown that Cognitive Behavioral Therapy for Insomnia (CBTi) is effective in this group of patients (Tang et al., 2015, Selvanathan et al., 2021), but the availability of therapist educated in CBTi is very limited, and treatment is rather time-consuming. One solution could be the “stepped care” approach presented by (Espie, 2009). He presents a hierarchy of interventions from self-help to sleep specialists where patients are referred depending on initial assessment. To implement such an idea, it is important to evaluate the effect on insomnia symptoms achieved by common interventions in the usual care of chronic pain such as physical exercise and psychological interventions. Although physical exercise is a well-established treatment for several chronic pain conditions, the use of ACT-based stress management (ACT-bsm) is not. Nevertheless, it has been implemented in different Swedish care settings. Further, the effects of physical exercise and ACT-based stress management on insomnia symptoms in chronic pain patients are unknown. When the work with this thesis was initiated in 2015, the only published study on the effect of physical exercise on insomnia symptoms comorbid to chronic pain was Eadie et al. (2013).

Besides, when treatment as usual is not enough there is a need for interventions directed towards insomnia symptoms per se. Internet-delivered CBTi (ICBT-i) has proven effective for insomnia disorder in general (Blom et al., 2015b), but it has not been evaluated in chronic pain patients. Given this background, the aims of this thesis are:

- To map clusters of comorbidities linked to insomnia symptoms in chronic pain (**Study I**).
- To analyse the distribution of insomnia severity in patients seeking specialized care for chronic pain (**Study I**).
- To evaluate the effect of physical exercise and ACT-based stress management on insomnia symptoms, in patients with chronic pain (**Study II**).
- To investigate the role of insomnia severity as a risk factor for spreading of pre-existing pain (**Study III**).
- To evaluate the effect of brief ICBT-i in patients seeking specialized care for chronic pain, compared to an active control condition (**Study IV**).

SUBJECTS AND METHODS

Subjects

The majority of participants in all four studies are women (59.5-83.3 %; Table 1). In Study I, all data is collected retrieved from SQRP concerning patients (n=845) referred to the Pain and rehabilitation Centre, University hospital, Linköping, Sweden in 2010 i.e., patients in specialized pain care and an average pain duration of 2954 days.

Subjects in Study II (randomized n=299) were recruited from different sources. Initially medical records of former patients in specialized pain care were screened. Those with chronic back and/or neck pain were sent a postal initiation. Thereafter, advertisement in the local newspaper was used to recruit more patients with chronic back and/or neck pain. An additional group (12 subjects) were referred from another study.

The dataset in Study III was collected by Statistics Sweden. The sample was stratified to represent the general adult population (16-85 years) in south-eastern Sweden. 9 000 surveys were sent to screen for pain conditions. 4 774 (53 %) surveys were returned. An additional extended survey was sent to 2 983 (62.5 %) who reported pain during the last seven days. 1 939 surveys (65.0 %) were returned. 1 485 answered the two-year follow-up. Those who answered all three surveys and reported relatively localized pain at baseline constituted the study sample in Study III (n=959).

SQRP was also used for recruitment in Study IV. Former and current patients aged 18-65 years, with an initial ISI-score of > 14 were invited by mail or by their physician. Those who volunteered and registered online were also called for a telephone interview to ensure insomnia diagnose and check for inclusion and exclusion criteria. In total 54 subjects were randomized to either ICBT-i or Applied Relaxation.

Self-reported symptom measures

Self-report measures are the primary source of data in psychological research and behavioral medicine. Validated measures exist for a wide range of symptoms and diagnoses. These can be put together into surveys that cover several aspects of health and disease. Which to use depends on many aspects such as

length, overlap with other measures, psychometric properties, and use in previous studies etcetera. The development of new forms makes constant progress and therefore, every researcher must question their habitual use of forms when designing a new study. A selection of the most important self-reported symptom measures included in this thesis is described in detail below. Table 1 also provides a full description of methods used per study. Additional measures are described in the respective studies.

Insomnia symptoms

In the literature on sleep and chronic pain researchers have chosen to define and assess sleep disturbances in different ways. In epidemiological studies, single questions are quite common (Mundal et al., 2014, Mork and Nilsen, 2012) whereas treatment studies often rely on different sleep scales such as the Insomnia Symptom Questionnaire (Edinger et al., 2005), Pittsburgh Sleep Quality Index (PSQI) (Martinez et al., 2013, Currie et al., 2000) or Insomnia Severity Index (ISI) (Jungquist et al., 2012). Alsaadi et al. (2013) evaluated PSQI, ISI, Epworth Sleepiness Scale, and a single question regarding sleep from the Roland and Morris Disability Questionnaire in a population of low back pain patients (acute and chronic). Their results support the use of PSQI and ISI to detect insomnia in this population and conclude that neither daytime sleepiness nor a single question about disrupted sleep, is enough to detect probable insomnia diagnosis. Our group has evaluated the psychometric properties of the Swedish version of ISI with data from the Swedish Quality Registry for Pain Rehabilitation (SQRP) (Dragioti et al., 2015).

Some features are evident when comparing PSQI and ISI. First, the ISI is shorter than the PSQI. A brief format is especially important when sleep is monitored multiple times throughout treatment. Second, the PSQI contains an item regarding the frequency of pain interfering with sleep, that can contribute to a problematic overlap with other variables in studies covering both pain and sleep.

Sleep diary

In study IV, ISI was supplemented by a sleep diary to calculate sleep parameters (Sleep Onset Latency [SOL], Waketime After Sleep Onset [WASO], Early Morning Awakenings [EMA], and Total Sleep Time [TST]) based on the recommendations for a standard research assessment of insomnia (Buysse et al., 2006).

Table 1. Brief characteristics of the four studies including instruments used.

	Study I (SQRP)	Study II (FACTA)	Study III (SwePain)	Study IV (SoV-study)
Design	Cross-sectional	RCT (3 armed)	Longitudinal cohort	RCT (2 armed)
Intervention	-	ACT-bsm Physical exercise	-	ICBT-i
Control condition	-	Non-specific factors component control (CON)	-	Specific factors component control (AR)
Number of participants (female)	845 (67.8 %)	299 (65.2 %)	959 (59.5 %)	54 (83.3 %)
Main outcome, time of assessment	-	Baseline, post, 6 mo, 12 mo	Baseline, 24 mo	Baseline, w1, w2, w3, w4, w5, 6 mo
Instruments used				
Sleep	ISI	ISI	ISI	ISI, Sleep diary
Pain	Pain intensity last 7 days (NRS) No. of pain regions Pain duration Persistent pain duration	Pain intensity last 7 days (NRS)	Pain intensity last 7 days (NRS) 4 categories of spreading of pain	Pain intensity last 7 days (NRS)
Psychological measures	HADS-A HADS-D	HADS-A HADS-D	GWBS Tension-Anxiety GWBS Depression PCS	GAD-7 PHQ-9
Health	EQ-5D SF36	-	-	EQ-5D VAS
Function	MPI	-	-	PDI

Notes: AR = Applied Relaxation, ACT-bsm = Acceptance and Commitment Therapy-based stress management, CON = Controls, EQ-5D = EuroQol 5 dimensions, FACTA = Fysisk träning, Acceptance and Commitment Therapy & Aktiv kontrollgrupp (Physical exercises, Acceptance and Commitment Therapy & Active control group) GWBS = General Well-Being Schedule, HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale, HADS-D = Hospital Anxiety and Depression Scale – Depression subscale, ICBT-i = Internet administrated Cognitive Behavioral Therapy for Insomnia, MPI = Multidimensional Pain Inventory, PCS = Pain Catastrophizing Scale, PDI = Pain Disability Index, RCT = Randomized Controlled Trial, SF36 = Short Form Health Survey, SoV-studien = Sömn och Värk-studien (Sleep and Pain Study), SQRP = Swedish Quality Registry for Pain rehabilitation, VAS = Visual Analog Scale.

