Insomnia in older adults

Consequences, assessment and treatment

Børge Sivertsen

Dissertation for the degree of philosophiae doctor (PhD)
University of Bergen, Norway
2006

UNIVERSITETET I BERGEN

Table of contents

Acknowledgements

I would like to thank all those people who made this thesis possible and an enjoyable experience for me. First of all, I would like to thank all participants who contributed with their time and effort to help this thesis become reality.

I wish to express my sincere gratitude to Inger Hilde Nordhus and Ståle Pallesen who guided this work and made my years as a PhD-student a joyful experience. My colleague and research fellow Siri Omvik also deserves a warm thanks for our collaboration the last 3 years. I am especially indebted to Odd E. Havik who was of invaluable help both in Bergen and especially during our research stay in New Zealand, and Bjørn Bjorvatn deserves a special thank for his many insightful and constructive inputs. I am also grateful to Gerd Kvale and Geir Høstmark Nielsen for all their help and contributions in the Sleep Research Group at the Faculty of Psychology.

I would also like to thank Arnstein Mykletun and Simon Øverland at the Research Centre for Health Promotion, University of Bergen, for the many cheerful and important research meetings. I look forward to continuing our enthusiastic collaboration.

I am very thankful to Keith J. Petrie at Auckland University, New Zealand, for introducing me to the exciting world of health psychology and psychosomatic medicine. Our close collaboration has been most rewarding, both on a scientific and personal level.

I further wish to thank and recognize Holger Ursin and Hege R. Eriksen for believing in me already as a psychology student and giving me the opportunity to work in a very stimulating research environment.

I would like to acknowledge the financial support by the EXTRA funds from the Norwegian

List of papers

Paper I   Sivertsen, B., Overland, S., Neckelmann, D., Glozier, N., Krokstad, S., Pallesen, S., Bjorvatn, B. & Mykletun, A. (2006). The long-term effect of insomnia on work disability. The HUNT-2 historical cohort study. *American Journal of Epidemiology, 163*(11), 1018-1024.

Paper II   Sivertsen, B., Omvik, S., Pallesen, S., Bjorvatn, B., Havik, O. E., Kvale, G., Nielsen, G. H., Nordhus, I. H. (2006). Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults. A randomized controlled trial. *JAMA, 295*(24), 2851-2858.

Paper III   Sivertsen, B., Omvik, S., Havik, O. E., Pallesen, S., Bjorvatn, B., Nielsen, G. H., Straume, S. & Nordhus, I. H. (2006). A comparison of actigraphy and polysomnography in older adults treated for chronic primary insomnia. *Sleep, 29*(10), 1353-1358.

Summary

Objective

Insomnia is one of the most common conditions in older adults, affecting almost one third of adults aged 55 years or older. Insomnia has been linked to a number of individual adverse medical and psychological consequences, in addition to having large socioeconomic consequences in terms of lost productivity and risk of accidents. Still, only ten percent of chronic insomniacs receive treatment for their condition, of which the vast majority is treated pharmacologically. Psychological treatment options have previously been successfully applied in younger adults, but only a few studies have focused on non-pharmacological treatment in the elderly.

In the first paper of this thesis, we investigated empirically the contribution of insomnia to the award of disability pensions. The aim of the study was to estimate the independent effect of insomnia on permanent work disability by statistically controlling for a range of possible confounders.

In the second paper we examined both the short- and long-term treatment effect of cognitive-behavior therapy (CBT) and pharmacological treatment in older adults suffering from insomnia.

In the third paper, we compared both the psychometric properties and clinical utility of two objective measures of sleep (polysomnography and actigraphy) in the same study sample as in paper II.

Methods

In the first paper we used a historical cohort design to estimate the effect of DSM-IV defined insomnia on permanent work disability. Baseline data comprised 37 308 working age people from a large population based Norwegian health study. The outcome was subsequent award of a disability pension 18 to 48 months after baseline assessment, as registered in the National Insurance Administration. In order to estimate the independent contribution of insomnia, we statistically controlled for a range of possible confounders. These included both physical and mental symptoms and diagnoses, as well as lifestyle behaviors, shift work and other potential socio-demographic factors.

The two papers from the treatment study are based on a double-blinded randomized controlled trial of 46 patients with chronic primary insomnia who received either cognitive-behavior therapy (CBT, n=18), sleep medication (7.5 mg zopiclone daily, n=16), or placebo (n=12). All active treatments lasted 6 weeks with follow-ups conducted at 6 months. Ambulant clinical polysomnography (PSG), actigraphy and sleep diaries were used on all three assessment points. In paper II we primarily focused on the treatment effect of the two active interventions, while we in paper III explored the ability of actigraphy to correctly classify sleep/wake patterns.

Results

From the first paper it is concluded that insomnia is a robust and independent predictor of subsequent permanent work disability. Socio-demographic and shift work characteristics barely affected the association, which also remained significant after adjusting for both psychiatric and physical morbidity and health-related behaviors.

In the treatment study (paper II) we found that CBT produced significantly better short- and

long-term treatment effect than zopiclone. We found no significant outcome differences between zopiclone and placebo. Patients receiving CBT spent significantly less time awake and had higher sleep efficiency than patients treated pharmacologically. Patients in the CBT condition spent significantly more time in slow wave sleep (stages 3/4) than either of the two other conditions.

In paper III we found that actigraphy performed poorly in detecting wakefulness, and consequently overestimated the patients' total sleep time and sleep efficiency. Compared with PSG, actigraphy captured only part of the treatment effects on total wake time and sleep onset latency, and failed to detect significant changes in sleep efficiency.

Conclusions

Even though a diagnosis of insomnia is legally insufficient for the award of a disability pension, we found that insomnia is an independent predictor of subsequent work disability. Considering the direct costs of disability expenditures, in addition to the indirect costs from lost productivity, sleep medications and sleep-related accidents, we believe that early detection and interventions for insomnia should receive increased focus.

Based on the findings from the treatment study we conclude that interventions based on CBT are superior to zopiclone treatment, both in terms of short- and long-term management of insomnia in older adults. We also conclude that the clinical utility of actigraphy is still suboptimal in older insomniacs, and should hence not be used in a clinical setting without parallel use of additional assessment tools.

Abbreviations

ANCOVA	Analysis of Covariance
ASDA	American Sleep Disorders Association
BDI	Beck Depression Inventory
CBT	Cognitive-Behavior Therapy
CI	Confidence Interval
CNS	Central Nervous System
DSM-III	Diagnostic and Statistical Manual of Mental Disorders. 3rd edition.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. 4th edition.
ES	Effect-Size
GDP	Gross Domestic Products
HADS	The Hospital Anxiety and Depression Scale
HEMIL	Research Centre for Health Promotion, University of Bergen, Norway
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
HUNT	The Health Study of Nord-Trøndelag County
HUNT-2	The Second Health Study of Nord-Trøndelag County in 1995-97
HUSK	The Hordaland Health Study in 1997-1999
ICD-8	The International Classification of Diseases, 8th edition
ICD-9	The International Classification of Diseases, 9th edition
ICD-10	The International Classification of Diseases, 10th edition
ICSD	The International Classification of Sleep Disorders
NOK	Norwegian Kroner
OECD	Organization of Economic Cooperation and Development

OR	Odds Ratio
PAF	Population Attributable Fraction
PLMD	Periodic Limb Movement Disorder
PLMS	Periodic Limb Movements in Sleep
PSG	Polysomnography
PTSD	Post Traumatic Stress Disorder
RCT	Randomized Controlled Trial
REM	Rapid Eye Movement
RLS	Restless Legs Syndrome
SCID-I	The Structured Clinical Interview for DSM-IV, Axis I
SES	Socio Economic Status
TIB	Time in Bed
TS	True Sleep
TW	True Wake
UK	United Kingdom
USA, US	United States of America
WHO	The World Health Organization

1. Introduction

"Disease exists, if either sleep or watchfulness be excessive"

(Hippocrates, Aphorism LXXI) (Sateia & Nowell, 2004)

Health problems resulting from sleep disturbances have since long been acknowledged by health professionals. Despite the improvements in the field of sleep medicine during the last decades, available treatment options are still insufficient, suffering from lack of both recognition and understanding. Nowhere is this more apparent than in the elderly. As with various somatic diseases, the prevalence of sleep problems increases with advancing age. In light of the rapid changes in the age distribution in all Western industrialized countries, it is important to examine the implications and consequences of insomnia, both on an individual level, but also in a societal perspective. In line with this, it is equally important to establish viable and effective treatments to cope with a problem area that most likely will increase in the years to come. On a methodological level, establishing methods for assessing sleep that are both valid and reliable, but also cost-effective and minimally invasive to the patients, would be of great benefit in advancing the field of sleep medicine.

The aim of this thesis is to provide further knowledge and understanding of some of the societal consequences of insomnia. Perhaps most importantly, the thesis will examine the clinical efficacy of two treatments for insomnia among older adults, in addition to comparing two instruments designed to measure human sleep / wake patterns. As an introduction, an overview of the insomnia field in general will be provided.

1.1 Definition and diagnosis

There are three different diagnostic systems that each provides a definition of insomnia. In the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) sleep disorders are organized into four major sections according to presumed etiology. These are 1) Primary Sleep Disorders (not caused by a medical, psychiatric or substance factor), 2) Sleep Disorder Related to Another Mental Disorder, 3) Sleep Disorder Due to a General Medical Condition and 4) Substance-Induced Sleep Disorder. Primary Sleep Disorders are further subdivided into "Dyssomnias" which are characterized by abnormalities in the amount, quality, or timing of sleep, and "Parasomnias" which in turn are characterized by abnormal behavioral or physiological events occurring in association with sleep, specific sleep stages or sleep-wake transitions. Throughout this thesis, the term insomnia will refer to the DSM-IV-definition of "Primary Insomnia", which encompasses difficulties initiating or maintaining sleep or experiencing non-restorative sleep that results in clinically significant distress or impairment in daytime functioning. The DSM-IV criteria for primary insomnia are listed in the Appendix, highlighting that the diagnosis should only be given when the sleep problems do not occur during the course of another primary sleep or psychiatric disorder, and is not caused by substance abuse or a medical disorder. As noted by Edinger, primary insomnia is perhaps best conceptualized as a diagnosis established by the exclusion of other forms of sleep disturbances (Edinger & Means, 2005). A clinical interview is usually sufficient to establish the diagnosis (Chesson & et al., 1995).

The two other diagnostic classification system are International Classification of Diseases (ICD-10) (World Health Organization, 2004) from The World Health Organization (WHO), and the International Classification of Sleep Disorders (ICSD) (Diagnostic Classification

Steering Committee, 1990) from American Sleep Disorders Association (ASDA). While the DSM-IV and ICD-10 systems have relatively similar definitions of insomnia , the ICSD ICSD system has been criticized for arbitrary classification of sleep disorders, and for lacking validity (Morin, 1993; Reynolds, Kupfer, Buysse, Coble, & Yeager, 1991).

1.1.1 Sleep disorders

While the diagnosis of primary insomnia is used when the sleep problems are not caused by any known physical or mental conditions, secondary insomnia refers to poor sleep that is either caused or worsened by another disorder, either physical or mental. Approximately 25% of chronic insomniacs are thought to suffer from primary insomnia, with no known secondary etiology (Bixler, Vgontzas, Lin, Vela-Bueno, & Kales, 2002). As some sleep disorders may present themselves as primary insomnia (Pallesen, Nordhus, Havik, & Nielsen, 2001), knowledge of other sleep disorders is necessary to verify a diagnosis of primary insomnia. In the following sections, the symptoms of other sleep disorders and their distinguishing characteristics are outlined.

Sleep apnea. Primary insomnia and sleep apnea have some common characteristics; e.g. patients of both diagnoses complain of impaired sleep and daytime somnolence. However, certain characteristics are unique to sleep apnea, including frequent periodic cessations of breathing during sleep (apneas). Apneas are usually experienced as noisy snoring interrupted by silence (apneic episodes) with an explosive and loud expiratory reprise. Some patients can also experience a feeling of choking which interrupts their sleep. Nocturia and heavy sweating are also common symptoms of sleep apnea, and many patients report headaches in the morning. The apneic episodes symptoms occur when tissue in the upper airway collapse during sleep, which leads to lowered oxygen saturation in the blood. As a consequence, the patient experiences many arousals during the night, finally leading to non-restorative sleep.

Furthermore, sleep apnea has been shown to be related to cardiovascular morbidity (Lavie, Silverberg, Oksenberg, & Hoffstein, 2001), in addition to having profound negative impact on quality of life (Yang et al., 2000). If awaken during the night, patients with sleep apnea often quickly fall back to sleep due to excessive sleep deprivation, which rarely is the case in patients with primary insomnia.

Restless legs syndrome (RLS). The main characteristics of RLS are unpleasant sensations in the legs. The symptoms mostly occur in the evening or early part of the night, generating an irresistible need to keep the legs moving. While moving the legs will alleviate the symptoms, it also contributes to disturb the sleep and may cause symptoms of insomnia. The prevalence is estimated to around 11-12 % in the general population, and is somewhat more frequent in women than in men (13 % vs. 9 %) (Bjorvatn et al., 2005). Little is known regarding the etiology of RLS, but abnormalities in the central nervous system (CNS) seem to be an important factor (Jones & Derodra, 1997). RLS is normally treated with dopamine agonists (Hening, Allen, Earley, Picchietti, & Silber, 2004).

