

https://dspace.org/

The effect of the short term use of Zolpidem MR on poor sleep, daily pain and depression in arthritis patients

Benjamin, Daniela

2015-04-17
http://hdl.handle.net/10539/17443

Downloaded from a DSpace repository. https://dspace.org/

The effect of the short term use of Zolpidem MR on poor sleep, daily pain and depression in arthritis patients

By Daniela Benjamin

Supervisors

Dr Alison Bentley

Dr Karine Scheuermaier

A dissertation submitted to the Faculty of Health Science, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Science in medicine.

Johannesburg 2014

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Science in medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

Daniela Benjamin

____ th day of_____October_____2014

ABSTRACT

Introduction: The presence of pain during sleep causes patients with chronic daily pain, such as in Rheumatoid and Osteoarthritis, to experience insomnia, fragmented sleep and an increased number of night-time awakenings. This poor sleep results in an increased sensitivity to pain during the day. The effect of improving sleep on pain, sleep and mood after taking Zolpidem MR was the aim of this study.

Methods: 11 patients from Chris Hani Baragwanath Hospital in Soweto South Africa who reported insomnia and daily pain spent 4 weeks in this crossover design, double blinded, placebo controlled study. Week 1- baseline, week 2 and 4 were Intervention weeks – either placebo or Zolpidem MR, week 3 was a Washout week. Data collected included actigraphy, McGill Pain Questionnaire, PSQI, BDI, physical activity questionnaire and daily sleep and pain diaries containing VAS scales for sleep and pain.

Results: No significant changes were found in the pain or physical activity levels in any of the patients. Sleep quality, as measured by an isolated PSQI question, was improved by Zolpidem MR ($p=0.0075$). PSQI was decreased in the final week of the study compared to baseline (8.7 vs. 11.3, $p=0.0106$) and BDI was lower in week 4 than baseline (7.7 vs. 15.85, $p=0.0003$), BDI was also lower in week 4 compared to week 2 (7.7 vs. 12.8, $p<0.05$). However the changes in PSQI and BDI were a result of the order of the weeks, with patients interacting with the researcher and were not due to either Zolpidem MR or placebo. Anecdotal reports include feeling more energised and capable of living life.

Conclusion: This study has shown that human interaction is an important component of treatment for insomnia and chronic pain as there is a positive effect on sleep disruption and depression.

ACKNOWLEDGEMENTS

I would like to thank my supervisors Dr Alison Bentley and Dr Karine Scheuermaier for teaching me, encouraging me and guiding me through this Masters. Without their continued support I would not have been able to do this project.

I would like to thank Professor Mohammed Tikly and the entire Arthritis department at Chris Hani Baragwanath Hospital. I especially want to thank the patients without whom this study would not have been possible.

Thank you to the Sleep Laboratory at Wits University for their financial support, to the members of the sleep lab for all their help and particular thanks go to my lab partner Ryan Inkley for being in the trenches with me.

My gratitude goes out to my friends for their emotional support and encouragement throughout this project. Lastly and most importantly I would like to thank my parents who have been my rock throughout this Masters, who have been there for me through all the blood, sweat and tears and without whom I would never have managed to do anything in life, especially this Masters.

TABLE OF CONTENTS

DECLARATION ii

ABSTRACT iii

ACKNOWLEDGEMENTS iv

LIST OF FIGURES vii

LIST OF TABLES viii

LIST OF ABBREVIATIONS ix

CHAPTER ONE – LITERATURE REVIEW

1.1 Introduction 2

1.2 Sleep physiology 2
1.2.1 Sleep and wake promoting systems 2
1.2.2 Measurement of sleep - Objective 3
1.2.3 Measurement of sleep - Subjective 6

1.2.4.3 Insomnia 7
1.2.4.3.1 Definition/ diagnosis of insomnia 7
1.2.4.3.2 3P Model of primary insomnia 9
16 1.2.4.3.4 Epidemiology 10