Symptoms of anxiety and depression in study I, II, III and IV

Three different measures of anxiety and three different measures of depression have been used in this thesis. The Hospital Anxiety and Depression Scale (HADS) was used in studies I and II, the General Well-Being Schedule (GWBS) was used in study III, and the Generalised Anxiety Disorder 7-item scale (GAD-7) and the Patient Health Questionnaire (PHQ-9), was used in study IV. Hopefully, this diversity of measures is an expression of progress in psychometrics but also an expression of progress achieved by postgraduate education.

Although frequently used for almost 40 years, the HADS has demonstrated several shortcomings. Despite two separate subscales for anxiety and depression, CFA has shown a three-factor solution (Coyne and van Sonderen, 2012). The construction of items and answers has also received critic for its excessive focus on anhedonia and inconsistent predefined answers. Further, both subscales of the HADS have demonstrated deficient sensitivity of changes in subjects with chronic pain (Angst et al., 2008). After analysing SGRP-data from 35 545 subjects, Lo Martire et al. (2019) argue for a general emotional distress factor rather than the division into the anxiety and depression subscales.

Generally, there is a lack of literature about the psychometric properties of the GWBS subscales Tension-Anxiety and Depression. The only identified study on subjects with pain was on ankylosing spondylitis (Wang et al., 2016) reporting excellent internal consistency of the full GWBS. The use of this general well-being instrument to assess anxiety and depression is problematic for more reasons than one. First, it is not known whether the subscales correspond to actual depressive or anxious symptoms. Second, results from unusual instruments are harder to interpret and compare to other studies in this field of research. The decision to include GWBS in **Study III** was based upon a copyright issue regarding another health measure and avoid getting subjects to fill in multiple measures on anxiety and depressive symptoms.

In study IV, the choice fell on GAD-7 (measuring anxiety) and PHQ-9 (measuring depression). These scales are developed by the same researchers (Kroenke et al., 2001, Spitzer et al., 2006) and have been widely used in psychological research in recent years. Both measures are brief compared to their relative competitors and have proven convincing psychometric properties. PHQ-9 was found to correlate strongly with the Beck Depression Inventory-II and the Montgomery Åsberg Depression Rating Scale (Hawley et al., 2013) and in one comparing study, PHQ-9 was found to perform even better than the other two (Pettersson et al., 2015). The total scores correspond well to a general factor for each scale and are suitable for repeated measurements in longitudinal trials (Stochl et al., 2020).

Pain

In all four studies, an eleven-point numeric rating scale was used to assess the average pain intensity concerning the last seven days. In acute pain, this measure has shown to be more sensitive to changes than scales with fewer points and is recommended as part of a more holistic assessment in chronic pain (Breivik et al., 2008). Asking about an average from the last week can induce a recall bias, and ratings can be affected by contextual factors. Nevertheless, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends the use of a weekly average NRS in proper study designs (Dworkin et al., 2005).

Spread of pain

In studies I and IV, the number of anatomical areas was used as a continuous variable to measure the spread of pain. Subjects were presented to a list of 36 anatomical areas and were asked to tick the option(s) corresponding to their pain experience. In study III, four categories were defined to mirror clinical subgroups, taking localization into account (e.g., axial pain to specify chronic widespread pain). Subjects were presented to two manikins (Fig. 1) with 45 numbered anatomical areas (Margolis et al., 1986). They were asked to tick the numbers corresponding to their pain experience in a list. Areas corresponding to the same anatomical structure (i.e., front, and backside of the left lower leg) were collapsed so that one or two positive answers (front or/and back) indicated pain in that structure. This gave an index ranging from 0-23. The first category, denoted local pain, contains subjects reporting one or two painful areas. Moderate regional pain contains subjects reporting three to six areas, substantial regional pain contains subjects reporting seven-17 areas, and widespread pain contains subjects reporting at least two areas in two collateral limbs and axial pain reported at the front, as well as the backside, of the manikin. This definition of widespread pain is more strict than the one used by MacFarlane et al. (1996). The use of categories allows for the study of risk ratios by generalized linear models.

Figure 1. To the left, the manikin as showed to subjects in study III. To the right, anatomical regions as merged in the analysis in study III.

Interventions

Study II and IV are intervention studies. Study II evaluates physical exercise and Acceptance and Commitment Therapy (ACT) based stress management. Study IV evaluates Internet administrated Cognitive Behavioral Therapy for Insomnia (ICBT-i). The interventions and their control conditions are briefly reviewed below.

ACT-based stress management (ACT-bsm) in study II

Study IV aimed to evaluate ACT-based stress management (ACT-bsm) and its effect on insomnia symptoms in subjects with chronic pain. The stress management intervention was originally developed by Flaxman and co-workers as a workplace intervention targeting the therapeutic processes in ACT (e.g. cognitive flexibility) aiming to create “mindful and effective employees” (Flaxman et al., 2013).

The Swedish version was further developed by Livheim. When the study was designed, the ACT-bsm was marketed as a promising intervention for numerous conditions including chronic pain. About that time, conceptual publications on the role of cognitive flexibility in primary insomnia had started to emerge in the literature (Ong et al., 2012, Lundh, 2005) and even for insomnia in patients with chronic pain (McCracken et al., 2011). Learning new flexible ways to deal with discomforts such as pain, stress, thoughts, and feelings was an overall purpose of the intervention. In contrast to relaxation, the aim is not to lower arousal per se, but it might as well be the consequence.

Physical exercise in study II

A recent systematic review (Wang and Boros, 2019) supported the beneficial effects of physical exercise on sleep quality in healthy subjects. They conclude that exercise of moderate intensity seems to have the largest impact on sleep quality. The effect of physical exercise on subjects with insomnia disorder (or insomnia symptoms) also demonstrates beneficial effects (Lowe et al., 2019), primary in subjects with insomnia disorder and on subjective measures (ISI and PSQI). However, the number of available studies is very limited and there are considerable methodological shortcomings. Looking at studies evaluating the effect of physical exercise insomnia disorder or insomnia symptoms in chronic pain patients restricts the literature even more. Two separate studies were identified at the beginning of the year 2021 (Eadie et al., 2013, Roseen et al., 2020). Both studies are on low back pain and physical exercise does not perform better than the control condition on subjective measures (ISI and/or PSQI) in any of the two studies. According to the definition by Gold et al. (2017), physical exercise in study II is an active comparator to ACT-based stress management.

Non-specific factors component control in study II

The control condition (CON) in study II was designed to control for assessment, attention from the therapist, time spent, and treatment group participation. No exercises or techniques regarded as therapeutic were included. The group was moderated by a medical student, psychologist student, research nurse, or licensed psychologist instructed to facilitate discussion but not to intervene. Sessions had proposed topics e.g., pain affecting work, leisure, and relationships, experiences of social insurance, employment services, and health care. Participants were free to choose from these or to come up with own topics. Gold et al. (2017) nominated this as a “*non-specific factors component control*” that can be expected to have some efficacy of its own and thereby affecting the effect sizes in a randomized controlled trial like study II.