Periodic limb movement disorder (PLMD). PLMD is characterized by repetitive stereotypic leg movements, and as with sleep apnea, patients with PLMD experience frequent awakenings and loss of deep sleep, resulting in both daytime somnolence and subsequently negative impact on work performance, and social and family life. The severity of PLMD is determined by the periodic limb movement (PLM) index, which equals the number of periodic limb movements per hour of sleep. The disorder co-occurs with a wide variety of sleep disorders, and the co-morbidity with RLS is especially high. There are however, issues concerning the validity of the PLMD diagnosis (Chervin, 2001; Mahowald, 2001), and some have suggested that no significant association exists between periodic limb movements and either objective or symptomatic reports of insomnia or daytime sleepiness.

Moreover, while periodic limb movements are rarely diagnosed in patients under than age 30, nearly 50 % of persons older than 65 years meet the diagnostic criteria for the diagnosis (Coleman, Bliwise, Sajben, & et al, 1988), casting doubt to the validity of PLMD as a distinct sleep disorder (Feinsilver, 2003). The treatment is primarily pharmacological (Montplaisir, Nicolas, Godbout, & Walters, 2000).

Circadian rhythm disorders. Circadian rhythm disorders are disorders that are related to the timing of sleep within the 24-hour day. While some of these disorders are influenced by the timing of the sleep period that is under the individual's control (e.g., time zone travel or shift work), others disorders in this group have a neurological basis, including *irregular sleep-wake pattern* and *delayed sleep phase syndrome*. Especially the latter disorder can be mistaken for sleep onset insomnia, as the first major sleep episode is delayed by 2 or more hours of the desired bedtime. As opposed to insomniacs, patients with delayed sleep phase syndrome usually have normal length of sleep time, which often will result in waking up in the middle of the day. In *advanced sleep phase syndrome,* early evening sleep onset and early morning awakening constitute the major symptoms. Other sleep disorders in this group include *non-24-hour sleep-wake syndrome*, and *irregular sleep-wake pattern,* which are disorders in which sleep onsets and rise times occur either irregularly or completely at random. The prevalence of the circadian rhythm disorders is estimated to be quite low (Sand, Hagen, & Schrader, 2003), and although the etiology and pathophysiology are scarcely elucidated, the evidence that light therapy can affect circadian rhythms and improve symptoms suggests that these disorders are caused by a dysfunctional circadian clock (Rosenthal et al., 1990; Watanabe, Kajimura, Kato, Sekimoto, & Takahashi, 1999).

1.2 Etiology and development

The mechanisms underlying the pathophysiology of insomnia are still poorly understood. Deficiencies in endogenous melatonin receptors have been suggested to be important in the development of insomnia, and a recent therapeutic trial of melatonin in primary insomnia yield promising results (Zemlan et al., 2005). Others have suggested that hyperactivity of corticotrophin releasing factor neurons may contribute to the development of primary insomnia (Richardson & Roth, 2001). There may also be hereditary or genetic factors that are important contributors in the etiology of insomnia (Yves et al., 2003), but genetic aberrations specific to insomnia have yet to be identified.

Everyone is to various degrees predisposed to experience sleep problems. Whether a person will develop chronic insomnia or not depends on several factors, as outlined in a conceptual framework proposed by Spielman (Spielman, 1986; Spielman & Glovinsky, 1991). In this
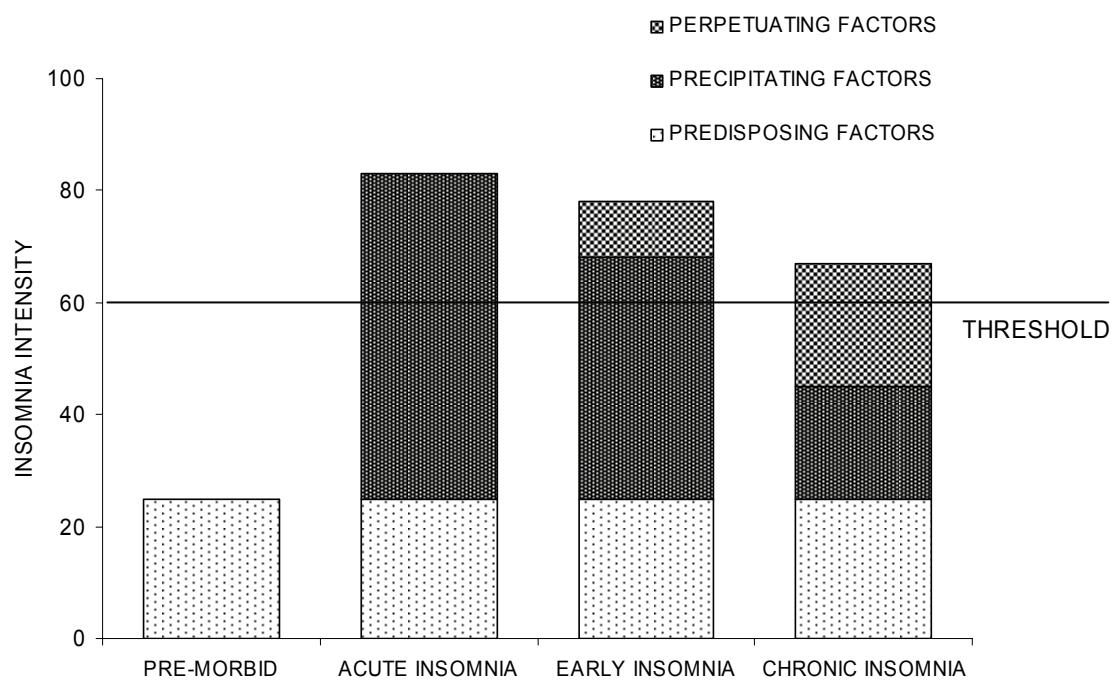
Figure 1. A conceptual model of how insomnia develops over time.

Adapted from Spielman & Glovinsky (1991).

perspective, the natural history of insomnia depends on both predisposing traits, precipitating events and perpetuating conditions. For example, acute insomnia in usually precipitated by a physical illness, psychosocial stressor or other life event, but is usually short lasting as the adverse event or condition alleviates after some time. However, some people continue to experience sleep problems long after the evoking factors have disappeared (Morin, 1993). Figure 1 outlines the development of insomnia over time from a situational problem to a chronic condition. In chronic insomnia, there is now general consensus that cognitive and behavioral mechanisms play important factors in both maintaining and exacerbating the sleep problems, as illustrated in Figure 2. Misattributions about the causes of sleep problems and the negative consequences are quite common in the early phase of insomnia, as are erroneous and worry-related expectations
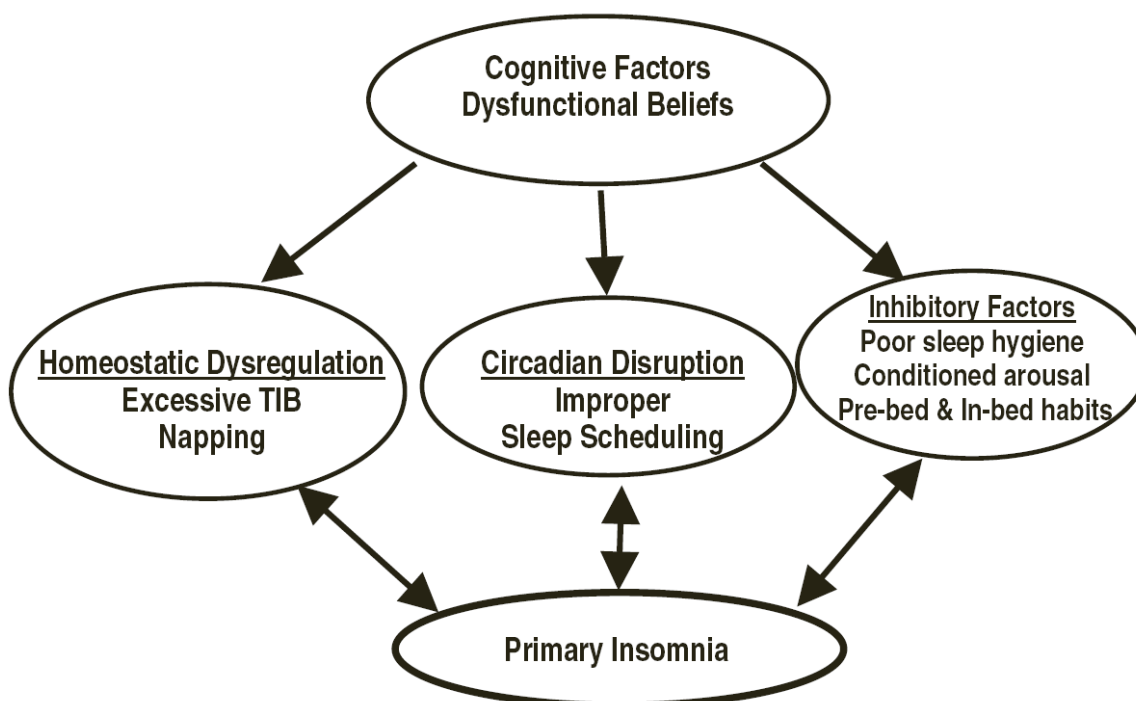
Figure 2. Interplay of cognitive and behavioral mechanisms in primary insomnia.

Adapted from Edinger & Means (2005).

regarding how much sleep one really needs. Combined, these factors may inhibit good sleep by sustaining sleep-disruptive habits (e.g., daytime napping) and obstruct a person's normal sleep drive by interfering with the homeostatic mechanisms of the CNS(Edinger & Means, 2005). Furthermore, staying in bed significantly longer than the normal rising time may disrupt the body's circadian rhythm or mechanisms which control the timing of sleep and wakefulness in the 24-hour day. Also, frequent associations between the bedroom and wakefulness may ultimately give rise to conditioned arousals in the sleeping environment, delaying the person's sleep onset. Overall, these factors may both contribute in the development and maintenance of insomnia (Bootzin & Epstein, 2000; Edinger & Means, 2005; Edinger & Wohlgemuth, 1999).

1.3 Sleep and aging

There are several characteristics that separate sleep and sleep patterns among elderly from younger adults. Compared to middle-aged samples, total sleep time among older adults is reduced from 7 hours per night to 6–6.5 hours (Nau, McCrae, Cook, & Lichstein, 2005). Polysomnographic data show a significant reduction in the slow wave sleep (delta sleep) in older adults, with a corresponding increase in the proportion of stage one and two (Miles & Dement, 1980). The amount of REM sleep appear to be relatively stable throughout life, although some studies report a small decrease in REM sleep with advancing age. As a consequence of the lack of slow wave sleep, older adults typically experience frequent awakenings during the night, which results in a significant decrease in sleep efficiency (percentage of time in bed actually spent asleep) (Miles & Dement, 1980). Moreover, the number of daytime naps increase in this age cohort (Zepelin, 1973), and some studies have also demonstrated a decreased amplitude of the endogenous circadian rhythm with

advancing age (Monk, 1991). Another complicating factor is that the prevalence of specific sleep disorders, such as sleep apnea and periodic limb movement disorder (PLMD) increase dramatically with age (Ancoli-Israel et al., 1991a, 1991b). Similarly, older adults have in general more somatic diseases, in addition to an increase in the consumption of drugs (Salzman, 1982), some of which may cause sleep problems (Schweitzer, 2000).

1.4 Epidemiology

1.4.1 Inadequate identification

Despite advances in our understanding of chronic insomnia, the condition remains inadequately identified. It is estimated that nearly 50 % of all primary care patients experience sleep difficulties, but most of these are left undetected by health professionals (Allaert & Urbinelli, 2004; Haponik et al., 1996). Numerous studies have focused on the epidemiology of insomnia, but the results vary due to large differences in the definition of insomnia, as well as the population examined (Roth & Roehrs, 2003). However, despite the many differences in approaches to this research field, some conclusions can be derived from the literature.