1.3 Pain physiology 11
1.3.1 Definition 11
1.3.2 Measurement of pain 12
1.3.3 The effect of pain on sleep 12
1.3.4 Impact of sleep deprivation on physiological function 14
1.3.5 The effect of sleep deprivation on pain 16

1.4. Arthritis 17
1.4.1 Osteoarthritis 17
1.4.2 Rheumatoid arthritis 18
1.4.3 Epidemiology 18
1.4.4 Arthritis pain and sleep 19

1.5 Confounders-depression 21
1.5.1 Depression and sleep 21
1.5.2 Depression and pain 22

1.6 Physical activity 24

1.7 Treatment 26
1.7.1 Treating pain 26
1.7.2 Treating pain and insomnia in arthritis 27
1.7.3 Non – pharmacological treatment of insomnia 30
1.7.4 Pharmacological treatment of insomnia 31
1.7.4.1 Benzodiazepines 31

1.7.4.2 Non – benzodiazepines 32
1.7.4.2.1 Zolpidem 33

1.8 Literature review conclusion and objectives of this study 36

CHAPTER TWO – MATERIALS AND METHODS

2.1 Materials and methods 39

2.1.1 Participants 39

2.1.2 Study design 40
2.1.2.1 First meeting with Doctor 40
2.1.2.2 Baseline week 41
2.1.2.3 Washout week 41
2.1.2.4 Intervention 1/ intervention 2 41
2.1.2.5 Fifth meeting 42

2.1.3 Weekly Questionnaires 42
2.1.4 Actigraphy 44
2.1.5 Daily sleep diary 45
2.1.6 Medication 45

2.1.7 Data analysis 46
2.1.7.1 Weekly measurements 46
2.1.7.2 Daily measurements 48
2.1.7.3 Actigraphy measurements 48
2.1.8 Ethics 49

CHAPTER THREE - RESULTS

3.1 Results 51

3.1.1 Weekly measurements 52
3.1.2 Daily measurements 57
3.1.3 Actigraphy 58
3.1.4 Anecdotal report back from participants 59

CHAPTER FOUR – DISCUSSION

4.1 Discussion 62

REFERENCES 74

LIST OF FIGURES

Figure 1. A diagram of the study design shown along a timeline 40

Figure 2. The BDI score before and after testing for the 'hands on' effect 54

Figure 3. The McGill, PPI and PSQI scores after testing for the 'hands on' effect 55

Figure 4. Total minutes of physical activity of all intensities during baseline and washout weeks 55

Figure 5. A comparison between baseline week, placebo week and Zolpidem MR week for the combined number of minutes for the week 56

Figure 6. A comparison between baseline week, placebo week and Zolpidem MR week for the number of minutes spent in sedentary activities 56

Figure 7. A comparison between baseline week, placebo week and Zolpidem MR week for the number of minutes spent in light to moderate intensity activities 56

Figure 8. A comparison between baseline week, placebo week and Zolpidem MR week for the number of minutes spent in high intensity activities 56

Figure 9. Sum vector data taken from actigraphy represented as units of gravity (g). Figure 7a represents the sum vectors for the morning i.e. from wake time to midday; figure 7b represents the sum vectors for the afternoon i.e. from midday to bedtime and figure 7c represents the sum vectors for the night-time i.e. from bedtime to wake time 58

LIST OF TABLES

Table 1. Table showing the effects of hypnotics on pain and sleep in painful disorders 34

Table 2. Demographic, anthropometric and baseline data for all study participants 51

Table 3. Values for the weekly McGill (PRI) and PPI tests; PSQI total test, BDI and physical activity questionnaire score during baseline and washout weeks 52

Table 4. Values for the weekly McGill (PRI) and PPI tests; PSQI total test and physical activity questionnaire score during baseline and intervention weeks 52

Table 5. Values for selected individual PSQI questions during baseline and washout weeks 53