Internet-delivered Cognitive Behavioral Therapy for Insomnia (ICBT-i) in study IV

Both the European guideline for the diagnosis and treatment of insomnia (Riemann et al., 2017) and the American Academy of Sleep Medicine (Schutte-Rodin et al., 2008) recommend Cognitive Behavioral Therapy as the first-line intervention for chronic and comorbid insomnia. In a previous publication (not included in this thesis) (Blom et al., 2015b), we showed that internet-delivered CBT-i led to outcomes comparable with CBT-i delivered as face-to-face group treatment. However, at the planning of this study ICBT-i had never been evaluated in patients with chronic pain. Therefore, a new ICBT-i treatment was developed with some adaptations to this clinical patient group. The number of sessions was reduced to five based on unpublished data from the Blom et al. (2015b) study indicating that SOL was the shortest after five weeks of treatment

and then increased slightly the during the last weeks of treatment. Later results from the meta-analysis by van Straten et al. (2018) show that treatments longer than 4 sessions have larger treatment effects on SOL, SE, and ISI. Text length was also kept to a minimum. No session contains more than two A4 sheets of text and all texts are also available as YouTube clips with a PowerPoint presentation and a speaker's voice. Session four, concerning daytime activity, was adapted so that it would not exacerbate pain through excessive effort (Andrews et al., 2014). The main focus was on sleep restriction and stimulus control. Because of the short format, several common CBT-i components were left out (Baglioni et al., 2019). Since therapist support has shown to increase the efficacy of internet treatments in depression (Andersson and Cuijpers, 2009), therapist support was offered every week with no restriction to amount and content. The efficacy of CBT-i on cohorts with chronic pain has been shown in several studies (Tang et al., 2015, Selvanathan et al., 2021). The novelty of study IV is the use of the internet to assess and treat insomnia in this population.

Applied relaxation (AR) in study IV

Relaxation is a common component in CBT-i (Riemann et al., 2017) with large acute effect sizes on SOL as a “stand-alone treatment” for insomnia disorder (van Straten et al., 2018). AR was used as an active control condition in study IV since it meets the criteria for a *specific factors component control* formulated by Gold et al. (2017). The aim is to provide the same expectations, assessment, attention/support from the therapist, time spent, and non-specific treatment factors. Expectations and satisfaction treatment was assessed multiple times, during treatment and follow-up. Also, the AR group used the responsive sleep diary that could be a potent part of assessment/measurement. AR was presented to subjects as one out of two treatments in a comparative trial (comparing AR and CBTi).

Statistics

The diversity of design and data in this thesis requires the use of different statistical methods. Statistics is a field of research of its own making constant progress. New applications gain spread in the scientific community over time. This chapter will give a short introduction to some of the methods used in this thesis and to some degree contrast them with older methods.

Generalized linear models (GLM)

GLM is a generalization of general linear regression that enables the application of different distribution functions besides the Gaussian (Nelder and Wedderburn, 1972). As a result, GLM can handle binary, discrete, and continuous outcomes. In study III, GLM (for the binominal family) was used to modulate relative risks (RRs). Compared to odds ratios received by logistic regression,

RRs are easier to interpret and not miss leading when outcomes are common. Also, GLM has the advantage that it handles missing data (McCullagh and Nelder, 1989).

Principal component analysis (PCA)

PCA is a multivariate correlation analysis used in the study I to explore the interdependence between variables from the SQRP. For this purpose, the software SIMCA-P+ was used (Eriksson, 2006). Latent nontrivial components were identified by cross-validation. The identified components contrast each other and are therefore not correlated. SQRP-variables with high (positive or negative) loadings on the same component are (positively or negatively) correlated. Accordingly, variables close to origin are not. In other words, PCA reduces the complexity of multidimensional data (and can be interpreted as a multivariate correlation analysis) and may present two (or several) latent variables (principal components) that need to be interpreted based on the variables with the highest loadings.

Orthogonal partial least square (OPLS) regression

OPLS is a multivariate regression analysis and can be used to regress observed variables (Eriksson, 2006). It was used in the study I to assess the SQRP-variables with the greatest impact on insomnia symptoms and perceived health. In contrast to multiple linear regression as implemented in traditional statistical programs e.g., SPSS, OPLS does not assume independence (low correlations) between regressors and handles missing data. The importance of the regressors (x-variables) is expressed by the Variable Influence on Projection (VIP) value. VIP-values > 1 are considered as significant.

Linear mixed models (LMM)

LMM is a form of multi-level analysis controlling for the correlation between repeated observations within the subject (Twisk et al., 2013). Each subject is allowed to have their own mean value over time and a random intercept as well. It is also possible to modulate a unique β -coefficient for each subject by allowing a random slope. Thus, LMM can include both fixed and random effects.

On the second level, it is possible to add contextual variables, such as treatment condition or cohort, into the analysis (Field, 2018). Then, individual differences are handled on the first level and group differences are modulated at the second. In LMM different co-variance structures can be applied based on the structure of the data. Building a LMM is an iterative process to improve model fit (expressed by the $-2 \log$ -likelihood value). Another advantage with LMM in longitudinal studies is that LMM can handle missing data and does not require imputation procedures (Twisk et al., 2013).

Intention-to-treat (ITT) analysis

Randomized controlled trials are struggling with compliance and missed measurements. One way of dealing with this is the principles of ITT (Gupta, 2011), or the saying “ones randomized, always analyzed”. The risk with other procedures, i.e., analyzing an ad hoc selection of subjects, is the potential bias that can affect the results. ITT analysis has several other advantages. The inclusion of all available subjects helps to maintain sample size and thereby statistical power. Further, the generalizability of results is increased when a treatment's “true” drop-out rate is reflected in the analysis.

However, an ITT approach can be problematic when subjects receiving no, or minimal treatment is included in the evaluation of that treatment. In designs with waitlist control, that can even lead to contamination between study arms. Therefore, modified ITT approaches have been developed but given the lack of strict criteria, such as those for ITT, this may be a difficult approach. One could argue that different modified approaches are more suitable for studies assessing treatment components (where exposure to that specific component is essential) or novel treatments, whereas a strict ITT approach is required in effectiveness trials (where the effect of a treatment is evaluated in a regular care setting). However, modified ITT analyses were performed in study II whereas strict ITT analyses were performed in study IV.

RESULTS

The most important results, with respect to the aims formulated at the end of the introduction chapter, will be presented below. More outcomes, sample characteristics, and flowcharts etcetera are reported in each paper.

Study I

Study I - *Comorbid insomnia in patients with chronic pain: a study based on the Swedish quality registry for pain rehabilitation (SQRP)*, is based on cross-sectional data (n=845). The mean ISI-score was 16.3, mean pain duration was 2954 days, mean pain intensity (last seven days) was 7.2 on an eleven-point NRS, and the average subject reported 12.4 pain regions. The majority (67.8 %) of the sample were women. The prevalence of clinical insomnia (moderate and severe) according to the Insomnia Severity Index is 65.3 % in patients seeking specialized care for chronic pain (Fig. 2). Additionally, there is a group of 20.6 % reporting sub-threshold insomnia.

Figure 2. Distribution of insomnia symptoms in chronic pain patients. Categorization based on Insomnia Severity Index-scores (No insomnia 0-7 points, Sub-Threshold 8-14 points, Moderate 15-21 points, and Severe 22-28 points).

The OPLS regression shows (Fig. 3) that three variables reflecting psychological distress (Multidimensional Pain Inventory [MPI]-distress, HADS-Anxiety, and HADS-Depression) are the most influential on insomnia symptoms (ISI scores). Two other indexes from the MPI reflecting pain (MPI-pain interference and MPI-pain severity) were also significant regressors together with two measures of coping (Chronic pain acceptance questionnaire- engagement and MPI-Life control) that correlated negatively with insomnia symptoms.