1.4.2 Prevalence

While many epidemiological studies have used a single item to estimate the prevalence of insomnia, only a few studies have attempted to employ more formal diagnostic systems in their operationalization. Most of these studies estimate that chronic insomnia occurs in about 10% in the general population (Figure 3) (Ancoli-Israel & Roth, 1999; Ford & Kamerow, 1989; Ohayon, 1997; Pallesen et al., 2001; Simon & VonKorff, 1997). The prevalence of insomnia is greater in women than among men (Nau, McCrae, Cook, & Lichstein, 2005), and occur more frequently in low socioeconomic status (Ford & Kamerow, 1989; Ohayon &

Caulet, 1996). As with most sleep disorders, the prevalence of insomnia increases

significantly with advancing age; estimates ranging from 9 to 25 % in people aged 55 or

more (Ancoli-Israel & Roth, 1999; Ford & Kamerow, 1989; Ohayon, 1997, 2002; Pallesen et

al., 2001).
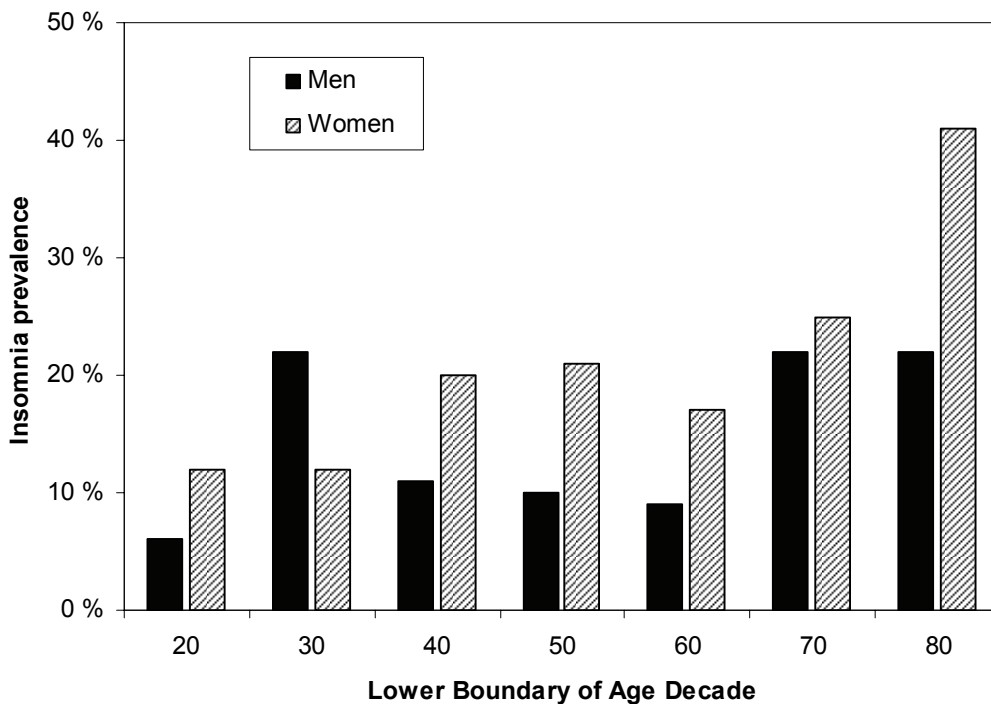
Figure 3. Prevalence of insomnia by gender and age.

Adapted from Lichstein (2004).

1.4.3 Consequences

The adverse individual consequences of insomnia are well documented. Poor sleep is

associated with both cognitive and intellectual impairment (Pilcher & Huffcutt, 1996; Simon

& VonKorff, 1997; Szelenberger & Niemcewicz, 2000), as well as current and subsequent

affective disorders (Mellinger, Balter, & Uhlenhuth, 1985; Vollrath, Wicki, & Angst, 1989).

Patients suffering from insomnia commonly report significant reduction in quality of life

(Zammit, Weiner, Damato, Sillup, & McMillan, 1999) and impaired coping abilities (Morin,

Rodrigue, & Ivers, 2003; Sadeh, Keinan, & Daon, 2004). Insomnia has also been linked to reduced immune function (Savard, Laroche, Simard, Ivers, & Morin, 2003), and several studies of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis have revealed increased arousal in insomniacs (Bixler, Vgontzas, Lin, Vela-Bueno, & Kales, 2002; Vgontzas et al., 2001).

Few studies have focused on the societal impact of insomnia. Poor sleep has been shown to be associated with lower working capacity (Linton & Bryngelsson, 2000), dissatisfaction with work and high levels of work stress (Rosmond, Lapidus, & Bjorntorp, 1998), and self-reported sick-leave (Ingemarsson, Nordholm, & Sivik, 1997; Leigh, 1991). A recent analysis of the economic burden of insomnia in the USA estimates the direct medical costs of insomnia to be US$13.9 billion annually (Walsh & Engelhardt, 1999), an estimation the increases to $ 92-107 billions when including indirect costs from sleep-related accidents and lost productivity (Stoller, 1994). Similarly, economic costs resulting from sleep disorders in Australia have recently been estimated to represent 0.8 % ($4.5 billion) of the Australian gross domestic product (Hillman, Murphy, Antic, & Pezzullo, 2006), independent of the cost of suffering. The suffering and premature death associated with sleep disorders are estimated to impose an additional non-financial cost of $3 billion, which in sum represents 1.4 % of the total burden of disease in Australia. Although these costs are substantial, they are not that surprising given the pervasive effects of impaired sleep on both accidents and lost productivity (Hillman, Murphy, Antic, & Pezzullo, 2006).

1.5 Assessment of sleep

Over the years, several assessment tools have been developed in an attempt to obtain a measurement of sleep that is as accurate as possible. Since the introduction of polysomnography (PSG) in the 1950s, this method has been regarded as the gold standard

for objective assessment of sleep (Sateia, Doghramji, Hauri, & Morin, 2002), providing precise and extensive information on both sleep physiology as well as sleep behaviors. PSG is of vital importance in order to detect a range of sleep disorders, such as sleep apnea and PLMD. However, the role of PSG to establish the diagnosis of primary insomnia is debated. PSG evaluations of all insomniacs would be both impractical as well as very expensive, and routine use of PSG in insomnia is therefore not recommended (Reite, Buysse, Reynolds, & Mendelson, 1995; Spielman, 1986). Self-rated sleep diaries have been widely used as a less costly and more user-friendly alternative, with the advantage of providing information about sleep in a more ecological valid setting over extended periods of time. The reliability and validity of sleep diaries have been questioned, however, as patients' self-reported sleep time has been shown to deviate from findings based on PSG, ranging from underestimations to overestimations (Edinger & Fins, 1995). Actigraphy is another alternative assessment method to PSG. Actigraphy consists of an accelerometer and memory storage, both fitted into a watch-like device worn around the wrist. Based on differences in movements associated with wakefulness and sleep, actigraphy provides an estimate of sleep-wake schedules. Being independent of patients' ratings and personal judgments of their sleep, actigraphy may offer a less time-consuming and less expensive alternative to PSG. In addition, actigraphy is regarded as a less invasive measure. However, the clinical utility of actigraphy is still unclear, and to date only a few studies have examined to what extent actigraphy is sensitive to detect treatment changes compared to PSG (Brooks, Friedman, Bliwise, & Yesavage, 1993; Friedman et al., 2000; Vallieres & Morin, 2003; Verbeek, Arends, Declerk, & Beecher, 1994).

Specific sleep questionnaires are also available, providing a subjective sleep evaluation. Some examples of broad and general sleep questionnaires are the Pittburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the Sleep Impairment Index

(Morin, 1993). Such questionnaires are generally easy to administer, easy to score, and are far less expensive than both actigraphy and PSG. However, as sleep questionnaires are retrospective in their approach to assess sleep, they are vulnerable to various biases which may affect their validity and reliability.

A final method of assessing sleep is by conducting a sleep interview. A sleep interview normally includes a thorough assessment of the patient's view of etiology of his or her current sleep problems, as well as a consideration of symptoms of other sleep disorders. Prior sleep history and current sleep habits should also be included in a sleep interview. Furthermore, information from a patient's bed partner may also be valuable in order to obtain supplementary information regarding e.g. snoring and leg movements during the night (Spielman, 1986).

1.6 Treatment of insomnia

It is estimated that 85 % of chronic insomniacs receive no treatment for their condition (Mellinger, Balter, & Uhlenhuth, 1985; Riedel & Lichstein, 2001), and two-thirds of individuals with poor sleep have no, or poor knowledge about available treatment options. In addition, nearly 20 % of these resort to either untested remedies or alcohol in attempts to improve their sleep (Roth & Ancoli-Israel, 1999). Behavioral and cognitive interventions for a variety of clinical problems appeared as early as the mid-1960s. Still, it is only recently that these treatment options have become integrated in the clinical management of insomnia. Until the mid 1980s there were hardly any studies that had examined alternatives to pharmacotherapy for insomnia in older adults (Lichstein & Fischer, 1985), as this age group was judged to be poor candidates for psychological interventions (Lichstein & Morin, 2000). Since then, substantial progress has been made both with regard to non-pharmacological treatment options for late-life insomnia, in addition to newer and arguably better sleep

medications.

1.6.1 Pharmacological treatment

Pharmacological treatment for insomnia is generally recommended in acute and short-lasting

insomnia (Kupfer & Reynolds, 1997). Due to the risks of side effects, dependence, tolerance,

and withdrawal symptoms, it is widely recognized that sleep medications should be used

with caution and preferably avoided in patients with chronic insomnia (Hajak, 1999; Noble,

Langtry, & Lamb, 1998). However, prolonged use of hypnotics is quite common in the

clinical setting (Bassa, Law, & Goldberg, 1994; Ohayon & Caulet, 1996). Benzodiazepines

have been the most widely used pharmacological treatment for insomnia. Since their

introduction in the 1970s, numerous studies have demonstrated their efficacy, and they are

generally well tolerated if used with caution. When used on a regular basis benzodiazepines

are associated with both rebound insomnia and withdrawal reactions, in addition to having a

well documented risk of dependency (Ashton, 1994; Lahmeyer, 1995). Around 35 % of

patients who use benzodiazepines on a regular basis for more than 4 weeks become

dependent on their effects (Ashton, 1994), which may explain why the use of

benzodiazepines has decreased in recent years. The general decrease in benzodiazepine use

can also be ascribed to the introduction in the late 1980s of newer non-benzodiazepine sleep

medications, such as zopiclone and Zolpidem. There are numerous clinical trials showing

that short term use zopiclone is at least as effective as benzodiazepines in patients with

insomnia (Noble, Langtry, & Lamb, 1998). Zopiclone appears to cause fewer adverse side

effects compared to benzodiazepines, and it does not change the sleep architecture to the

same extent as benzodiazepines. In benzodiazepines there is a significant loss of efficacy

when used more than a few weeks, but as almost no studies have investigated the long-term

effects of zopiclone, the potential for tolerance to this hypnotic agent has yet to be accurately

evaluated. One should also note that especially elderly patients are often faced with polypharmacy. Unexpected drug interactions may have serious side-effects for the patient (Linjakumpu et al., 2002). In sum, zopiclone has shown to be both an effective and well tolerated hypnotic agent, and clearly stands out as a better alternative to the benzodiazepines in short term pharmacological management of insomnia.

1.6.2 Non-pharmacological treatment

Non-pharmacological interventions are increasingly being regarded as an effective alternative to hypnotic treatment of insomnia. Cognitive-behavior therapy (CBT) is the most widely used psychological intervention for insomnia. These interventions typically include 6-8 brief sessions focused on several behavioral and educational components, including stimulus control, sleep restriction, relaxation, identification and change of dysfunctional cognitions related to sleep and sleep hygiene education (Morin, 1993). These multi-component treatment regimes based on CBT are supported by three recent meta-analyses (Irwin, Cole, & Nicassio, 2006; Morin, Culbert, & Schwartz, 1994; Murtagh & Greenwood, 1995), concluding that 70-80% of adults with insomnia (mean age 44 years) will benefit from such interventions. However, the evidence of CBT is limited in the case of insomnia in older adults, as recently stated in a Cochrane review (Montgomery & Dennis, 2003). Compared to placebo and no treatment, CBT was associated with sleep improvements (Edinger & Means, 2005; Montgomery & Dennis, 2004; Pallesen, Nordhus, & Kvale, 1998), but effects were not as great as for CBT used with younger adults (Pallesen, Nordhus, & Kvale, 1998). Also, a recent comparative meta-analysis concluded that behavioral interventions were more effective in the younger cohort in improving both total sleep time and sleep efficiency (Irwin, Cole, & Nicassio, 2006). This meta-analysis did not include objective polysomnographic evaluations of sleep outcomes due to lack of studies.

Surprisingly, only one well controlled randomized clinical trial by Morin and colleagues (Morin, Colecchi, Stone, Sood, & Brink, 1999) has directly compared the clinical efficacy of both sleep medication (temazepam) and psychological interventions in older adults suffering from primary insomnia. Morin's study showed that CBT and pharmacological interventions produce similar short-term effects, but that CBT was superior at follow-up as indicated by sleep diaries. Temazepam is a benzodiazepine derivative hypnotic drug which was introduced in the early 1980s, and no studies have compared CBT with the newer non-benzodiazepines (such as zopiclone). Also, to our knowledge, no studies have examined to what extent slow wave sleep (stages 3 and 4) is subject to change following CBT of insomnia. This is of particular interest, as lack of slow wave sleep has been hypothesized to be responsible for much of the day-time impairments seen in insomniacs (Moldofsky, 2001).

1.7 The present research aims

1.7.1 Aim I

1) Using operational definitions of insomnia based on DSM-IV inclusion criteria, what is the effect of insomnia on subsequent permanent work disability using a historical cohort design?

2) What is the independent effect of primary insomnia when adjusting for physical and mental symptoms and conditions, in addition to lifestyle factors and potential socio-demographic confounders?