Table 6. Values for selected individual PSQI questions during baseline and intervention weeks 53

Table 7. Values for the daily VAS scores of combined sleepiness and fatigue; morning pain and evening pain during baseline and washout weeks 57

Table 8. Values for the daily VAS scores of combined sleepiness and fatigue; morning pain and evening pain during baseline and intervention weeks 57

LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
CBT-I	Cognitive Behavioural Therapy for Insomnia
DSM IV-TR	Diagnostic and Statistic Manual version 4 Text Revised
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth Sleepiness Scale
GABA	Gamma Aminobutyric Acid
GH	Growth Hormone
HPA	Hypothalamic-Pituitary-Adrenal
ICD-10	International Classification of Disease version 10
ICSD-2	International Classification of Sleep Disorders version 2
ISI	Insomnia Severity Index
MOA	Monoaminergic Neurons
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NREM	Non Rapid Eye movement

NSAID	Non Steroidal Anti Inflammatory Drugs
OA	Osteoarthritis
OSA	Obstructive Sleep Apnea
PAG	Periaquaductal Gray
PLMS	Periodic Limb Movements
PPI	Present Pain Intensity
PRI	Pain Rating Index
PSG	Polysomnogram
PSQI	Pittsburgh Sleep Quality Index
RA	Rheumatoid arthritis
REM	Rapid Eye Movement
RLS	Restless Leg Syndrome
SCN	Suprachiasmatic Nucleus
SNS	Sensory Nervous System
SWS	Slow Wave Sleep
VAS	Visual Analogue Scale
VLPO	Ventrolateral Preoptic Area of the Hypothalamus

CHAPTER ONE

Literature review

1.1 Introduction

This dissertation is based on chronic arthritis and investigates how the pain of arthritis interferes with sleep, as well as how an intervention to improve sleep can impact pain levels. The effect that sleep has on pain is important not only in daily life, but especially in illnesses which have chronic pain as a defining feature, such as arthritis. The level of pain experienced by these patients determines whether they believe treatment is effective, and anything which improves or worsens pain can greatly affect illness behaviour and prognosis. The next section is the literature review. It will be focusing on the negative impact disrupted sleep has on pain as well as the negative impact of high levels of pain on sleep. Specifically it will cover the topics of pain and sleep; a general introduction to sleep and its measurements; a general introduction to pain and its measurements and the interactions of sleep and pain in the context of arthritis. Included in the literature review will be a review on how depression may confound the relationship between pain and sleep, as well as how sleep and pain may impact physical activity.

1.2 Sleep physiology

1.2.1 Sleep and wake promoting systems

Wake promoting neurons consist of cholinergic neurons (located in the pedunculopontine and laterodorsal tegmental nuclei); monoaminergic neurons (MOA) (located in the locus coeruleus and ventral periaquaductal grey) as well as the serotonergic dorsal raphe nucleus and histaminergic tuberomammillary nucleus (Saper et al. 2005). Sleep promoting neurons are GABAergic and are found in the ventrolateral preoptic area of the hypothalamus (VLPO) (Gallopin et al. 2000; Lu et al. 2000). Sleep and wake pathways interact via a "flip-flop switch" between different brain regions (Saper et al. 2001). The "flip-flop switch" is co-

ordinated and maintained by hypocretin neurons located in the perifornical area of the lateral hypothalamus.

The typical length of a sleep episode during adult life is between 7 and 9 hours. Sleep itself is divided into non rapid eye movement (NREM) and rapid eye movement (REM) sleep, which make up four (new classification of sleep of the American Association of Sleep Medicine) (Iber et al. 2007) or five (older classification of sleep as described by Rechtschaffen and Kales (Rechtschaffen & Kales 1968)) distinct sleep stages: stage 1 (N1 in the new classification), stage 2 (N2 in the new classification), stage 3 and stage 4 (collectively called slow wave sleep and regrouped as one stage, N3, in the new classification) and Rapid eye movement (REM) sleep (R in the new classification). Stages 3 and 4 are termed slow wave sleep (SWS). Towards the beginning of the sleep episode the most dominant sleep stage is SWS while towards the end of the sleep episode REM sleep is more dominant (Rechtschaffen & Kales 1968; Porth 2009).