Figure 3. Variable influence on projection (VIP) values obtained in the orthogonal partial least square (OPLS) regression of ISI (Y-variable) using different symptoms/parameters as regressors (X-variables). VIP > 1 is considered significant, and VIP between 0.8 and 1.0 is considered borderline significant: $R^2=0.23$ (goodness of fit) and $Q^2=0.22$ (goodness of prediction). The errors bars are jack-knife uncertainty bars.

In terms of conventional correlations the following parameters were significantly correlated with ISI-scores; Pain intensity last seven days ($r = 0.31$, $p < 0.001$); Number of pain regions ($r = 0.24$, $p < 0.001$); HADS – Anxiety ($r = 0.39$, $p < 0.001$); HADS – Depression ($r = 0.37$, $p < 0.001$); Chronic Pain Acceptance Questionnaire – Engagement ($r = -0.27$, $p < 0.001$); Chronic Pain Acceptance Questionnaire – Willingness ($r = -0.19$, $p < 0.001$); and Tampa scale of Kinesiophobia ($r = 0.22$, $p < 0.001$).

Study II

Study II - *Is sleep disturbance in patients with chronic pain affected by physical exercise or ACT-based stress management? – A randomized controlled study*, reports the outcomes at three time points (post-treatment, six-month follow-up, and one-year follow-up). Two hundred ninety-nine subjects (195 women) were recruited from three different sources (advertisements in the local newspaper, journal screening, and referral from another ongoing study). The effect sizes are compared to a non-specific factors component control (Gold et al., 2017). The physical exercise arm improved 2.31 points at the insomnia severity index over twelve months (Fig. 4). This corresponds with an effect size (d) of -0.25 (Lenhard and Lenhard, 2015) according to the modified ITT analysis performed. The acute effect (post-treatment) was somewhat larger with an effect size of $d = -0.32$, even though the improvement on ISI was smaller (1.85 points) because of a temporary increase of ISI-scores in the control condition. For ACT-bsm changes were not significant at any time point according to the modified ITT analysis.

Figure 4. ISI (mean) for each treatment arm (completers) before treatment (T₀), after treatment (T₁), after six months (T₂), and after twelve months (T₃). Note that Y-axis is not illustrated from zero.

There were comparable significant improvements in *average pain last seven days* in the exercise and the control condition at six and twelve months compared to baseline. However, at post-treatment there was a 1.24-point decrease on the numeric rating scale in the exercise group, corresponding to a medium effect size ($d = -0.46$) compared to the change in the control group. For ACT-

bsm changes in pain were not significant at any time point according to the modified ITT analysis.

Study III

Study III - *Insomnia is a risk factor for spreading of chronic pain: A Swedish longitudinal population study (SwePain)*, includes 959 subjects (571 women) with local pain or moderate regional pain. The mean age was 55.8 years, the mean pain intensity (last seven days) was 4.9 on an eleven-point NRS, and the average participant scored 14.2 on the Pain Catastrophizing Scale.

Throughout the study (from baseline to the 24-moth follow-up) 85 subjects developed severe regional pain or widespread pain. 23.1 % of subjects reporting severe insomnia symptoms at baseline developed severe regional pain or widespread pain. This corresponds to a risk ratio of 4.26 (95 % CI: 1.27-14.35) in the fully adjusted generalized linear model. 14.6 % of subjects reporting moderate insomnia symptoms at baseline developed severe regional pain or widespread pain (Figure 5). This corresponds to a risk ratio of 2.47 (95 % CI: 1.23-4.93) in the fully adjusted model. Subjects with sub-threshold insomnia symptoms (8-14 points on ISI) had no demonstrated increase in risk. Age over 45 years, female sex, and no university education all had risk ratios in the span 2.15-2.67 (Fig. 5). The strongest risk factor was having moderate regional pain at baseline (risk ratio = 6.95 compared to local pain).

Figure 5. Risk ratios and 95 % CI according to the fully adjusted model. CIs including 1 indicate no statistically significant increase in risk. Note that the x-axis is broken between risk ratios 8 and 14.

Study IV

Study IV - Internet-delivered cognitive behavioral therapy for insomnia comorbid with chronic pain – a randomized controlled trial, reports acute and long-term effects (six-month follow-up). Fifty-four subjects (45 women, mean age 48.2 years) with a mean ISI-score of 21.4 (SD = 3.3) were randomized to Internet-delivered Cognitive Behavioral Therapy for Insomnia (ICBT-i) or internet administrated Applied Relaxation (AR).

At baseline the sample report an average pain (last seven days) of 6.3 on an eleven-point NRS, 13.6 pain regions, and 67 % report pain duration > 5 years. After five weeks of treatment ISI-scores had declined 8.4 (SD = 4.7) in the ICBT-i group compared to 5.0 (SD = 5.4) in the AR (Fig. 6). The linear mixed model confirmed an interaction effect (time by treatment) which means that there is a 95 % probability that the difference in change rate between groups (post-treatment) is not caused by chance. That difference had ceased to exist after six months as the mean change scores had approached each other (ICBT-i: 6.7 [SD = 5.4], AR: 6.1 [SD 5.2]).

Several of the secondary outcomes (SOL, WASO, SE, and EMA) show a similar pattern i.e., significant acute effects and no long-term effects. The acute effect was significant when modelled as linear as well as quadratic for these four outcomes.

Another interesting finding in study IV was that 59 % of participants reported that the pain problem preceded the sleep problem. 15 % report that sleep preceded pain problems, 24 % report that they occurred simultaneously, and 2 % say that they don't know which came first (unpublished data).

Figure 6. Sleep measures for iCBT-i and applied relaxation (AR) respectively over time

Note: Mean scores for each treatment arm. Baseline (BL) data is only presented for ISI. Active treatment period is illustrated by dots and six-month follow-up (FU) data by diamonds. Note that Y-axes are not illustrated from zero.

DISCUSSION

This chapter summarizes the main findings of the four papers. Thereafter, some paragraphs discuss how the papers relate to one another and relevant literature. Lastly, there is an outlook for methodological challenges and future directions in this field of research.

Main findings

Study I highlighted the high prevalence rates of insomnia symptoms in patients with chronic pain conditions. Roughly, insomnia was six times more common in our sample compared to the general population. We also showed that there was a connection between ISI scores and other variables, primarily psychological symptoms, and pain intensity. Although extremely significant, the strength of the correlations was limited ($r = .22$ to $.39$). One subscale related to acceptance (CPAQ - Engagement) reoccurred as significant (negatively correlated with ISI) in the different analyses.

In **Study II** physical exercise was more efficacious than ACT-based stress management and the active control group in reducing insomnia symptoms and pain intensity short term. Improvements in physical exercise were largely maintained after twelve months but pain intensity had then also declined in the control group. No improvements in the ACT-based stress management remain significant when the intention to treat principles were applied.

In **Study III**, a dose-dependent increase in risk for spreading of pain was confirmed in subjects reporting moderate and severe insomnia symptoms. Though, there was no increase in the risk of pain spreading in subjects reporting sub-threshold insomnia symptoms (according to the Insomnia Severity Index).

In **Study IV** patients randomized to Internet-delivered Cognitive Behavioral Therapy for insomnia (ICBT-i) showed a more rapid improvement in insomnia symptoms than patients randomized to internet-delivered applied relaxation (AR). The effect of ICBT-i had declined slightly after six months and the AR-group had continued to improve, leading to the comparable outcome on the ISI at six-month follow-up.