1.7.2 Aim II

1) Do psychological treatment (CBT) and pharmacological interventions differ from placebo in their effectiveness and on what specific outcome measures are there significant changes at post-treatment? Are there any differences in treatment effects between CBT and zopiclone?

2) Do potential treatment gains remain significant 6 months after treatment completion?

1.7.3 Aim III

1) What are the psychometric properties of actigraphy as compared to polysomnography (PSG) in terms of its sensitivity, specificity and accuracy for sleep/wakefulness categorization?

2) To what extent is actigraphy able to detect treatment changes compared with PSG in older adults treated for chronic primary insomnia?

2. Methods

2.1 Samples and procedures

2.1.1 Sample and procedure: Paper I

All inhabitants of Nord-Trøndelag County, Norway, aged 20 years or older were invited to a clinical examination as part of a general health screening. In all, 92,100 persons aged 20–89 years were sent an initial questionnaire and an invitation to participate in HUNT-2. Of these, 65,648 (71 percent) attended the physical examination, where they received a second set of questionnaires, which 52,814 (80 percent) completed. Retired persons and individuals reaching the retirement age of 67 years during follow-up were excluded (n = 11,123); retirement because of old age precludes the award of a disability pension. HUNT-2 responders who were receiving a disability pension at baseline (n = 3,964) or who were granted a disability pension within 18 months after baseline (n = 419) were also excluded. Thus, the final study population included 37,308 persons: 19,936 women and 17,372 men. Using a historical cohort design, we linked baseline data from the HUNT-2 study with official data from The National Insurance Administration on all grants of disability pension in Norway. The outcome variable was a disability pension award from 18 to 48 months after participation in HUNT-2.

2.1.2 Sample and procedure: Paper II and III

Participants were recruited through newspaper advertisements to a randomized, controlled study of treatment of insomnia. Inclusion criteria were 1) age 55 years or older, 2) fulfillment of the DSM-IV criteria for insomnia, including difficulties initiating sleep, maintaining sleep, and/or early morning awakenings without returning to sleep, 3) duration

of at least 6 months, and 4) complaints of impaired daytime functioning. The following exclusion criteria were used: 1) use of hypnotic medication the last 4 weeks before project start, 2) use of antidepressive or antipsychotic medications, 3) signs of cognitive impairment defined by a score under 25 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), 4) presence of a major depressive disorder or other severe mental disorder as identified by clinical assessment based on The Structured Clinical Interview for DSM-IV (SCID-I), Axis-I (First, 1995), 5) presence of sleep apnea (A/H index > 15) or periodic limb movements during sleep (PLM index with arousal > 15), 6) working nightshifts and unable or unwilling to discontinue this work pattern, 7) unwillingness or inability to stop taking sleep medication before start, or 8) the presence of a serious somatic conditions preventing further participation.

Participants who responded to the advertisement (n=92) underwent several screening processes before they were included. A short telephone interview (15 min) by two clinical psychologists (BS & SO) assured that prospective participants fulfilled the basic criteria for inclusion. Accepted participants (n=75) met at the Outpatients Clinic for Adults and the Elderly, Department of Clinical Psychology, for a diagnostic interview (SCID-I), screening for severe psychopathology and cognitive impairment. The final screening phase included two consecutive nights of ambulatory polysomnography. In all, 46 participants were enrolled in a 6-week treatment program, and were randomized into either cognitive-behavior therapy (CBT), 7.5 mg of zopiclone or placebo treatment. Participants in the placebo condition were randomized into one of the two active treatment conditions after 6 weeks.

2.2 Treatment conditions in paper II and III

2.2.1 Cognitive-behavior therapy

Participants receiving CBT attended 6 weekly individual treatment sessions each lasting

approximately 50 minutes. The rationale for this treatment condition is based on a

manualized multi-component approach which includes several modules introduced at

different stages in the treatment (Morin, 1993). The manual outlines the structure of each

session and provides information regarding issues to be covered. Session 1 provided an

overview of the treatment program. The key theme was an educational component focusing

on different aspects of insomnia, in addition to normal age-related physiological changes in

sleep patterns (Morgan, Thompson, Dixon, Tomeny, & Mathers, 2003). The rationale of

sleep restriction, stimulus control and sleep hygiene education was introduced during session

1, and continued as the main foci of session 2. *Sleep restriction* seeks to increase

homeostatic sleep drive through partial sleep deprivation (Morin, 1999). It involves a strict

schedule of bedtimes and rising times, restricting patients' allowed time in bed to the actual

sleeping time according the patients' sleep diary. The rising time is fixed; while the bedtime

is adjusted according to the previous week's reported sleep-efficiency, which is calculated

before each session starts. If the average sleep-efficiency for the last week reached 85 % or

more, the patients were allowed to go to bed 20 minutes earlier than the previous week. The

aim of *Stimulus control* was to break associations between the sleep environment and

wakefulness (Bootzin & Nicassio, 1978). This was done by teaching the participant not to

engage in bedroom activities "incompatible" with sleep, as well as to stay in the bedroom

only when asleep or sleepy. The participants were told to get out of bed if they were unable

to fall asleep within 20-30 minutes; and were allowed to return to bed only when they felt

sleepy. This step was repeated as often as necessary during the night. *Sleep hygiene*

education aimed to teach the patients about the impact of lifestyle habits such as exercise,

diet, alcohol use and the influence of environmental factors such as light, noise and temperature (Hauri, 1991). In Session 3 the main *cognitive components* were introduced, with the aims of modifying unrealistic beliefs and irrational fears regarding sleep or the loss of sleep. This approach followed the standard cognitive rationale as described by Beck (Beck, 1976), in which the objective is to identify, challenge and replace these beliefs and fears with realistic expectations regarding sleep and daytime function. In addition to maintaining and focusing on the before mentioned components, Session 4 introduced a 20 minute *progressive relaxation* technique, in which the patients were taught how to recognize and possibly control muscular tension (Jacobsen, 1938). Participants were given the exercise instructions on pre-recorded tape or CD, and were told to practice the technique at home on a daily basis. In the last two sessions no new components were introduced; rather the focus was on maintaining and developing the learned techniques. Furthermore, the participants were prepared to continue to use their new skills to uphold their sleep pattern once the treatment ends. The therapy sessions were given by two certified clinical psychologists (BS & SO), with training in cognitive-behavior therapy. An experienced clinical psychologist (IHN) supervised the treatment sessions.

2.2.2 Zopiclone

Zopiclone was first introduced in 1988, and is a cyclopyrrolone derivative chemically unrelated to benzodiazepines or barbiturates. Zopiclone works by enhancing the actions of the neurotransmitter GABA, and is a racemic mixture of two stereoisomers, only one of which is active. The active stereoisomer, eszopiclone, was introduced on the US marked in April 2005, and although the dosages are different (7.5 mg zopiclone is equivalent to about 3.75 mg eszopiclone), the two drugs are identical in effect. Zopiclone has demonstrated efficacy equivalent and in some cases greater to that of both long- and short-acting

benzodiazepines (Hajak, 1999; Noble, Langtry, & Lamb, 1998). Zopiclone is documented to be well tolerated in elderly patients, and is generally less likely to produce adverse effects compared to benzodiazepines (Noble, Langtry, & Lamb, 1998). Zopiclone was chosen since it has been the most commonly prescribed hypnotic in Norway during the last decade, and overall this hypnotic agent has a market share of 45 % of the total sales of hypnotics and tranquillizers in Norway (Norwegian Institute of Public Health, 2004). Participants in the active sleep medication group were prescribed 7.5 mg zopiclone by a MD. Participants met at the sleep laboratory every week for a short meeting (10 min) to report any adverse effects, and to get the following week's dosage of 7 pills. No behavioral recommendations regarding sleep were given during these short meetings, and the main focus was on encouraging the participants to adhere to the treatment program. After treatment completion, the patients were given the opportunity to continue their medication for 6 additional months.

2.2.3 Placebo

Participants receiving placebo treatment were subject to the same treatment protocol as those in the active medication group. As with zopiclone, the placebo capsules were made of gelatine and there were no differences in appearance, smell and flavor between the active and inactive pills. After the 6 weeks, participants in the placebo group were immediately randomized into one of the two active treatment conditions. Thus, the present study provides no follow-up data after 6 months for the placebo condition. Data from participants who received an active treatment following the placebo condition, were not considered in any of the statistical comparisons conducted. The rationale for omitting these data was to retain a comparison of solely the effects of CBT versus zopiclone, without including participants who had received both placebo medication and subsequently either zopiclone or CBT. As the zopiclone and placebo condition were administered in a standard double-blind fashion,

neither the patients nor the therapists knew whether the patient received the active or inactive treatment.

2.3 Instruments

2.3.1 Instruments in paper I

Disability Pension Award (dependent variable)

The National Insurance Administration records all grants of disability pensions, which is solely a public responsibility in Norway. Correct registration is a prerequisite for transfers of payments; thus, the records are highly accurate. The criterion for being awarded a disability pension is an application from the general practitioner stating cause-specific and lasting reduced functional ability due to an acknowledged medical condition. Further examinations from organ-specific medical specialists are generally undertaken when appropriate, although independent examination is not required.

Insomnia

In paper I, a proxy for the DSM-IV insomnia diagnosis was based on three items, encompassing persons reporting sleep onset or maintenance insomnia "often" or "almost every night" in the last month, in addition to reporting impaired work performance caused by the sleep problems during the last year.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a self-report questionnaire comprising 14 four-point Likert-scaled items, seven for anxiety (HADS-A) and seven for depression (HADS-D). No somatic items or items regarding sleeping difficulties are included. A cut-off score of 8 on either subscale gives an optimal balance between sensitivity and specificity at about 0.80 for both depression and anxiety according to DSM-III and IV, ICD-8 and 9 (Bjelland, Dahl, Haug, & Neckelmann, 2002).

Physical health in HUNT-2

Physical health was assessed in two separate ways, as previously described by Mykletun et al. (in press). 1) An index for somatic symptoms was computed as the sum of organ systems from which symptoms were reported. These organ systems were weighted as described in the analyses (see Paper I for details). 2) An index for self-reported somatic diagnoses.

Socio-demographic variables and health-related behavior

Information on age and gender at the time of the HUNT-2 study was obtained from the national population registry. Socioeconomic status (SES) and educational level have previously been shown to be associated with disability pension (Krokstad & Westin, 2004). SES was measured by using a validated approximation from the HUNT-2 study (Krokstad & Westin, 2002). Educational level (3 levels), night/shift work, daily cigarette smoking, having consumed too much alcohol during the last 14 days, and being physically active for one or more hours in the last week were based on self-report.

2.3.2 Measures and instruments in paper II and paper III

Polysomnography.

Sleep variables were assessed by ambulant clinical polysomnography (PSG) at pre- and post-treatment and at 6 months follow-up. To allow for patient adaptation, PSG-data from the first night were not used. At both post-treatment and follow-up assessment, only one night of polysomnography was recorded, as recent studies have demonstrated that the so-called "first night effect" primarily is present in the first night in the first assessment period (Lorenzo & Barbanoj, 2002).

Actigraphy (not reported in paper II)

Actigraphic data were collected using the Actiwatch Plus unit manufactured by Cambridge Neurotechnology. The sensitivity of the actigraphy was set to the medium level, and 30 seconds epochs were used to allow epoch-by-epoch comparison with PSG. This actigraph had a button that enabled the participants to signal when they tried to fall asleep and when they got out of bed in the morning.

Sleep diaries (not reported in paper III)

Participants completed sleep diaries (Lichstein & Riedel, 1994) every morning for two weeks at pre-treatment, during treatment, post-treatment and follow-up. The sleep diary provides self-rated information about the same sleep parameters as collected from PSG-registration, including total wake time, total sleep time, sleep onset latency and sleep efficiency.

2.4 Statistics

SPSS for Windows 13 was used for all statistical analyses.

2.4.1 Statistics in Paper I

Logistic regression analysis was used to examine the relationship between insomnia and award of a disability pension. Possible confounders were entered into the model for adjustment. Pearson Chi-Square Tests were used to examine differences of baseline demographic and clinical characteristics in 1995-1997 on permanent work disability at follow-up. Pearson Chi-Square Test was also used to examine the causes of permanent work disability in those with and without insomnia.

2.4.2 Statistics in Paper II

Intention-to-treat analyses based on endpoint data were used throughout the study. Pre-treatment data were brought forward and used as post- and follow-up data for participants who dropped out during treatment (n=1), whereas post-data were used as follow-up (n=7) for those lost during follow-up. A 2 × 3 (Time × Intervention) ANCOVA analysis with Bonferroni post-hoc comparison was used to investigate differences between the interventions in terms of treatment effects. ANCOVAs were also used to examine the treatment effects at follow-up, and Paired Sample t-tests were used to compare the post- and follow-up levels. The clinical significance of the treatment effects was estimated by the proportion of participants who reached PSG-recorded sleep efficiency level of at least 85 % (Morin, Colecchi, Stone, Sood, & Brink, 1999), and Pearson Chi-Square Tests were used test for group differences. Within-group effect-sizes (pooled SD) were calculated using Cohen's d – formula (Cohen, 1988).