1.2.2 Measurement of sleep - Objective

The two main categories of sleep measurements are objective measurements and subjective measurements. The gold standard for the objective measures of sleep is polysomnography followed by actigraphy. The polysomnogram (PSG) is the method in which sleep is recorded. A PSG utilises electroencephalography (EEG), electrooculography (EOG) to record eye movements (crucial to detect REM sleep) and an electromyography (EMG) which records the amount of activity occurring in the muscles and can thus detect atonia (Porth 2009),the PSG details important aspects of sleep such as the time taken to fall asleep (sleep onset latency), the proportion of time spent in NREM sleep vs. REM sleep, the number of awakenings during the night (termed ‘wake after sleep onset’ or WASO) as well as the amount of time taken to start REM sleep from the beginning of the sleep period (REM sleep onset latency).

The PSG also allows for measurement of abnormal sleep such as sleep fragmentation and alpha intrusion (Porth 2009).

Sleep fragmentation can occur when a normal sleep EEG is interrupted by bursts of alpha activity or an increased EEG frequency, causing brief arousals (± 3 seconds) (Stepanski et al. 1984). Sleep fragmentation can also be a result of breathing disorders during sleep such as obstructive sleep apnea or movement during sleep such as periodic limb movements. The focus of this review will be alpha intrusion as this is the most frequent type of fragmentation in patients suffering from chronic pain. These arousals may not cause conscious awakenings during the night but may cause the restorative aspects of sleep to be lost (Bonnet 1985; Bonnet 1986; Levine et al. 1987). Sleep fragmentation occurs in response to elements which have a disruptive effect on sleep, such as the chronic pain experienced by arthritis patients (Lavie et al. 1992; Taylor-Gjevre et al. 2011b). Alpha intrusion is commonly seen in chronic pain disorders, such as fibromyalgia or arthritis, as a side effect of the pain during the day (Drewes et al. 1998b; Roizenblatt et al. 2001). Alpha intrusion is characterised by higher than normal amounts of high frequency alpha waves in the EEG in places where lower frequency waves are expected such as during SWS. The side effects of alpha intrusion include problems with sleep maintenance and daytime sleepiness (Nicassio & Wallston 1992; Drewes et al. 1998b; Roizenblatt et al. 2001).

Actigraphy is an easy way to obtain information about a person's daily level of activity as well as their night-time activity whilst asleep. Actigraphy measures are generated by using devices worn on the wrist, hip or ankle that use accelerometers to monitor and measure movement (Chung & Tso 2010). Due to the fact that Osteoarthritis (OA) and Rheumatoid Arthritis (RA) patients have movements in their sleep (which can also cause sleep fragmentation, as a result of pain) actigraphy is clinically useful in detecting abnormal

movements during sleep in arthritis (Lavie et al. 1992). As the devices are small, mobile and relatively unobtrusive they are a good way to collect continuous data over a long period of time in order to get an idea of a patient's sleep-wake cycle (Martin & Hakim 2011). Actigraphy is clinically useful in cases of sleep deprivation and insomnia, in determining the effect that poor sleep has on different sleep measures such as total sleep time, wake time after sleep onset, sleep efficiency and night-time awakenings (Lavie et al. 1992; Lichstein et al. 2006) as well as in studies where the effect that treatment has on poor sleep needs to be measured (Friedman et al. 2000; Vallieres & Morin 2003).