The role of acceptance for insomnia symptoms

After all, acceptance is not one of the most important parameters related to insomnia symptoms. The regression model in **Study I** rank the regressors with respect to their influence on ISI scores. CPAQ – engagement is ranked seventh and touches the level of significance. In the light of these results, it is not surprising that the attempt to improve insomnia symptoms via an acceptance-based intervention in **Study II** failed. No matter how successful that intervention would be in fostering acceptance and engagement, it would have been hard to influence insomnia severity with correlations of that magnitude. Other researchers have also paid attention to the role of acceptance in insomnia and chronic pain (McCracken et al., 2011). Our findings largely confirm their findings of overall weak correlations between measures of pain-related acceptance and level of insomnia symptoms as measured by the ISI. Further, a network matrix analysis (Åkerblom et al., 2021) of a wide array of symptoms related to chronic pain indicates that acceptance plays a much more central role for other psychological measures than for insomnia symptoms. Insomnia symptoms, on the other hand, seem to relate more closely to the spreading of pain, pain intensity, and pain interference. Although there were high hopes and multiple conceptual publications on the role of acceptance and insomnia in the early 2000s (Lundh, 2005, Ong et al., 2012, McCracken et al., 2011), the revolutionary results on insomnia severity in treatment studies have been lacking so far (Salari et al., 2020). While acceptance-based treatment has some positive impact on insomnia symptoms, CBT-i outperforms (Geiger-Brown et al., 2015). Perhaps, acceptance has greater potential in conditions where effective treatments for symptom reduction are not available such as chronic pain (Veehof et al., 2016, Hughes et al., 2017).

The effect of physical exercise on sleep and pain

The results in **Study II** indicated that physical exercise is a salutogenic factor for both sleep and pain. The follow-up data suggest that the positive effects on sleep are relatively stable over time. Adding a guided physical exercise module to multi-component treatments such as ICBT-i could increase the effect through mechanisms that are not targeted in current treatments. That would require the development of a physiotherapist-led internet administered exercise intervention adapted to chronic pain. Such an intervention must be comprehensive enough with respect to pain intensity, frequency, and duration. If such an intervention was added, ICBT-i would no longer be a unimodal treatment since it requires two therapists (a psychologist and a physiotherapist). Perhaps the most efficient way of dealing with this would be to train physiotherapists in ICBT-i.

Although statistically significant effects of physical exercise, effect sizes on insomnia symptoms are not clinically significant. In **Study II** the immediate

effect was $d = 0.32$ and the effect of a full multimodal rehabilitation program (without correction for control group change) was $d = 0.49$ (Åkerblom et al., 2021). If physical exercise was added to ICBT-i together with other and probably more effective interventions, the additive effect on the final treatment outcome would probably be even less.

Treatment components in CBT-i and ICBT-i

Cognitive-behavioral therapies consist of a set of interventions and the combination of treatment content is occasionally a little arbitrary. The strive for optimal treatment must be compared to what can be achieved by minimal treatment. For example, a medium effect size on the ISI can be gained by a single CBT-i session (in combination with repeated sleep diaries) in patients with acute insomnia and varying degrees of comorbidities (Ellis et al., 2015). Every component added makes the treatment more laborious for both patients and caregivers. Nevertheless, a future gold standard treatment for insomnia symptoms comorbid to chronic pain should include components of different theoretical origins and with a diversity of effective mechanisms that have proven their usefulness as “stand-alone” treatments for pain and/or insomnia symptoms. A recent study (Blanken et al., 2021) on treatment specific effects confirmed that behavioral therapy and cognitive therapy for insomnia disorder affect different aspects of insomnia symptoms as measured by ISI. Also, a mediation analysis (Harvey et al., 2017) has shown that patients with higher symptom burden benefit from a combination of cognitive and behavioral interventions.

Although theoretically different, there is an overlap between different treatment components in terms of actual behavioral changes. For example, stimulus control when correctly applied will lead to a reduction of time in bed just as sleep restriction does. Likewise, a successful sleep restriction will lead to conditioning between the bedroom and sleep. Further, behavioral experiments in cognitive therapy, as implemented by Sunnhed and co-workers (Sunnhed et al., 2020), including to challenge negative automatic thoughts about what happens when not receiving enough sleep, which is reducing time in bed.

Earlier attempts on hybrid treatments have combined CBT-components from CBT for pain (physical activation, relaxation, activity pacing etcetera) and CBT-i (Vitiello et al., 2013, Pigeon et al., 2012, Tang et al., 2012a). However, a recent meta-analysis could not confirm the superiority of such an approach in reducing pain intensity (Selvanathan et al., 2021). Perhaps there is a divide here when designing new treatments, whether to develop the best insomnia treatment with or without chronic pain adaptations, or to develop the best multimodal rehabilitation program by including CBT-i/ICBT-i? There is a need for studies on both.

In addition to physical exercise, a future internet-delivered insomnia treatment could arguably include some sort of relaxation based on the long-term outcomes in **Study IV** and previous research (van Straten et al., 2018). Adding other pain-specific components should be done with some caution given the weak correlations reported in **Study I**, suggesting that indirect effects on insomnia severity are less likely. Also, insomnia symptoms comorbid to chronic pain are essentially similar to insomnia disorder (Tang et al., 2012b) and respond to regular CBT-i (Selvanathan et al., 2021). However, Tang and co-workers found that chronic pain patients with insomnia tend to worry less than patients with insomnia disorder. The benefit of cognitive interventions targeting worry and dysfunctional beliefs about sleep is therefore not obvious.

Based on a previous study (Andrews et al., 2014) we developed a treatment module to target activity modulation in **Study IV**. Based on the day-to-day (or day-to-night) effect of daytime activity on subsequent sleep described by Andrews et al., treatment content in our module problematizes both too much and too little daytime activity. The importance of time for unwinding in the evenings and daylight before noon is also highlighted. This treatment component has not been evaluated as a “stand-alone” treatment and might not be enough to offer an effect, just as advice about sleep hygiene (Tang, 2018). Again, the gains of adding more treatment content must outweigh the extra work done and this treatment module might not live up to that.

The ICBT-i treatment developed for **Study IV** was designed to be brief as this was one of the adaptations made for this burdened group of patients. Treatment content was shorter than seven A4pages (worksheets excluded). While short, sleep restriction is perceived as rather aversive to patients according to the free text answers collected at post-treatment and follow-up (unpublished). Given the rather immediate impact of sleep homeostasis, the “sleep window” must be applied continuously to maintain the treatment effect. If the gains in sleep quality etcetera are not reinforcing the maintenance of new bedtimes and the new habits are perceived as aversive, then there is an imminent risk that the behavioral change will be extinguished over time. The specific factor component control (AR) in **Study IV** may constitute a more appetitive approach on its own, although with slower onset of treatment effect. The results presented above indicate comparable outcomes on the ISI after six months. If these results are replicated, it could be up to the patient to decide the treatment approach according to preference.

Results in **Study III** points out insomnia symptoms as a risk factor for spreading of pre-existing pain, but there is no indication of a decrease in the Number of Pain Regions six months after treatment starts in our specialized care sample

in **Study IV**. Possibly, this is due to the short follow-up period or that treatment comes too late in the course of the disease. Previous findings (Davies et al., 2008) show that restorative sleep increases the chance of no longer fulfilling the criteria for chronic widespread pain fifteen months later. In the supplementary material attached to **Study III** can be seen that a significant amount of the participants moves to a category with less spread compared to baseline. Future studies should focus on these potentially modifiable risk/protective factors and experimentally manipulate them since it cannot be ruled out that they express an underlying factor that actually predicts the outcome.