2.4.3 Statistics in Paper III

Agreement or disagreement between actigraphic data and PSG was assessed for each 30 seconds epoch. Sensitivity was defined as the ability of actigraphy to detect sleep when a participant was sleeping according to polysomnography, while specificity was defined as the ability of actigraphy to detect wake when a participant was awake according to polysomnography. Objective sleep estimates (OSE) was computed using the following formula as proposed by Edinger and Fins (Edinger & Fins, 1995): actigraphy measure / PSG-measure * 100. An OSE value of 100% indicates a perfect concordance between the actigraphy and PSG assessment. Paired samples t-tests were used to examine differences between pre- and post assessments, while Pearson correlations were used to examine the relationship between the participants' PSG-registered sleep efficiency and the accuracy level

of their actigraphy recordings. Wilcoxon Signed Ranks Tests were used to examine to what extent actigraphy over- or underestimated the sleep measures compared to PSG. Intragroup (pre-post) effect-sizes (ES) were calculated using Cohen's d – formula (Cohen, 1988).

3. Results

3.1 Paper Abstracts

3.1.1 Paper I

Sivertsen, B., Overland, S., Neckelmann, D., Glozier, N., Krokstad, S., Pallesen, S., Bjorvatn, B. & Mykletun, A. (2006). The long-term effect of insomnia on work disability. The HUNT-2 historical cohort study. *American Journal of Epidemiology, 163*(11), 1018-1024.

Chronic insomnia is common in the general population. Its effect on functioning and disability is usually attributed to an underlying condition, so the diagnosis of insomnia does not qualify award of a disability pension in the United States or Europe. The aim of this study was to investigate whether insomnia, defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, contributed to long-term work disability. Using a historical cohort design, the authors gathered baseline data from a population-based Norwegian health study of 37,308 working-age people not claiming a disability pension through 1995–1997. The outcome was subsequent award of a disability pension (18–48 months after the health screening) as registered by the National Insurance Administration. Insomnia was a strong predictor of subsequent permanent work disability (adjusted odds ratio = 3.90, 95% confidence interval: 3.20 - 4.76). Sociodemographic and shift-work characteristics had little confounding effect (adjusted odds ratio = 3.69, 95% confidence interval: 3.00 - 4.53), and this association remained significant after adjustment for psychiatric and physical morbidity and for health-related behaviors (adjusted odds ratio = 1.75, 95% confidence interval: 1.40 - 2.20). This study suggests that insomnia should receive increased attention as a robust predictor of subsequent work disability.

3.1.2 Paper II

Sivertsen, B., Omvik, S., Pallesen, S., Bjorvatn, B., Havik, O. E., Kvale, G., Nielsen, G. H., Nordhus, I. H. (2006). Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults. A randomized controlled trial. *JAMA, 295*(24), 2851-2858.

Context: Insomnia is a common condition in older adults and is associated with a number of adverse medical, social, and psychological consequences. Previous research has suggested beneficial outcomes of both psychological and pharmacological treatments, but blinded placebo-controlled trials comparing the effects of these treatments are lacking.

Objective: To examine short- and long-term clinical efficacy of cognitive behavioral therapy (CBT) and pharmacological treatment in older adults experiencing chronic primary insomnia.

Design, Setting, and Participants: A randomized, double-blinded, controlled trial of 46 adults (mean age 60.8 y; 22 women) with chronic primary insomnia conducted between January 2004 and December 2005 in a single university-based outpatient clinic for adults and elderly patients.

Intervention: CBT (sleep hygiene, sleep restriction, stimulus control, cognitive therapy, and relaxation; n = 18), sleep medication (7.5 mg zopiclone each night; n = 16), or placebo medication (n = 12). All treatment duration was 6 weeks and the 2 active treatments were followed up at 6 months.

Main Outcome Measures: Ambulant clinical polysomnographic data and sleep diaries were used to determine total wake time, total sleep time, sleep efficiency, and slow-wave sleep (only assessed using polysonmography) on all 3 assessment points.

Results: CBT resulted in much better short- and long-term outcomes than zopiclone on 3 out of 4 outcome measures. For most outcomes, zopiclone did not differ from placebo. Participants receiving CBT improved their sleep efficiency from 81.4% at pre-treatment to 90.1% at 6 month follow-up, compared with a decrease from 82.3% to 81.9% in the zopiclone group. Participants in the CBT group spent much more time in slow-wave sleep (stages 3 and 4) compared with those in other groups, and spent less time awake during the night. Total sleep time was similar in all 3 groups; at 6 months patients receiving CBT had better sleep efficiency using polysomnography than those taking zopiclone.

Conclusions: Our results suggest that interventions based on CBT are superior to zopiclone treatment both in short- and long-term management of insomnia in older adults.

3.1.3 Paper III

Sivertsen, B., Omvik, S., Havik, O. E., Pallesen, S., Bjorvatn, B., Nielsen, G. H., Straume, S. & Nordhus, I. H. (2006). A comparison of actigraphy and polysomnography in older adults treated for chronic primary insomnia. *Sleep, 29*(10), 1353-1358.

Study Objectives: The present study explores the accuracy and clinical utility of actigraphy compared with polysomnography (PSG) in older adults treated for chronic primary insomnia.

Design: Polysomnographic and actigraphic data were collected at pre- and post-treatment.

Setting: A university-based outpatient clinic for adults and elderly.

Participants: Thirty-four participants with chronic primary insomnia. Mean age was 60.5 years.

Interventions: Participants received either a manualized treatment package based on cognitive-behaviors therapy (CBT) and sleep management, or hypnotic drug treatment (7.5

mg zopiclone) for 6 weeks (these findings are reported elsewhere).

Measurements and results: While the sensitivity of actigraphy to detect sleep was very high (95.2 %), actigraphy performed poorly in detecting wakefulness (specificity: 36.3 %), yielding on overall level of accuracy of 83.1 %. However, the level of actigraphy accuracy was dependent upon PSG-registered sleep efficiency. Actigraphy underestimated total wake time and sleep onset latency, and consequently overestimated total sleep time and sleep efficiency. Compared with PSG, actigraphy captured only part of the treatment effects on total wake time and sleep onset latency, and failed to detect significant changes in sleep efficiency.

Conclusions: The present findings suggest that the clinical utility of actigraphy is still suboptimal in older adults treated for chronic primary insomnia, and should hence be used in this clinical setting with the concurrent use of supplementary assessment methods.

4. Discussion

4.1 Summary of findings

In Paper I we found that insomnia at baseline was a significant risk factor for subsequent award of disability pensions. Almost half of this effect was not explained by insomnia being associated with anxiety and depression, somatic diagnoses, and somatic symptoms (secondary insomnia).

In Paper II, CBT proved to have significantly better short-term and lasting treatment effects compared with zopiclone. On average, participants receiving CBT improved their PSG-registered sleep efficiency by 9.2 % at post-treatment, as compared a deterioration of 1 % in the zopiclone condition, a difference that was both statistical and clinical significant. Furthermore, participants in the CBT group spent significantly more time in slow wave sleep (stage 3/4) following treatment as compared to the other conditions. All significant group differences were maintained at follow-up, with between group effect-sized (ES) of 1.4 (total wake time), 1.0 (sleep efficiency) and 0.9 (slow wave sleep) at follow-up.

In Paper III we found actigraphy to have a relatively high level of accuracy using PSG as the standard. However, its ability to detect wakefulness was relatively poor suggesting that actigraphy remains less than ideal in the study of sleep disorders, which per definition involves much wake-time. Consequently, we still consider it to be somewhat premature as the sole instrument in such studies. In terms of the ability of actigraphy to detected treatment changes, it captured significant effects (although lower effect sizes) on two of three outcome measures, failing to detect significant changes on sleep efficiency.

4.2 Methodological limitations

4.2.1 Methodological limitations in paper I

In this epidemiological study, no data on disability awards were available in the non-response group, and selection bias cannot thus be ruled out. In the HUSK study (comparable to the HUNT study in population size, but with a more limited age-range), the rate of disability pensioning was higher amongst the non-attendees than amongst participants, and this is likely also to be the case in the HUNT study. Second, the measurement of insomnia was established by self-report rather than clinical diagnosis, and does not encompass an item on the duration of insomnia. Beyond the duration criterion, the questions in this study were tailored to meet the criteria for insomnia as specified by DSM-IV. The prevalence rate found in the present study is somewhat lower than previously reported, suggesting that the present criteria gave a conservative estimate (Ohayon, 1997; Pallesen et al., 2001). The absence of the duration criterion in our questions on insomnia may reduce the specificity of the measure, and thus cause an underestimation of the true association. However, when considering the curvilinear association between age and insomnia, the prevalence rates most likely depict a reasonable estimate of insomnia as our population consists of working persons under the age of 67. Third, our adjustments in the final analyses will most likely not capture and fully attenuate all possible confounding factors from chronic somatic or psychiatric conditions. Self-report instruments are prone to error and residual confounding cannot be ruled out. Screening for psychiatric morbidity was limited to symptoms of anxiety and depression only, and through a relatively short inventory not including vegetative symptoms of anxiety and depression. In some cases, depression may be largely presented and experienced through these kinds of symptoms (Davidson & Turnbull, 1986). As such, those with sub-threshold depression may be over-represented within the insomniacs, thus causing an underestimation of the true confounding effect of psychiatric morbidity.

Furthermore, the impacts of, for example, psychoses or other psychiatric conditions which are often associated with impaired sleep (Tandon et al., 1992), are likely to have been only partly captured. Although the participants had one open answer category for "other diseases", this option is not sufficient to capture all relevant diseases and symptoms as it demands subjective insight in psychiatric morbidity. However, it is commonly held that serious psychopathology increases the risk of being a non-attendee in epidemiological studies (Eaton et al., 1984), thus limiting the potential problem of psychopathology not being registered by the procedures employed here. Information on somatic diagnoses and symptoms were self-reported, and the categories used were not exhaustive. If such diagnosis and symptoms were under-reported, the effect of insomnia may in turn be overestimated. However in our fully adjusted model, insomnia is only considered to predict disability pension if reported somatic diagnoses, somatic symptoms, anxiety or depression do not serve as a possible alternative explanation. As this model assumes the insomnia is secondary in all cases of simultaneous occurrences, there is a risk that we have underestimated the strength of the association of insomnia with later disability pension. Finally, there are other potential confounders such as incipient cognitive decline, poor coping and work pressures which have not been captured in our measures yet may be related to both baseline insomnia (sleep disturbance symptoms are far more prevalent in the population than the diagnoses used in these regression models) and later disability pension. The lower association of disability with insomnia without impairment suggests that work problems and other functional limitations may be acting as unmeasured confounders.

4.2.2 Methodological limitations in paper II

In this treatment study, only participants with chronic primary insomnia were included, and our results may thus not generalize to patients whose sleep problems are secondary to mental

and somatic conditions, although a growing body of literature now shows that CBT for secondary insomnia may yield similar positive results (Lichstein, Wilson, & Johnson, 2000; Smith, Huang, & Manber, 2005). No information was available to examine the prolonged treatment effects beyond the last follow-up assessment at six months after treatment completion. However, as the treatment effects in the CBT condition were actually stronger at follow-up than at post-treatment, our findings suggest that the durability of CBT is quite convincing. Furthermore, the group sizes in the present study were relatively small. Patients who completed the placebo treatment were all randomized into an active treatment, but these were excluded from the final analyses. When conducting the statistical analyses of *all* treated patients (CBT=23, zopiclone=22), we found approximately identical or higher effect sizes in the CBT-group, while the zopiclone group remained mostly unchanged. It should also be noted that we were unable to blind the CBT condition, and that no non-pharmacological placebo group was used in the present study. We also have no data specifically addressing daytime sleepiness, which would have been interesting in line with the observed changes in slow wave sleep. Finally, care should be taken with regard to generalizing the present findings of zopiclone to other sleep medications.

4.2.3 Methodological limitations in paper III

Due to technical problems with some of the actigraphs, the number of participants is lower than originally enrolled in the treatment study. The sample size was additionally reduced as some participants forgot to wear their actigraph at the night of PSG-registration. We also excluded participants who did not complete the treatment protocol. Although we cannot rule out selection biases, we consider this less likely as the participants lost in the study did not differ from those included. Second, the average sleep quality at pre-treatment assessment was relatively adequate (PSG sleep efficiency of 81.8%), which may limit the

generalizability to people whose sleep is more severely affected. The results may also not generalize to people whose sleep problems are secondary to psychiatric or medical conditions. It should also be noted that both the hardware and software used for the registration and scoring in the present study may differ from other studies, and may complicate direct comparisons of results across studies. Furthermore, we did not assess the stability of actigraphy over several nights. In a study by van Hilten et al. (van Hilten et al., 1993) on older healthy participants, the authors found significant internight and intrasubject variability, although no evidence of a "first-night effect" was found. Future research should seek to explore the stability of actigraphy in samples with sleep problems. Finally, it should be noted that actigraphy might have other potential utilities such as weekly progress reinforcement or compliance verification during treatment.