In sleep research actigraphy is a useful tool in cases where performing a polysomnogram (PSG) is not possible (Vallieres & Morin 2003; Lichstein et al. 2006; Sanchez-Ortuno et al. 2010). PSG is the main method used to objectively diagnose insomnia and other sleep disorders; however PSG is expensive and obtrusive (Vallieres & Morin 2003). Data for total sleep time, awakenings at night and sleep efficiency obtained by a PSG correlate well with similar data obtained by actigraphy (Vallieres & Morin 2003; Lichstein et al. 2006; Sanchez-Ortuno et al. 2010).

Actigraphy is clinically able to measure total sleep time and wake time after sleep onset but it is not good at measuring sleep onset latency as actigraphy cannot differentiate between inactivity due to sleep or inactivity due to a patient lying awake in bed (as in the case of insomnia), watching TV or any other time where people are motionless but not sleeping (Lichstein et al. 2006). Actigraphy also becomes a problem in terms of patient compliance (Sadeh & Acebo 2002). Patients may alter actigraphy readings by forgetting to put the activity monitoring device on after a bath or taking medication that can affect movement (Sadeh & Acebo 2002). Another limitation is that actigraphy measuring devices can malfunction, break or lose accurate calibration over time (Sadeh & Acebo 2002). For these

reasons and to improve the accuracy of the actigraphy record, it is recommended that these activity monitoring devices be used in conjunction with sleep diaries (Vallieres & Morin 2003).

1.2.3 Measurement of sleep - Subjective

Subjective measurements of sleep are questionnaire based. There are many questionnaires used in sleep research and in the clinical field to diagnose and treat sleep disorders. There are questionnaires available for children, adolescents and adults; however this review will focus on adult questionnaires. All sleep questionnaires can be split into four categories: questionnaires to diagnose a sleep disorder; questionnaires to determine the specifics of the sleep episode or "night"; questionnaires regarding the daytime consequences of the sleep episode and non-specific questionnaires which attempt to cover more than one of the above.

Questionnaires that ask details about the sleep episode are usually presented in the form of sleep diaries. There is no standard sleep diary that is used in all circumstances, but usually sleep diaries contain questions about everything that occurs in the period between bed time and wake time. Such questions include: time taken to fall asleep; number of awakenings during the night and sleep quality during the night, in addition to bed time and wake time (Walsh et al. 1996; Drewes et al. 1998b; Kushida et al. 2001; O'Donnel et al. 2009; Roth et al. 2009; Krystal et al. 2012). Sleep diaries are important for differentiating between restful inactivity and sleep and are often used in conjunction with actigraphy (Wilson et al. 1998; O'Brien et al. 2011; Vallieres & Morin 2003; Lunde et al. 2010). Sleep diaries also often contain visual analogue scale (VAS) measures of sleep parameters. Visual Analog Scales are scales which ask a person to rate their experience of a condition at the appropriate point on a line of 100 millimetres, the start and end anchors of which usually represent the extremes of

the condition being discussed. Examples of the scales used in this study to analyse daily sleepiness and fatigue are given in the appendix.

The last category of questionnaires is for all the non-specific questionnaires. These questionnaires ask about sleep and the effects of sleep, but they do not ask about a specific sleep disorder, they are more generalised sleep questionnaires. An example of a non-specific questionnaire is the Pittsburgh Sleep Quality Index (PSQI) which assesses sleep with regard to its quality, duration, maintenance and efficiency. The PSQI also assesses the use of sleeping aids and daytime dysfunction (Buysse et al. 1989).

1.2.4.3 Insomnia

1.2.4.3.1 Definition/ diagnosis of insomnia

Insomnia can be defined and diagnosed according to three diagnostic manuals: the International Classification of Sleep Disorders version 2 (ICSD-2); the Diagnostic and Statistic Manual version 4 text revised (DSM IV-TR) and the International Classification of Disease version 10 (ICD-10).