Anxiety and depression

The link between affective disorders and chronic pain is constantly recurring in the literature. Anxiety and depression (as measured by HADS) were both significant regressors for ISI-scores in **Study I**. Although, when measured by the GWBS they were not significant risk factors for spreading of pain in **Study III**. The results in **Study III** are in line with the results in a study on almost 40 000 patients from the Swedish Quality Registry for Pain Rehabilitation (Gerdle et al., 2021), HADS-Anxiety and HADS-Depression did not play a central role in the spreading of pain in the OPLS regression model built on cross-sectional data. It is important to keep in mind that the diagnostic criteria for depression (2013) include a criterion regarding affected sleep. The same goes for anxiety (Generalized anxiety disorder and Posttraumatic stress disorder) resulting in a potential selection bias for the occurrence of insomnia symptoms as an outcome in epidemiological studies (Cole et al., 2010). Both PHQ-9 and GWBS include items regarding sleep/non-restorative sleep making the overlap even more pronounced.

In the RCTs (**Studies II and IV**) there are some time effects, but no time by treatment effects on anxiety and depression (GAD-7 and PHQ-9). This could be explained by regression to the mean but in the cases of **Study IV** (where the average participant had elevated scores on PHQ-9), previous studies have shown anti-depressive effects of insomnia treatment in patients with both insomnia and depression (Blom et al., 2015a). Noteworthy, that ICBT-i treatment included components of behavioral activation, scheduled worry time, and worry delay. A comparative study (Emery et al., 2014) on chronic pain patients with and without comorbid depression revealed no difference in sleep diary measures but greater pre-sleep arousal, more dysfunctional beliefs about sleep, and poorer sleep hygiene in those diagnosed with major depressive disorder. Based on these accentuated symptoms it could be argued to add treatment components e.g., applied relaxation and worry delay directed towards pre-sleep arousal, and cognitive interventions directed towards dysfunctional beliefs about sleep.

The most recent review and meta-analysis on CBT-i for chronic pain patients (Selvanathan et al., 2021) found immediate effects on depression but no long-term effects based on eight studies with a considerable diversity of treatment components included. The meta-analysis on anxiety included only four studies and could not confirm either short- or long-term effects of CBT-i. Given the studies above, it is fair to argue that the treatment effects occur on the outcomes that are related to the treatment components included (given that the symptom levels are high enough at baseline). The diversity in effect on secondary outcomes likely reflects the diversity in treatment components marketed as CBT-i or hybrid treatments.

Severe stress and psychological trauma are other factors closely linked to anxiety and depression. None of the studies included in this thesis monitored symptoms of posttraumatic stress disorder (PTSD) or exposure to negative life events. However, studies on the link between PTSD and chronic pain reveal that the occurrence of PTSD is associated with more severe pain, pain interference, and depressive symptoms (Åkerblom et al., 2018). These observed links between affective disorders and a worse clinical presentation of pain have also gained some support from an animal model for stress and pain (Singaravelu et al., 2021). Rats exposed to nerve growth factor and stressful treatment developed sensitization with lowered pain thresholds and increased spread receptive fields compared to controls (only receiving nerve growth factor). At least in part, this could illuminate the mechanisms behind the observed link between stress/trauma and worsening of pain intensity during the transition from acute to chronic pain (Young Casey et al., 2008). Perhaps, it can also explain the aggravating effect of depression, anxiety, and posttraumatic stress on pain (Beck and Clapp, 2011).

Transdiagnostic approaches

When comorbidities are pronounced transdiagnostic approaches have been suggested as a potential improvements of treatment (Harvey, 2008). If CBT-i is considered as such a transdiagnostic treatment it can constitute a compliment to other diagnose-specific treatments. An alternative view is that we should look for transdiagnostic factors that might improve insomnia symptoms and perhaps also chronic pain. In the light of the results from **Study II** (targeting psychological flexibility as a transdiagnostic factor), this seems as a more far-fetched approach. Although, physical exercise and applied relaxation might constitute such transdiagnostic treatments. Until there are convincing evidence that such transdiagnostic approaches are more effective than diagnose-specific treatments they should be considered as experimental treatments that can come into question when comorbidities hinders specific treatments that are evidence based.

Insomnia and other risk factors for spreading of pain

In addition to insomnia symptoms, four other risk factors were identified in **Study III**. The strongest was moderate regional pain at baseline i.e., more pain regions. The number of pain regions also constitutes a basis for the outcome variable, even though in a more severe form. Subjects who are close to the cut-off at baseline have a greater risk of ending up in a worse category. It would not be fair to argue that the outcome is a risk factor for itself and the addition of this variable to the fully adjusted model should rather be considered as an adjustment for this circumstance. The findings that age and female sex are risk factors for spreading of pain are not unexpected but unfortunately, they are not potential targets for interventions on an individual level. The doubled risk in those that lacking university education might be more possible to influence. Likely, this latter variable expresses latent risk factors such as working environment, economic inequality, and shift work, rather than an effect of academic achievements per se. If so, workplace adaptations and different working hours might reduce the influence of education level.

Baseline pain variables influence the risk for spreading of pain. In **Study III** pain intensity was significant with a risk ratio of 1.25 when added to the initial adjusted model. However, when baseline spreading of pain (moderate regional pain) was added in the fully adjusted model, the risk of pain intensity approached 1 and this variable was no longer significant. Although, more recent data from SwePain (Larsson et al., 2019) based on almost 4 000 subjects show that pain intensity, pain sensitivity, and pre-existing spread of pain all predict more spreading of pain over 24 months. As in **Study III**, Larsson et al. found female sex to be a significant risk factor for spreading of pain. Age and education level were no longer significant when baseline pain characteristics were added to their model. This highlights the importance of adjusting for baseline pain variables and having large enough sample sizes to detect risk ratios that are close to 1.

In pain, patient-reported outcomes measuring psychological and coping variables tend to be intercorrelated when assessed cross-sectionally (**Study I**) and some of them seem to have predictive value for the long-term outcome of pain (Larsson et al., 2019). Interestingly, when pain characteristics (certainly also patient-reported) are taken into consideration, the predictive value of the former is no longer significant. This is in line with the results of **Study III**, where anxiety, depression, and catastrophizing were not found as risk factors for spreading of pre-existing pain. There is no reason to doubt the presence of psychological variables and individual differences in coping ability, but their role in predicting spreading of pain is more uncertain.

The role of spreading of pain for other symptoms

Cross-sectional data illustrate that more spreading of pain is associated with more severe symptoms over all (Gerdle et al., 2021). The same applies for increasing insomnia symptoms as described in **Study I**. This phenomenon, that more severe symptoms are associated with having more severe symptoms over all is important to bear in mind when interpreting cross-sectional correlational studies and group differences. One way of dealing with this could be to develop an index of “overall symptom severity”. Quantifying general symptom burden enables to control for that variable, to make sub-group analysis of the most affected, and to set up longitudinal trials to investigate risk factors for ending up in the group with overall high symptoms.

Strengths and limitations

Strengths and limitations are addressed in each paper, but some general aspects are addressed below. The use of ISI in all four papers, the randomised controlled design (**Study II** and **IV**), and the application of modern statistics are all strengths worthy of attention. Nevertheless, there are some general limitations. First, all results are based on patient-reported outcomes. Most of them are well-established and reliable but there are some general problems associated with self-reports in the field of sleep research as well as in pain research. Self-reports can be affected by demographic factors such as age or education level (Levin-Aspenson and Watson, 2018) and by recall bias (Colombo et al., 2020), individual differences in introspective ability, and social desirability etcetera (Demetriou et al., 2014).