4.3 Study implications and general discussion

4.3.1 Insomnia and work disability

This study is the first to document an independent association between insomnia and subsequent permanent work disability in a prospective study. In contrast to all previous studies, this study uses official records of disability pensions as the measure of work disability. Self-reports of work disability are likely to be less accurate than official records (Mykletun, in press), leaving open the possibility that subjective experience of work disability is being measured, and not de facto work disability. As previous research largely has been cross-sectional, the direction of the relationship and causal pathways have been difficult to determine (Linton & Bryngelsson, 2000). The association between poor sleep and work disability is commonly thought to be mediated through somatic or psychological factors which may serve as an explanation for the previous neglect of this topic. This assumption is well founded as, in addition to being linked to various medical conditions

(Shapiro, Devins, & Hussain, 1993), impaired sleep often is a core symptom of several psychiatric disorders (American Psychiatric Association, 1994), and has been shown to precede both depression and anxiety (Ford & Kamerow, 1989; Vgontzas & Kales, 1999). Psychological morbidity, in turn, has been shown to play a considerable role in explaining permanent work disability (Mykletun, in press). However, although we cannot rule out the possibility of residual confounding, our study suggests that insomnia is independently associated with subsequent work disability, and that this relationship remains significant even after adjustment for a range of possible clinical and demographic confounders. Furthermore common behavioral factors often linked with sleep disturbance such as shift working, physical exercise and alcohol intake did not attenuate, or mediate, this association.

4.3.2 Consequences of disability pensioning for the society

Following decades of steady increase, disability expenditure (including disability pensions, income maintenance and support) now accounts for a significant proportion of national income both in Europe and the US (OECD, 2003, 2004), despite overall improvements in several objective health indicators (McKee & Jacobson, 2000). At the end of 2004, there were 302 369 permanent disability pensioners in Norway, and additional 8515 on time-limited disability pension (according to revised rules for award of disability pension) (Olsen, 2005). Disability expenditure accounts for 5 % of Gross Domestic Products (GDP) in Norway (OECD, 2003), and the direct expenses to permanent disability pensions were 41 billion NOK (7 NOK = $1) in 2004, accounting for 18% of the total expenses to social security in Norway (Olsen, 2005). Mental disorders are now estimated to account for one third of workers disability claims in OECD countries (OECD, 2003), and a recent large population study from Norway suggests that the importance of anxiety and depression for the award of disability pensions may be underestimated (Mykletun, in press). Contrasting

our findings expressed through the population attributable fractions (PAFs – additional analyses [not reported here]) to the study in the same population, a reduction of exposure to insomnia may serve as an equally significant intervention against rising disability expenditure as improved recognition and treatment of depression. Despite insomnia being an acknowledged diagnosis in all three diagnostic systems, it is considered insufficient for issuing disability pensions, probably due to the tendency to regard insomnia as secondary to most other co-occurring disorders. Our results suggest that an increased focus on insomnia as a primary diagnosis but also as a symptom secondary to other disorders, may contribute to reduce the societal burden from work disability.

4.3.3 Treatment of insomnia in older adults

A Cochrane Review concluded with only a mild effect of CBT for sleep problems in older adults (Montgomery & Dennis, 2003). By contrast, our findings indicate a much stronger effect, with within-group effect sizes (ES) of CBT ranging from 0.6 to 1.7 at follow-up on total wake time, sleep efficiency and slow wave sleep. Although we found no significant changes in PSG-registered total sleep time, the participants' sleep diaries yielded significant treatment gains across the treatment conditions. Extending the findings by Morin (Morin, Colecchi, Stone, Sood, & Brink, 1999), the present study provides additional evidence that CBT produces both short- and long-lasting treatment effects in older adults suffering from insomnia. The clinical significance of the CBT was underscored with 72 % of the participants having a PSG-registered sleep efficiency level of at least 85 % at post-treatment assessment, compared to 33 % at pre-treatment.

In contrast to the results by Morin and colleagues, we found no significant treatment effects in the pharmacological group, neither at post-treatment or 6 months later. Zopiclone showed no better effect than placebo, and produced significantly *less* slow wave sleep at post-

treatment compared to pre-treatment. This is somewhat surprising, as numerous clinical trials have shown that short-term use of zopiclone is at least as effective as the older benzodiazepines in patients with insomnia (Noble, Langtry, & Lamb, 1998). However, almost no studies have investigated the effects of zopiclone beyond 4 weeks, and we cannot rule out that participants in this condition may have developed tolerance when they were assessed after 6 weeks. Furthermore, some of the enrolled participants expressed dissatisfaction about being randomized into the medication (zopiclone or placebo) condition due to previous use of medication, which may have influenced the treatment outcome.

The observed discrepancies between changes in objective and subjective sleep time in both active treatment conditions should be noted. However, the reliability and validity of sleep diaries have previously been questioned, as patients' self-reported sleep time has been shown to deviate from findings based on PSG, ranging from underestimations to overestimations (Edinger & Fins, 1995).

4.3.4 Discontinuation of sleep medications

Although pharmacotherapy may be indicated for situational insomnia, prolonged use beyond 2-4 weeks is usually not recommended. Still, more than 65% of those who use sleep medications continue to do so for more than 1 year, and as many as 30% for more than 5 years (Morgan, 2000; Morgan, Dallosso, Ebrahim, Arie, & Fentem, 1988; Ohayon & Caulet, 1996). In a recent study by Sivertsen et al. on chronic hypnotic users (> 1 year on a daily basis), polysomnographic registrations showed that almost 70 % of the participants satisfied the diagnostic criteria for either sleep apnea, PLMS or both (Sivertsen, Omvik, Pallesen, Nordhus, & Bjorvatn, 2004). Such findings are unsettling, as sleep medications are contraindicated for sleep apnea, as they may worsen the symptoms.

Discontinuation of sleep medication for insomnia can be a difficult task, and involves

significant challenges for the patient, even when they have been used at low therapeutic

doses (Schneider-Helmert, 1988). A few studies have evaluated behavioral interventions

aimed at reducing sleep medications. These show that setting up a step-by-step withdrawal

protocol closely monitored by health personnel, may yield better results in terms of reducing

the use of hypnotics, compared to simply encouraging patients to reduce their medication.

Also, such supervised medication tapering regimens are more likely to be successful when

implemented gradually and not abruptly (Morin et al., 2004). A common problem with many

discontinuation studies has been high relapse rates following discontinuation (often

exceeding 50% at follow-up). However, a recent study by Morin et al. suggests that booster

sessions based on CBT might prove useful in preventing relapse (Morin, Belanger, Bastien,

& Vallieres, 2005).

4.3.5 Treatment of secondary insomnia

Until recently, the majority of the literature on psychological interventions for insomnia has

mainly focused on primary insomnia, and it remained unclear to what extent and how this

approach could be effectively applied to treat individuals with psychiatric and medical

comorbidity. But as both clinicians and researchers recognized the need to adapt and test the

efficacy of CBT-based interventions in patients with such co-morbidities, there is now an

emerging body of evidence suggesting that the efficacy of CBT for chronic secondary

insomnia is encouraging (Smith, Huang, & Manber, 2005). To date, CBT has been

successfully used to relieve symptoms of insomnia in patients with cancer (Cannici,

Malcolm, & Peek, 1983; Davidson, MacLean, Brundage, & Schulze, 2002; Quesnel, Savard,

Simard, Ivers, & Morin, 2003; Simeit, Deck, & Conta-Marx, 2004), chronic pain (Currie,

Wilson, Pontefract, & deLaplante, 2000; Morin, Kowatch, & Wade, 1989), and HIV

(Dreher, 2003). CBT has also been successfully used for insomnia in some psychiatric conditions, including depression (Kuo, Manber, & Loewy, 2001; Manber et al., 2001; Morawetz, 2000), post traumatic stress disorder (PTSD) (Krakow et al., 2001), and alcoholism (Greeff & Conradie, 1998). Effect sizes across most of the studies are quite large and consistent with effect sizes reported for primary insomnia (Smith, Huang, & Manber, 2005). However, many of these studies suffer from methodological limitations, and there is clearly a need for randomized controlled trials to investigate the effect of CBT in both these and other illnesses and disorders, in which symptoms of insomnia frequently occur.

4.3.6 Actigrahy compared to PSG

Although previous studies have shown a good concordance between PSG and actigraphy (see e.g., Tryon, 1996), many of these studies have merely reported bivariate correlation coefficients or percent agreement, thus failing to correct for the expected chance agreement due to the high proportion of sleep epochs compared to wake epochs. Although the present findings suggest that the accuracy of the actigraphy in this study is similar or slightly better compared to studies on other sleep related disorders (Blood, Sack, Percy, & Pen, 1997; Kushida et al., 2001), the low specificity remains problematic as it indicates that a high base rate of sleep may still produce high accuracy despite modest performance in detecting wakefulness. Furthermore, there were large individual differences on the specificity measure of the actigraph, which underscores its problems on capturing wake-time in some people. Another important finding is that the accuracy level was dependent on the quality of sleep. This indicates that the level of accuracy in people with severely impaired sleep (a larger proportion of wake epochs) will be considerably lower, thus reducing the applicability of actigraphy in these persons. However, the actigraph accuracy was also low in some participants with relatively good sleep (PSG-registered sleep efficiency > 80). To further

improve the accuracy of actigraphy, the computer algorithms on which the actigraphs are based should be derived from a population that resembles the one being studied. An approach by weighting nighttime movements differently has previously been attempted in other sleep disorders (Hauri & Wisbey, 1992), and may also enhance the actigraphs ability to adequately capture sleep/wake patterns in elderly insomniacs.

As noted by Tryon (2004), one cannot expect the correspondence of actigraphy with PSG to exceed the reliability of PSG scorings. In an early study by Spiegel the reliability of stage 1-scoring in PSG was estimated to be only around 60 % (Spiegel, 1981), suggesting that a substantial proportion of the difference between PSG and actigraphy (sleep-wake scoring) may be ascribed to individual differences in scoring of stage 1 sleep in PSG (Tryon, 2004). In a more recent study, Whitney et al.(Whitney et al., 1998) showed that the percentage agreement on wakefulness scoring across scorers was between 87 – 90 %, suggesting a much higher reliability.

Despite systematic differences and errors between actigraphy and PSG: if actigraphy can still detect clinical improvements over time following treatments, the clinical utility of actigraphy can be supported. A few studies have demonstrated that actigraphy is able to detect treatment effects on several sleep parameters in middle-aged adults (Vallieres & Morin, 2003; Verbeek, Arends, Declerk, & Beecher, 1994). Likewise, two small scale studies of older adults have indicated a similar ability of actigraphy to detect changes following treatment (Brooks, Friedman, Bliwise, & Yesavage, 1993; Friedman et al., 2000). Our results are somewhat more ambiguous, with actigraphy failing to detected significant changes in sleep efficiency. This may partly be explained by the fact that actigraphy significantly overestimated both total sleep time and sleep efficiency at pre-treatment, and conversely underestimated the amount of wakefulness, leading to a ceiling effect. However,

actigraphy was still able to identify significant changes in both total sleep time and total wake time, underscoring the importance of using multiple sleep measures in treatment studies.

4.4 Conclusions

In paper I, we conclude that insomnia should be understood as an independent risk factor for subsequent work disability. Considering the direct costs of disability expenditures, in addition to the indirect costs from lost productivity, sleep medications and sleep-related accidents, we believe that early detection and interventions for insomnia should receive increased focus.

In paper II, we conclude that the demonstrated clinical efficacy of CBT should have important implications for the clinical management of chronic primary insomnia in older adults. Given the increased amount of evidence of CBT in insomnia in older adults, prescribed hypnotics should be limited to acute insomnia, especially as the present study found no improvement neither at 6 weeks or 6 months in the pharmacotherapy group. At present, CBT-based interventions for insomnia are not widely available in clinical practice, and future research should focus on implementing low-threshold treatment options for insomnia in primary care settings. As recently demonstrated by Bastien et al. (Bastien, Morin, Ouellet, Blais, & Bouchard, 2004), telephone consultations and CBT-based group therapy on younger insomniacs produced equally significant improvements as individual therapy sessions. Also, in a recent Swedish study, CBT delivered via the Internet in a self-help format showed significant improvements in chronic insomniacs (Strom, Pettersson, & Andersson, 2004). Recent findings suggest that self-help programs for insomnia based on CBT delivered in the context of community-based interventions, may offer significant clinical benefits (Morin, Beaulieu-Bonneau, LeBlanc, & Savard, 2005). Finally, future

research should seek to identify which single factors in the CBT-regime produce the best results, and to what extent "booster sessions" 12 or 24 months from initial treatment are necessary to maintain earlier improvements.

In paper III, we conclude that although recent reviews have suggested that actigraphy can be used as a reliable instrument for evaluating sleep patterns in adults (Ancoli-Israel et al., 2003; Sadeh & Acebo, 2002; Tryon, 2004), our findings indicate that this suggestion is not fully supported for older insomniacs. Future research should explore under which circumstances and for whom actigraphy may capture sufficient sleep information to be used in a clinical setting without the concurrent use of polysomnography.