The ICSD-2 separates the different types of insomnia according to either primary (Idiopathic) insomnia or secondary/ co-morbid (Psychopothalogic) insomnia. The diagnostic criteria for primary insomnia include “A complaint of insomnia, combined with a complaint of decreased functioning”; “The insomnia is long-standing, typically beginning in early childhood”; “No medical or mental disease can explain the early onset of insomnia” (American Academy of Sleep Medicine, 2005). The diagnostic criteria for secondary insomnia include “A complaint of insomnia is present and is combined with a complaint of decreased functioning during wakefulness”; “Indications of learned sleep-preventing associations are found” such as “trying too hard to fall asleep” (American Academy of Sleep

Medicine, 2005). The ICSD-2 manual also uses PSG as part of the diagnosis for both primary and secondary insomnia, with PSG measures of increased sleep onset latency, poor sleep efficiency and an increased number of awakenings during the night.

The DSM IV-TR diagnoses primary insomnia according to five criteria: 1.a "difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month" (American Psychiatric Association, 2000); 2. The sleep problem causes impairment in daytime functioning; 3. The sleep disturbance does not occur with narcolepsy, a breathing related disorder or parasomnias; 4. The sleep problem does not occur with a mental disorder; 5. The sleep disorder is not due to substance abuse. The sleep problem must occur at least three times a week for at least one month. The DSM IV-TR does not have specific diagnostic criteria for secondary/ co-morbid insomnia, instead it contains categories for insomnia related to mental disorders, general medical conditions or substance induced sleep disorder (American Psychiatric Association, 2000).

In May 2013 a new diagnostic manual was released by the American Psychiatric Association titled DSM V in which primary insomnia is renamed insomnia and sleep disorders related to mental, medical or substance conditions are deleted. This is to focus attention on the fact that sleep disorders exist independently of other conditions and must be the only focus of treatment. The DSM V has been criticised and an online petition has been created asking for outside review of the DSM V (http://dsm5-reform.com/ retrieved on 03/03/2014).

The ICD-10 diagnostic manual categorises insomnia based on the underlying pathology and defines insomnia as a "condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep or early awakening." (World Health Organisation, 1992). The diagnosis for the ICD-10 is based on poor quality of sleep, not less time spent asleep. The ICD-10 manual also

requires the sleep disturbance to be present at least three times a week for at least one month; the poor sleep must cause distress and impairment in daytime function.

Despite their varying criteria for insomnia diagnosis, the three diagnostic manuals are in congruence regarding the effect that in insomnia has in decreasing daytime functioning. The three manuals also agree that the complaint of poor sleep must be present for longer than a month i.e. the problem with sleep cannot occur once in a while, the problem must be very prevalent in the patient's life. The three manuals are clear in separating insomnia with no traceable cause (primary insomnia) from insomnia that occurs due to other mental or physical illness (secondary/ co-morbid insomnia) and the three manuals also agree that insomnia causes increased sleep onset latency and decreased sleep quality. Thus the main method for insomnia diagnosis, when it is not possible to perform a PSG, is via subjective sleep questionnaires.

1.2.4.3.2 3P Model of primary insomnia

The cause of insomnia is best described by the "3-p" model of insomnia proposed by Spielman (1987). This model explains that insomnia begins with Predisposing factors which determine the risk for developing insomnia. These predisposing factors can be a family history of insomnia or a propensity for stress related poor sleep (Spielman 1987; Buysse 2013). The second P stands for Precipitating factors, and these are the stressors which initiate insomnia. Precipitating factors can be medical, environmental or psychosocial. An example of a precipitating factor is the chronic pain associated with arthritis which can cause poor sleep (Spielman 1987; Buysse 2013). The last P is for Perpetuating factors, and these are the reasons for the continuation of insomnia over a long period of time. Perpetuating factors can be behavioural, such as in the case of bad sleep hygiene, or caused by other factors such as hyper arousal (Spielman 1987; Buysse 2013). A common perpetuating factor in cases of

rheumatoid arthritis is the hyper arousal that occurs as a result of the chronic pain (Bomholt et al. 2004).