For sleep (especially insomnia), the discrepancy of subjective and objective measures has been observed and studied for a long (Carskadon et al., 1976). Accelerometry could have provided valuable information on physical activity (**Study II**) and a complimentary sleep outcome in **Study II and IV**. The best available method for objective measurement of sleep is PSG and accelerometry has shown better accordance with PSG compared to sleep diary measures in patients with insomnia (Lichstein et al., 2006). Multiple PSG assessments (pre, post, and follow-up) would not be doable, neither practically nor financially. Even though it could have some scientific value, PSG is not recommended for clinical assessment of insomnia (Riemann et al., 2017). Still, accelerometry could have been a more convenient alternative.

Another caveat is the absence of data regarding the use of medications. Especially sleep and medications, but also other medications that have side-effects affecting sleep and pain. In **Study IV** subjects are advised to keep a constant medication throughout the treatment period while the randomised design in **Studies II and IV** deal with this issue by distributing the use of medication

randomly in both groups. Nevertheless, it cannot be ruled out that it has affected treatment responses either way. Further, when interpreting the results in Study I and III one must keep in mind that prescribing patterns in Sweden has changed considerably over the last decade possibly affecting the prevalence of insomnia symptoms in general population and by extension also in individuals with chronic pain (Fig. 7).

Figure 7. Prescribed hypnotics and sedatives in Sweden 2011-2020; number of patients per 1000 inhabitants 0-85 years. Data retrieved from The National Board of Health and Welfare's statistical database 2021-04-30.

The recruitment procedure in **Study II** was changed during the study. The first population constituted of present and former patients in specialised pain care that had not been included in the multimodal rehabilitation program. When the initial strategy was depleted, an additional application was sent to the ethical committee. The new strategy was based on advertisements in the local newspaper opening up for the general population and likely participants with less severe symptomatology, even though inclusion and exclusion criteria were not changed. This change was necessary to ensure enough statistical power in the three-armed study design, but it brings some questions about the generalizability of the results and might have affected the effect sizes found. Less severe symptoms at baseline restrict the room for improvement, but on the other hand patients outside specialised care are likely more untreated and therefore more receptive to treatment. The final sample reflects a broader population than first intended, but probably with a skewness towards more severe chronic pain compared to the general population.

Even though the use of the ISI is a methodological step forward compared to single items, it is not without shortcomings. For example, confirmatory factor analysis indicated that three items did not contribute to the proposed one-factor solution (Dragioti et al., 2015). The literature indicates that two of the items (1 & 3) belongs to the first part of ISI measuring night-time symptoms and refers to sleep onset latency and early morning awakenings respectively. Possibly, item 2 (referring to nightly awakenings) is more closely linked to daytime symptoms (Bonnet and Arand, 2003) and dissatisfaction (item 4, 5 & 7) and thereby loading on the same factor. The third problematic item (item 6) asks whether the impact of your sleeping problem is noticeable to others. In this pain population, answers on item 6 might be affected by the “noticeable” pain condition and its impact on the subject’s quality of life, rather than the impact of the sleep problem per se. Another source of error could be the Swedish translation even though it was cross-translated by Linton and co-workers. Since recommended cut-off scores, staging, and criteria for clinically significant change are based on the original-seven item version the full version was used in the four studies of this thesis.

Future directions

At the end of the day, long-term effects are what counts in chronic conditions such as chronic pain and insomnia. Therefore, future studies should be designed to monitor long term effects and find ways to measure adherence to treatment content throughout the follow-up period. If behavioral changes initiated by ICBT-i are not maintained, we cannot assume treatment effects to be maintained. A related question is that the relative effect of CBT-i components are not fully understood. As mentioned earlier, there are several interventions that lead to restricting time in bed. Therefore, the actual behavioral change caused by treatment needs to be operationalised and “isolated” so it can be manipulated and studied in a meaningful way.

Even though we have an arsenal of effective interventions for treating insomnia symptoms, there is still room for improvements. Future research should test out new ways to make treatment more user-friendly and less aversive. For instance, the first weeks of sleep restriction could be modified to either be brisker by starting with a wakeful night, or to be gentler by applying sleep compression instead (decreasing time in bed gradually).

Another direction that really could change accessibility is fully automated treatments. We know from the literature on internet treatments that therapist support has a positive effect on treatment effects in general. However, we don't know how the size of the effects that can be achieved by fully automated treatments in this group of patients, suffering also from a variety of physical and psychological symptoms.

One may argue against implementation of additional studies on hybrid treatments directed to pain and insomnia symptoms for two reasons. First, do we have evidence that ICBT-i has to be adapted for patients with comorbid chronic pain? More likely, sleep in chronic pain patients is governed by the same processes as all human (and most animals). Interventions that are developed to optimise processes governing normal sleep, reasonably would be beneficial also for patients with chronic pain. Second, existing evidence advocate *multimodal* rehabilitation programs as the primary treatment strategy for chronic benign pain and *unimodal* hybrid treatments are not. This doesn't say that new studies on the additional effect of CBT-i/ICBT-i to *multimodal* rehabilitation programs lack merit, rather the opposite.

Large epidemiological studies are industrious, expensive and hard to design, but no other tool can replace them in answering some of the most important research questions. Future studies should focus on the process of spreading of

pain per se rather than specific diagnoses and to capture the time window in which spreading occurs. Also, **Study III** needs to be replicated.

The majority of literature today focus on worsening and the development of chronic and widespread pain. Just as important is the study of prognostic factors for the resolution of chronic pain, investigating both relative improvements and full remission. Measures of physical exercise/activity could also be of great interest in addition to measures of sleep, demographic variables and pain characteristics, given the positive effects of physical exercise on pain and sleep seen in **Study II**.

Although Insomnia Severity Index is widely used self-report measure, we should move forward investigating its psychometric properties when applied to chronic pain patients. Measurement errors can be deceptive and result in false conclusions. As mentioned on the previous page, ISI is not unproblematic according to the confirmatory factor analysis (Dragioti et al., 2015) and perhaps the exclusion of some items can result in more reliable measurement of insomnia symptoms in chronic pain patients.

With this said, the benefit of additional cross-sectional studies on the co-occurrence of chronic pain and insomnia symptoms is probably limited.

CONCLUSIONS

In conclusion, insomnia symptoms are common in patients seeking specialized pain care. High levels of insomnia symptoms increase the risk of spreading of pre-existing pain and this in a dose-dependent manner. Physical exercise has significant, but not clinically meaningful effects on pain intensity and insomnia symptoms. Internet delivered Cognitive Behavioral Therapy for insomnia leads to a more rapid reduction of insomnia symptoms compared to applied relaxation, although long term effects are uncertain.

Hence, an early evaluation of, and interventions directed to, insomnia symptoms are of great importance when patients are seeking care for pain. Internet treatments can be one way to increase availability to non-pharmacological treatment for insomnia disorder in general and as an adjuvant treatment in pain care.

Future studies are needed to evaluate the long-term effects of Internet delivered Cognitive Behavioral Therapy for insomnia compared to treatment as usual and pharmacological treatments. Also, the role of insomnia symptoms as a risk factor for spreading of pre-existing pain needs to be replicated.