5. References

Allaert, F. A., & Urbinelli, R. (2004). Sociodemographic profile of insomniac patients across national surveys. *CNS Drugs, 18 Suppl 1*, 3-7.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed.). Washington, D.C: APA.

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. P. (2003). The role of actigraphy in the study of sleep and circadian rhythms. *Sleep, 26*(3), 342-392.

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R., & Kaplan, O. (1991a). Periodic limb movements in sleep in community-dwelling elderly. *Sleep, 14*(6), 496-500.

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R., & Kaplan, O. (1991b). Sleep-disordered breathing in community-dwelling elderly. *Sleep, 14*(6), 486-495.

Ancoli-Israel, S., & Roth, T. (1999). Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. *Sleep, 22 Suppl 2*, S347-353.

Ashton, H. (1994). Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs, 48*(1), 25-40.

Bassa, R., Law, J., & Goldberg, L. A. (1994). Hypnotics usage among elderly patients in homes and hospital wards in Salford. *Pharm J, 252*(6783), 474-476.

Bastien, C. H., Morin, C. M., Ouellet, M. C., Blais, F. C., & Bouchard, S. (2004). Cognitive-behavioral therapy for insomnia: comparison of individual therapy, group therapy, and telephone consultations. *J Consult Clin Psychol, 72*(4), 653-659.

Beck, A. T. (1976). *Cogntive therapy and the emotional disorders*. New York: International University Press.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Vela-Bueno, A., & Kales, A. (2002). Insomnia in central Pennsylvania. *J Psychosom Res, 53*(1), 589-592.

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res, 52*(2), 69-77.

Bjorvatn, B., Leissner, L., Ulfberg, J., Gyring, J., Karlsborg, M., Regeur, L., et al. (2005). Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. *Sleep Med, 6*(4), 307-312.

Blood, M., Sack, R., Percy, D., & Pen, J. (1997). A comparison of sleep detection by wrist actigraphy, behavioral response, and polysomnography. *Sleep, 20*, 388-395.

Bootzin, R. R., & Epstein, D. R. (2000). Stimulus control. In K. L. Lichstein & C. M. Morin (Eds.), *Treatment of late-life insomnia* (pp. 167–184). Thousand Oaks, CA: Sage.

Bootzin, R. R., & Nicassio, P. M. (1978). Behavioral treatments for insomnia. In M. Hersen, R. Eissler & P. Miller (Eds.), *Progress of Behavior Modification* (Vol. 6, pp. 1-45). New York, NY: Academic Press.

Brooks, J. O., III, Friedman, L., Bliwise, D. L., & Yesavage, J. A. (1993). Use of the wrist actigraph to study insomnia in older adults. *Sleep, 16*(2), 151-155.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213.

Cannici, J., Malcolm, R., & Peek, L. A. (1983). Treatment of insomnia in cancer patients using muscle relaxation training. *J Behav Ther Exp Psychiatry, 14*(3), 251-256.

Chervin, R. D. (2001). Periodic leg movements and sleepiness in patients evaluated for sleep-disordered breathing. *Am J Respir Crit Care Med, 164*(8 Pt 1), 1454-1458.

Chesson, A. L., & et al. (1995). Practice parameters for the use of polysomnography in the evaluation of insomnia. Standards of Practice Committee of the American Sleep Disorders Association. *Sleep, 18*(1), 55-57.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, N. J.: Laurence Erlbaum.

Coleman, R., Bliwise, N. G., Sajben, N., & et al. (1988). Epidemiology of periodic movements during sleep. In C. Guilleminault & E. Lugaresi (Eds.), *Sleep/wake disorders. Natural history, epidemiology and long term evolution.* (pp. 217-229). New York, NY: Raven Press.

Currie, S. R., Wilson, K. G., Pontefract, A. J., & deLaplante, L. (2000). Cognitive-behavioral treatment of insomnia secondary to chronic pain. *J Consult Clin Psychol, 68*(3), 407-416.

Davidson, J., & Turnbull, C. D. (1986). Diagnostic significance of vegetative symptoms in depression. *Br J Psychiatry, 148*, 442-446.

Davidson, J. R., MacLean, A. W., Brundage, M. D., & Schulze, K. (2002). Sleep disturbance in cancer patients. *Soc Sci Med, 54*(9), 1309-1321.

Diagnostic Classification Steering Committee. (1990). *ICSD - International classification of sleep disorders: Diagnostic and coding manual*. Rochester, Minnesota: American Sleep Disorders Association.

Dreher, H. M. (2003). The effect of caffeine reduction on sleep quality and well-being in persons with HIV. *J Psychosom Res, 54*(3), 191-198.

Eaton, W. W., Holzer, C. E., 3rd, Von Korff, M., Anthony, J. C., Helzer, J. E., George, L., et al. (1984). The design of the Epidemiologic Catchment Area surveys. The control and measurement of error. *Arch Gen Psychiatry, 41*(10), 942-948.

Edinger, J., & Fins, A. (1995). The distribution and clinical significance of sleep time misperceptions among insomniacs. *Sleep, 18*, 232-239.

Edinger, J. D., & Means, M. K. (2005). Cognitive-behavioral therapy for primary insomnia. *Clin Psychol Rev, 25*(5), 539-558.

Edinger, J. D., & Wohlgemuth, W. K. (1999). The significance and management of persistent primary insomnia: the past, present and future of behavioral insomnia therapies. *Sleep Med Rev, 3*(2), 101-118.

Feinsilver, S. H. (2003). Sleep in the elderly. What is normal? *Clin Geriatr Med, 19*(1), 177-188, viii.

First, M. B., Spitzer, R. L, Gibbon, M., & Williams, J. B. W. (1995). *Structural clinical interview for DSM-IV axis I disorders*. New York: Biometrics Research Department.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Ford, D. E., & Kamerow, D. B. (1989). Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA, 262*(11), 1479-1484.

Friedman, L., Benson, K., Noda, A., Zarcone, V., Wicks, D. A., O'Connell, K., et al. (2000). An actigraphic comparison of sleep restriction and sleep hygiene treatments for insomnia in older adults. *J Geriatr Psychiatry Neurol, 13*(1), 17-27.

Greeff, A. P., & Conradie, W. S. (1998). Use of progressive relaxation training for chronic alcoholics with insomnia. *Psychol Rep, 82*(2), 407-412.

Hajak, G. (1999). A comparative assessment of the risks and benefits of zopiclone: a review of 15 years' clinical experience. *Drug Saf, 21*(6), 457-469.

Haponik, E. F., Frye, A. W., Richards, B., Wymer, A., Hinds, A., Pearce, K., et al. (1996). Sleep history is neglected diagnostic information. Challenges for primary care physicians. *J Gen Intern Med, 11*(12), 759-761.

Hauri, P. (1991). *Case studies in insomnia*. New York: Plenum Medical Book.

Hauri, P. J., & Wisbey, J. (1992). Wrist actigraphy in insomnia. *Sleep, 15*(4), 293-301.

Hening, W. A., Allen, R. P., Earley, C. J., Picchietti, D. L., & Silber, M. H. (2004). An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep, 27*(3), 560-583.

Hillman, D. R., Murphy, A. S., Antic, R., & Pezzullo, L. (2006). The economic cost of sleep disorders. *Sleep, 29*(3), 299-305.

Ingemarsson, A. H., Nordholm, L., & Sivik, T. (1997). Risk of long-term disability among patients with back pain. *Scand J Rehabil Med, 29*(4), 205-212.

Irwin, M. R., Cole, J. C., & Nicassio, P. M. (2006). Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol, 25*(1), 3-14.

Jacobsen, E. (1938). *You can sleep well*. New York, NY: McGrac-Hill Book Company.

Jones, H. J., & Derodra, J. K. (1997). Restless legs syndrome - a review. *Eur J Vasc Endovasc Surg, 14*(6), 430-432.

Krakow, B., Johnston, L., Melendrez, D., Hollifield, M., Warner, T. D., Chavez-Kennedy, D., et al. (2001). An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. *Am J Psychiatry, 158*(12), 2043-2047.

Krokstad, S., & Westin, S. (2002). Health inequalities by socioeconomic status among men in the Nord-Trondelag Health Study, Norway. *Scand J Public Health, 30*(2), 113-124.

Krokstad, S., & Westin, S. (2004). Disability in society-medical and non-medical determinants for disability pension in a Norwegian total county population study. *Soc Sci Med, 58*(10), 1837-1848.

Kuo, T., Manber, R., & Loewy, D. (2001). Insomniacs with comorbid conditions achieved comparable improvemnt in a cognitive behavioral group treatment program as insomniacs without comorbid depression. *Sleep, 14*, A62.

Kupfer, D. J., & Reynolds, C. F., 3rd. (1997). Management of insomnia. *N Engl J Med, 336*(5), 341-346.

Kushida, C. A., Chang, A., Gadkary, C., Guilleminault, C., Carrillo, O., & Dement, W. C. (2001). Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med, 2*(5), 389-396.

Lahmeyer, H. (1995). Hypnotics: a powerful tool for a serious problem. *Pharmacol Ther, 20*, 438-455.

Lavie, P., Silverberg, D., Oksenberg, A., & Hoffstein, V. (2001). Obstructive sleep apnea and hypertension: from correlative to causative relationship. *J Clin Hypertens (Greenwich), 3*(5), 296-301.

Leigh, J. P. (1991). Employee and job attributes as predictors of absenteeism in a national sample of workers: the importance of health and dangerous working conditions. *Soc Sci Med, 33*(2), 127-137.

Lichstein, K. L. (2004). *Epidemiology of sleep: age, gender, and ethnicity*. Mahwah, N.J.: Lawrence Erlabaum Assoc.

Lichstein, K. L., & Fischer, S. M. (1985). Insomnia. In M. Hersen & A. S. Bellack (Eds.), *Handbook of clinical behavior therapy with adults* (pp. 319–352). New York: Plenum Press.

Lichstein, K. L., & Morin, C. M. (2000). *Treatment of late-life insomnia*. Thousand Oaks: Sage Publications, Inc.

Lichstein, K. L., & Riedel, B. W. (1994). Behavioral assessment and treatment of insomnia: A review with an emphasis on clinical application. *Behavior Therapy, 25*, 659-688.

Lichstein, K. L., Wilson, N. M., & Johnson, C. T. (2000). Psychological treatment of secondary insomnia. *Psychol Aging, 15*(2), 232-240.

Linjakumpu, T., Hartikainen, S., Klaukka, T., Veijola, J., Kivela, S. L., & Isoaho, R. (2002). Use of medications and polypharmacy are increasing among the elderly. *J Clin Epidemiol, 55*(8), 809-817.

Linton, S. J., & Bryngelsson, I. (2000). Insomnia and its relationship to work and health in a working-age population. *J Occup Rehabil, 10*(2), 169-183.

Lorenzo, J. L., & Barbanoj, M. J. (2002). Variability of sleep parameters across multiple laboratory sessions in healthy young subjects: the "very first night effect". *Psychophysiology, 39*(4), 409-413.

Mahowald, M. W. (2001). Con: assessment of periodic leg movements is not an essential component of an overnight sleep study. *Am J Respir Crit Care Med, 164*(8 Pt 1), 1340-1341; discussion 1341-1342.

Manber, R., Loewy, D., Kuo, T., Black, J., Palombini, L., & Koester, U. (2001). The efficacy of cognitive behavioral group intervention in a tertiary setting. *Sleep, 24*, A63.

McKee, M., & Jacobson, B. (2000). Public health in Europe. *Lancet, 356*(9230), 665-670.

Mellinger, G. D., Balter, M. B., & Uhlenhuth, E. H. (1985). Insomnia and its treatment. Prevalence and correlates. *Arch Gen Psychiatry, 42*(3), 225-232.

Miles, L. E., & Dement, W. C. (1980). Sleep and aging: objective sleep parameters in elderly men and women. *Sleep, 3*, 131-150.

Moldofsky, H. (2001). Sleep and pain. *Sleep Med Rev, 5*(5), 385-396.

Monk, T. H. (1991). Sleep and circadian rhythms. *Exp Gerontol, 26*(2-3), 233-243.

Montgomery, P., & Dennis, J. (2003). Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database Syst Rev*(1).

Montgomery, P., & Dennis, J. (2004). A systematic review of non-pharmacological therapies for sleep problems in later life. *Sleep Med Rev, 8*(1), 47-62.

Montplaisir, J., Nicolas, A., Godbout, R., & Walters, A. (2000). Restless legs syndrome and periodic limb movement disorders. In M. E. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (pp. 742-752). London: W. B. Saunders Company.

Morawetz, D. (2000). Depression and insomnia. *Aust Fam Physician, 29*(11), 1016.

Morgan, K. (2000). Sleep and aging. In K. L. Lichstein & C. M. Morin (Eds.), *Treatment of late-life insomnia* (pp. 3-36). Thousand Oaks, CA: Sage Publications Inc.

Morgan, K., Dallosso, H., Ebrahim, S., Arie, T., & Fentem, P. H. (1988). Prevalence, frequency, and duration of hypnotic drug use among the elderly living at home. *Br Med J (Clin Res Ed), 296*(6622), 601-602.