1.2.4.3.4 Epidemiology

A problem which arises from there being different criteria for diagnosing insomnia is that the prevalence of insomnia is varied according to whichever definition is used. In spite of this difficulty, studies using different definitions of insomnia have shown consistently that insomnia is more prevalent in women, older age groups (Mellinger et al. 1985; Chung & Tso 2010; Jungquist et al. 2010), lower income groups (Tang et al. 2012), people who have lower levels of physical activity (Nicassio & Wallston 1992; Morin et al. 2011) and people with medical and psychiatric disorders (Ford & Kamerow 1989; Budhiraja et al. 2011).

In studies and in this review insomnia is referred to in two ways, either by symptoms of insomnia or the insomnia disorder. Characteristics of the insomnia disorders are all the diagnostic requirements for insomnia i.e. longer sleep onset latency, decreased daytime function, increased awakenings at night, decreased sleep quality and PSG measures of fragmented sleep. Insomnia symptoms refers to the presence of one or more of these diagnostic factors, not necessarily all of them i.e. the patient has symptoms of insomnia; they do not have a clearly diagnosed disorder of insomnia. The prevalence of symptoms of insomnia in the adult population ranges from 25%-50% (Mellinger et al. 1985; Kuppermann et al. 1995, Sutton et al. 2001) and the prevalence of a diagnosed insomnia disorder ranges from 5%-20% (Ford & Kamerow 1989; Ohayon 1996; Simon & VonKorff 1997; Morin et al. 2011). The reason behind a large range of the prevalence of insomnia is due to the fact that each study was done with patients varied in age, gender, ethnicity etc.

Highlighting the prevalence of secondary insomnia, in a study done in the USA on insomnia patients, 30% of insomniacs had co-morbid depression and 19% had co-morbid organic

disorders (Radecki & Brunton 1993). In this study the prevalence of insomnia not due to secondary causes was 31%. Other studies have shown a significantly greater likelihood for symptoms of insomnia in patients with arthritis (23.1%) than patients without arthritis (16.4%) (Louie et al. 2011) and a high frequency of insomnia symptoms in patients with pain (50-70%) (Pilowsky et al. 1985; Atkinson et al. 1988; Morin et al. 1998).

1.3 Pain physiology

1.3.1 Definition

Pain is one of the most common reasons for people seeking medical care and according to the International Association for the Study of Pain (IASP), pain is an "unpleasant sensory experience due to actual or potential tissue damage" (Merskey & Bogduk 1994). Pain is multideimensional, affecting not only the body but also the mind and is a very subjective disorder (Stiefel 1993). Pain that is short term and is absent after recovery of the initial injury such as post operative pain or the pain experienced during an infection, is defined as acute (Litwack 2009). Pain is defined as chronic if it is still present after a patient has recovered from an illness or if it lasts longer than 3 months (Task force on Taxonomy for the International Association for the Study of Pain 1994). After experiencing daily pain for a long period of time there is an increased response to the pain stimulus called sensitisation wherein a minimal amount of pain can elicit the same response as a large pain stimulus and a small amount of pain can maintain the chronic pain state such as in the case of fibromyalgia (Staud & Spaeth 2008).

There are two types of chronic pain: nociceptive pain and neuropathic pain. Nociceptive pain is caused by stimulation of peripheral nerve fibers by nociceptors and this stimulus is then relayed to the nervous system. Neuropathic pain is caused by disease or damage to the

somatosensory system. (Litwack 2009). This literature review will focus on chronic nociceptive pain in arthritis patients.

1.3.2 Measurement of pain

All experimental measures of pain are subjective as all measurable outcomes rely on the patient's opinion. In the field of research devices that elicit pain with a measurable outcome are still considered subjective measurements. Examples of such devices are thermodes where an increasing temperature of either heat or cold is applied to the skin and the temperature at which the pain tolerance or threshold is reached can be measured (Bentley et al. 2003); as well as pressure algometers where the amount of pressure necessary to reach pain threshold can be measured (Granges & Littlejohn 1993) .