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Anna, när du kom förändrades allt. Natt blev dag, vardag blev fest och min avhandling blev en bisyssla. Du har ärvt min dygnsrytm och det är bara en av tusen saker som jag är tacksam för. Jag hade ingen aning om att en tvååring kunde vara så rolig, så musikalisk och ha sådan makt som du har. Arbetsdagen slutar kl 14:48 och det är den deadline som har fört detta arbete i mål.

Innan vi kommer till mina handledare vill jag lyfta fram några av de lärare som företrätt er. Ingall, Sanna, Inger, Kerstin, Mikael, Hasse och många andra. Ni är anledningen till att jag aldrig riktigt upphört att gå i skolan. I en annan tid hade jag fått kvarsittning, ovetta och reprimander. Det blev inte så och nu har jag själv fått både pekpinne och kateder.

Björn, du var oförsiktig nog att anställa mig som PTP-psykolog för tio år sedan. Det blev början på datainsamlingen till studie II. När Péter och Björn bjöd in mig till sin grupp med inriktning på sömn så var steget inte långt till att bli doktorand. Björn blev huvudhandledare, mentor och finansiär. Hela vägen har det funnits en generositet och välvilja som varit ovärderlig för mig. Stigen har varit upptrampad och manegen har varit krattad. Även Britt förtjänar att uppmärksammas här. Jag minns flera fina samtal på ditt kontor, vissa som handlat om forskning men framför allt de samtal som handlat om livet. Du ligger i mångt och mycket bakom Studie III och att du delade med dig av din mödosamt insamlade data är värt ett stort TACK!

Under de senaste åren har jag avverkat två huvudhandledare. Elena började som kollega, sedan blev vi grannar i radhusområdet och de senaste åren har du varit min huvudhandledare och närmaste medarbetare på forskningsavdelningen. Du kämpade med svenskan, jag kämpade med statistik. Nu när vi närmar oss mål så kan man konstatera att du har kommit längre än jag. Långt innan du blev min handledare tog du dig tid oavsett vad du hade för handen och oavsett vad mina förvirrade frågor gällde.

Péter, det märktes direkt att du är ödmjukheten själv men det visade sig också med tiden att du är en välciterad sömnforskare. Oavsett om vi har bemannat en poster, råkat sätta oss vid honnörsbordet eller paddlat kanot med våra fruar så har du alltid varit ett gott sällskap och en fin vän.

Jag måste erkänna att jag hade en baktanke när jag satte mig bredvid dig på lunchen när Smärtforum arrangerades i Linköping 2013. En tid senare fick du frågan om du kunde tänka dig att vara min handledare och att du tackade ja visade kanske på den kraft som finns i priming och nudging. Jag har alltid känt mig välkommen hos er på CHAMP och era konferenser har alltid varit årets vetenskapliga höjdpunkt. När du skickar en påskriven blankett så lägger du alltid med en liten hälsning, när vi har haft handledning följer en trevlig lunch. Steven, det kommer jag att sakna.

Gerhard såg till att mitt första pek kom till. Examensuppsatsen ledde vidare till studie IV och den forskning som faktiskt kan göra skillnad för de människor som lider av sömnlöshet och smärta. Tack vare den infrastruktur för internetbehandling som du har utvecklat kunde vi samla in den komplexa data som Philip hjälpte oss att få ordning på. Forskning är som bekant en lagsport och ni har verkligen varit nyckelspelare.

Martin och Eva på neurofys, det mesta jag kan om sömn har jag lärt mig av er! Ni är sanna entusiaster och ni har skapat goda lärmiljöer kring er forskargrupp på Universitetssjukhuset i Linköping och i Svensk Förening för Sömnforskning och Sömnmedicin. I detta sammanhang är det också omöjligt att inte också nämna Lena. Du satte av flera timmar för att prata sömn med mig när jag som psykologkandidat kom till neurologiska kliniken på USÖ. Där sådde du föret till denna avhandling och till min professionella bana inom beteendemedicin. Vikten av det samtalet kan inte betonas nog.

Jag är för feg för att studera utomlands och har för mycket ångest för att flyga, men eftersom du inte är som jag så har jag ändå fått se Paris. En gång tvingade jag dig att åka tåg till Berlin och det gjorde du utan att knorra. Jag är nog

egentligen för feg för att disputera också men eftersom du gjorde det först så vågar jag också. Emil, alla borde få ha en lång snygg teoretisk fysiker i sitt liv. Jag är så glad att jag har dig!

Peter, vi har hängt ihop sedan första terminen på psykologprogrammet och bara några veckor efter Emil så disputerade du. Du körde till mig och Nicolina till kyrkan, vi fick välkomna er hem från BB, vi byggde våra hus bara ett stenkast ifrån varandra och idag åt vi lunch. Hoppas att det kan får fortsätta så, i stort och i smått.

Martin och Marie, när vi påbörjade forskarutbildningen svor vi en ed att arbeta endast på kontorstid. Det har gått över förväntan och jag har ofta känt mig mindre dålig tack vare den överenskommelsen. Att vi följts åt under stora delar av doktorandtiden har gjort att det blivit mycket roligare och tänkandet har nått längre. Det var kul att läsa de obligatoriska kurserna på internat! Idag vet vi att inlärninng och vinpaket inte är någon bra kombination, det visste vi egentligen då med...

Statistiker Nadine Karlsson, du borde ha tackats redan i Studie II. När den egna förståelsen inte räcker till så är det fint att det finns sådana som du. Studie II hade också den stora fördelen att jag fick driva ett mastodontprojekt tillsammans med dig Anna Frumerie. Du är den vänligaste person som jag har träffa. I glädje och sorg, i sol och i snöstorm. Outtröttliga åkte vi till Norrköping, beställde fika och ringde in patienter. Det hade inte gått utan dig!

Kollegorna på Smärt- och rehabiliteringscentrum är erkänt trevliga. Ni är också erkänt kunniga. Jag har fått hjälp med att tejpa ett spräckt ögonbryn, att lägga om mitt löpsteg och ni har artigt lyssnat och ställt insatta frågor vid mina vetenskapliga seminarier. På grund av er har jag inte klarat av att arbeta hemifrån, inte kunnat byta jobb och tack vare er har jag orkat skriva klart den här avhandlingen. Vi är kanske den brokigaste kliniken i stan just för att vi också är den mest inkluderande.

Anna på VTI, du är aldrig mer än ett telefonsamtal bort. Du kan så mycket som jag inte kan och du är alltid lika hjälpsam. Jag önskar att vi hade haft ännu mer med varandra att göra och jag hoppas att våra vägar korsas snart igen!

Ganska tidigt under doktorandtiden fick jag mitt första externa anslag. Fibromyalgiförbundets forskningsstiftelse trodde på upplägget i Studie III och satsade en kvarts miljon kronor på ett oprövat kort. Tack för att ni var så

modiga! Region Östergötland har också stöttat med interna medel under årens lopp vilket har givit arbetet nödvändig förutsägbarhet och kontinuitet.

Anders, utan verksamhetschefens goda minne så blir det inga avhandlingar skrivna. Genom uppmuntran och generositet har du och ledningsgruppen skapat förutsättningar som fått doktorandkollegorna på andra arbetsplatser att bli gröna av avund. Jag tror att den bästa forskningen kommer till när de som utför den känner sig trygga och uppskattade, när tankarna får handla om vetenskap istället för försörjning och kamp för finansiering. Utan dessa fina förutsättningar hade jag aldrig övervägt denna bana i livet. Tack!

Slutligen vill jag tacka alla de patienter och studiedeltagare som bidragit med data. Sömnrestriktion är ingen lätt behandling och NRS-luntan är tjock. Förhoppningsvis håller ni med om att nyttan har varit större än lidandet.

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