Morgan, K., Thompson, J., Dixon, S., Tomeny, M., & Mathers, N. (2003). Predicting longer-term outcomes following psychological treatment for hypnotic-dependent chronic insomnia. *J Psychosom Res, 54*(1), 21-29.

Morin, C., Beaulieu-Bonneau, S., LeBlanc, M., & Savard, J. (2005). Self-Help Treatment for Insomnia: a Randomized Controlled Trial. *Sleep, 28*, 1319-1327.

Morin, C. M. (1993). *Insomnia: psychological assessment and management*. New York: Guilford Press.

Morin, C. M., Bastien, C., Guay, B., Radouco-Thomas, M., Leblanc, J., & Vallieres, A. (2004). Randomized clinical trial of supervised tapering and cognitive behavior

therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry, 161*(2), 332-342.

Morin, C. M., Belanger, L., Bastien, C., & Vallieres, A. (2005). Long-term outcome after discontinuation of benzodiazepines for insomnia: a survival analysis of relapse. *Behav Res Ther, 43*(1), 1-14.

Morin, C. M., Colecchi, C., Stone, J., Sood, R., & Brink, D. (1999). Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA, 281*(11), 991-999.

Morin, C. M., Culbert, J. P., & Schwartz, S. M. (1994). Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry, 151*(8), 1172-1180.

Morin, C. M., Hauri, P. J., Espie, C. A., Spielman, A. J., Buysse, D. J., & Bootzin, R. R. (1999). Nonpharmacological treatment of chronic insomnia. *Sleep, 22*, 1134-1156.

Morin, C. M., Kowatch, R. A., & Wade, J. B. (1989). Behavioral management of sleep disturbances secondary to chronic pain. *J Behav Ther Exp Psychiatry, 20*(4), 295-302.

Morin, C. M., Rodrigue, S., & Ivers, H. (2003). Role of stress, arousal, and coping skills in primary insomnia. *Psychosom Med, 65*(2), 259-267.

Murtagh, D. R., & Greenwood, K. M. (1995). Identifying effective psychological treatments for insomnia: a meta-analysis. *J Consult Clin Psychol, 63*(1), 79-89.

Mykletun, A., Overland, S, Dahl, A A, Krokstad, S, Bjerkeset, O, Glozier, N, Aaro, L E, Prince, M. (in press). A population-based cohort study of the effect of common mental disorder on disability pension awards *Am J Psychiatry*.

Nau, S. D., McCrae, C. S., Cook, K. G., & Lichstein, K. L. (2005). Treatment of insomnia in older adults. *Clin Psychol Rev, 25*(5), 645-672.

Noble, S., Langtry, H. D., & Lamb, H. M. (1998). Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs, 55*(2), 277-302.

Norwegian Institute of Public Health. (2004). *Drug Consumption in Norway*.

OECD. (2003). *Disability programmes in need of reform*: OECD Policy Brief.

OECD. (2004). *Transforming Disability into Ability. Policies to promote work and income security for disabled people*: OECD Publications Service.

Ohayon, M. M. (1997). Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *J Psychiatr Res, 31*(3), 333-346.

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Med Rev, 6*, 97-111.

Ohayon, M. M., & Caulet, M. (1996). Psychotropic medication and insomnia complaints in two epidemiological studies. *Can J Psychiatry, 41*(7), 457-464.

Olsen, H. (2005). *Trygdestatistisk årbok*: Rikstrygdeverket.

Pallesen, S., Nordhus, I. H., Havik, O. E., & Nielsen, G. H. (2001). Clinical assessment and treatment of insomnia. *Prof Psychol Res Pr, 32*(2), 115-124.

Pallesen, S., Nordhus, I. H., & Kvale, G. (1998). Nonpharmacological interventions for insomnia in older adults: A meta-analysis of treatment efficacy. *Psychotherapy, 35*(4), 472-482.

Pallesen, S., Nordhus, I. H., Nielsen, G. H., Havik, O. E., Kvale, G., Johnsen, B. H., et al. (2001). Prevalence of insomnia in the adult Norwegian population. *Sleep, 24*(7), 771-779.

Pilcher, J. J., & Huffcutt, A. I. (1996). Effects of sleep deprivation on performance: a meta-analysis. *Sleep, 19*(4), 318-326.

Quesnel, C., Savard, J., Simard, S., Ivers, H., & Morin, C. M. (2003). Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. *J Consult Clin Psychol, 71*(1), 189-200.

Reite, M., Buysse, D., Reynolds, C., & Mendelson, W. (1995). The use of polysomnography in the evaluation of insomnia. *Sleep, 18*(1), 58-70.

Reynolds, C. F., 3rd, Kupfer, D. J., Buysse, D. J., Coble, P. A., & Yeager, A. (1991). Subtyping DSM-III-R primary insomnia: a literature review by the DSM-IV Work Group on Sleep Disorders. *Am J Psychiatry, 148*(4), 432-438.

Richardson, G. S., & Roth, T. (2001). Future directions in the management of insomnia. *J Clin Psychiatry, 62 Suppl 10*, 39-45.

Riedel, B. W., & Lichstein, K. L. (2001). Strategies for evaluating adherence to sleep restriction treatment for insomnia. *Behav Res Ther, 39*(2), 201-212.

Rosenthal, N. E., Joseph-Vanderpool, J. R., Levendosky, A. A., Johnston, S. H., Allen, R., Kelly, K. A., et al. (1990). Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep, 13*(4), 354-361.

Rosmond, R., Lapidus, L., & Bjorntorp, P. (1998). A cross-sectional study of self-reported work conditions and psychiatric health in native Swedes and immigrants. *Occup Med (Lond), 48*(5), 309-314.

Roth, T., & Ancoli-Israel, S. (1999). Daytime consequences and correlates of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. II. *Sleep, 22 Suppl 2*, S354-358.

Roth, T., & Roehrs, T. (2003). Insomnia: epidemiology, characteristics, and consequences. *Clin Cornerstone, 5*(3), 5-15.

Sadeh, A., & Acebo, C. (2002). The role of actigraphy in sleep medicine. *Sleep Med Rev, 6*(2), 113-124.

Sadeh, A., Keinan, G., & Daon, K. (2004). Effects of stress on sleep: the moderating role of coping style. *Health Psychol, 23*(5), 542-545.

Salzman, C. (1982). Key concepts in geriatric psychopharmacology. Altered pharmacokinetics and polypharmacy. *Psychiatr Clin North Am, 5*(1), 181-190.

Sand, T., Hagen, K., & Schrader, H. (2003). Sleep apnoea and chronic headache. *Cephalalgia, 23*(2), 90-95.

Sateia, M. J., Doghramji, K., Hauri, P. J., & Morin, C. M. (2002). Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep, 23*, 243-248.

Sateia, M. J., & Nowell, P. D. (2004). Insomnia. *Lancet, 364*(9449), 1959-1973.

Savard, J., Laroche, L., Simard, S., Ivers, H., & Morin, C. M. (2003). Chronic insomnia and immune functioning. *Psychosom Med, 65*(2), 211-221.

Schneider-Helmert, D. (1988). Why low-dose benzodiazepine-dependent insomniacs can't escape their sleeping pills. *Acta Psychiatr Scand, 78*(6), 706-711.

Schweitzer, P. K. (2000). Drugs that disturb sleep and wakefulness. In M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (3rd ed., pp. 441- 461). London: W. B. Saunders.

Shapiro, C. M., Devins, G. M., & Hussain, M. R. (1993). ABC of sleep disorders. Sleep problems in patients with medical illness. *BMJ, 306*(6891), 1532-1535.

Simeit, R., Deck, R., & Conta-Marx, B. (2004). Sleep management training for cancer patients with insomnia. *Support Care Cancer, 12*(3), 176-183.

Simon, G. E., & VonKorff, M. (1997). Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry, 154*(10), 1417-1423.

Sivertsen, B., Omvik, S., Pallesen, S., Nordhus, I. H., & Bjorvatn, B. (2004). [Sleep disorders in elderly patients who take hypnotics on a regular basis]. *Tidsskr Nor Laegeforen, 124*(20), 2600-2602.

Smith, M. T., Huang, M. I., & Manber, R. (2005). Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clin Psychol Rev, 25*(5), 559-592.

Spiegel, R. (1981). *Sleep and Sleeplessness in Advanced Age*. New York: SP Medical & Scientific Books.

Spielman, A. J. (1986). Assessment of insomnia. *Clin Psychol Rev, 6*, 11-25.

Spielman, A. J., & Glovinsky, P. (1991). The varied nature of insomnia. In P. J. Hauri (Ed.), *Case studies in insomnia* (pp. 1-15). New York: Plenum Press.

Stoller, M. K. (1994). Economic effects of insomnia. *Clin Ther, 16*(5), 873-897; discussion 854.

Strom, L., Pettersson, R., & Andersson, G. (2004). Internet-based treatment for insomnia: a controlled evaluation. *J Consult Clin Psychol, 72*(1), 113-120.

Szelenberger, W., & Niemcewicz, S. (2000). Severity of insomnia correlates with cognitive impairment. *Acta Neurobiol Exp (Wars), 60*(3), 373.

Tandon, R., Shipley, J. E., Taylor, S., Greden, J. F., Eiser, A., DeQuardo, J., et al. (1992). Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. *Arch Gen Psychiatry, 49*(3), 185-194.

Tryon, W. W. (1996). Nocturnal activity and sleep assessment. *Clin Psychol Rev, 16*(3), 197-213.

Tryon, W. W. (2004). Issues of validity in actigraphic sleep assessment. *Sleep, 27*(1), 158-165.

Vallieres, A., & Morin, C. M. (2003). Actigraphy in the assessment of insomnia. *Sleep, 26*(7), 902-906.

van Hilten, J. J., Braat, E. A., van der Velde, E. A., Middelkoop, H. A., Kerkhof, G. A., & Kamphuisen, H. A. (1993). Ambulatory activity monitoring during sleep: an evaluation of internight and intrasubject variability in healthy persons aged 50-98 years. *Sleep, 16*(2), 146-150.

Verbeek, I., Arends, J., Declerk, G., & Beecher, L. (1994). Wrist actigraphy in comparison with polysomnography and subjective evaluation in insomnia. *Sleep-Wake Research in the Netherlands, 5*, 163-169.

Vgontzas, A. N., Bixler, E. O., Lin, H. M., Prolo, P., Mastorakos, G., Vela-Bueno, A., et al. (2001). Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab, 86*(8), 3787-3794.

Vgontzas, A. N., & Kales, A. (1999). Sleep and its disorders. *Annu Rev Med, 50*, 387-400.

Vollrath, M., Wicki, W., & Angst, J. (1989). The Zurich study. VIII. Insomnia: association with depression, anxiety, somatic syndromes, and course of insomnia. *Eur Arch Psychiatry Neurol Sci, 239*(2), 113-124.

Walsh, J., & Engelhardt, C. (1999). The direct economic costs of insomnia in the united states for 1995. *Sleep, 22*(Supl 2), S379-S393.

Watanabe, T., Kajimura, N., Kato, M., Sekimoto, M., & Takahashi, K. (1999). Effects of phototherapy in patients with delayed sleep phase syndrome. *Psychiatry Clin Neurosci, 53*(2), 231-233.

Whitney, C. W., Gottlieb, D. J., Redline, S., Norman, R. G., Dodge, R. R., Shahar, E., et al. (1998). Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep, 21*(7), 749-757.

World Health Organization. (2004). *ICD-10: International statistical classification of diseases and related health problems: 10th revision* (2nd ed.). Geneva: World Health Organization.

Yang, E. H., Hla, K. M., McHorney, C. A., Havighurst, T., Badr, M. S., & Weber, S. (2000). Sleep apnea and quality of life. *Sleep, 23*(4), 535-541.

Yves, E., Morin, C., Cervena, K., Carlander, R., Beset, A., & Billiard, M. (2003). Family studies in insomnia. *Sleep, 26*, A304.

Zammit, G. K., Weiner, J., Damato, N., Sillup, G. P., & McMillan, C. A. (1999). Quality of life in people with insomnia. *Sleep, 22 Suppl 2*, S379-385.

Zemlan, F. P., Mulchahey, J. J., Scharf, M. B., Mayleben, D. W., Rosenberg, R., & Lankford, A. (2005). The efficacy and safety of the melatonin agonist beta-methyl-6-chloromelatonin in primary insomnia: a randomized, placebo-controlled, crossover clinical trial. *J Clin Psychiatry, 66*(3), 384-390.

Zepelin, H. (1973). A survey of age differences in sleep patterns and dreamrecall among well-educated men and women. *Sleep Res, 2*(81).

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand, 67*(6), 361-370.

Appendix

Diagnostic criteria for primary insomnia (DSM-IV)

A.	The predominant complaint is difficulty initiating or maintaining sleep or nonrestorative sleep for at least 1 month.
B.	The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C.	The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
D.	The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, delirium).
E.	The disturbance is not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Diagnostic criteria taken from the Diagnostic and Statistical Manual, Fourth Edition, published by the American Psychiatric Association (1994).