Subjective measurements of pain are in the form of questionnaires and visual analogue scales (VAS). There are many different pain questionnaires available all of which differ according to the type of pain being measured, but the questionnaire of interest to this review is the McGill Pain Inventory which has been used successfully in studies on arthritis (Irwin et al. 2012).

1.3.3 The effect of pain on sleep

Pain resulting in insomnia can be found in many pain inducing disorders, for example, post-operative, burn injury or arthritis patients (Raymond et al. 2001; Tompkins et al. 2011; Sasaki et al. 2014). Co-morbid insomnia or pain related insomnia is similar to primary insomnia in terms of its effects on sleep and daytime functioning and as such the recommended treatments for primary insomnia should also work to treat co-morbid or pain related insomnia (Tang et al. 2012). Pain causes arousals during sleep, despite the fact that cognitive and motor reactions to pain are suppressed during sleep. Arousals are defined as shifts in the EEG to

patterns observed during waking, followed by a rapid return to sleep (American Sleep Disorders Assoc. EEG arousals scoring rules).

In a study done by Affleck et al. (1996) on patients with fibromyalgia, pain during the day predicted poor sleep that night. This is in contradiction to a study by Raymond et al. (2001) on hospitalised burn patients in which pain during the night caused poor sleep but pain during the day did not predict poor sleep that night. However, in general it can be assumed that increased amounts of pain lead to poor sleep (Moffitt et al. 1991; Nicassio & Wallston 1992) and fatigue (Nicassio et al. 2002). Ninety per cent of chronic pain patients report having at least one sleep disturbance which affects their daily life(McCracken & Iverson 2002). In a population of chronic musculoskeletal pain patients, 48% of patients report that their sleep disturbances began when their pain symptoms appeared (Currie et al. 2000) and in these patients, 65% had sleep onset and sleep maintenance insomnia.

The effects that chronic pain can have on different aspects of sleep include a higher PSQI score when compared to patients without chronic pain (10.9 vs. 4.6); a longer time taken to fall asleep than patients without pain (39.6% of chronic pain patients vs. 5.2% of controls took >30 minutes to fall asleep); less than six hours of sleep per night (47.4% of chronic pain patients vs. 15.6% of controls) and poor sleep quality (49.3% of chronic pain patients vs. 10.4% of controls) (Marty et al. 2008). Chronic pain also causes worse daily functioning, an increased number of awakenings at night, an increased time awake after sleep onset and decreased sleep efficiency (Lunde et al. 2010). Wilson et al. (1998) report that the presence of pain at bedtime results in a 28.1% increase in sleep onset latency, an 11.1% decrease in sleep time and a 24.4% decrease in sleep quality. Chronic pain has been shown to be associated with alpha intrusion which is further correlated with disrupted sleep (Wittig et al. 1982) and

in a study done by Lavigne et al. (2000) on healthy participants, heat pain applied during sleep caused arousals.

The reason for the close relationship between pain and sleep lies in shared brain circuitry. Periaquaductal gray (PAG) matter modulates both sleep and pain perception. The thalamus which is important for relaying nociceptive impulses from the brainstem to the cortex, also regulates sleep (Smith & Hawthornwaite 2004). Raphe magnus cells and reticular nucleus cells are important components of the descending pathway for the modulation of pain (Willis & Westlund 1997). The neurons of the brainstem are influenced by the neurons in the forebrain, limbic system and PAG matter. Raphe magnus and reticular nucleus cells either facilitate or suppress the transmission of painful stimuli to the cortex depending on a person's state of arousal (Foo & Mason 2003).Also important in facilitating both sleep and pain are GABAergic neurons. As previously mentioned GABAergic neurons are sleep promoting, but they are also antinocioceptive when present in the spinal cord (Malcangio & Bowery 1996). GABAergic neurons prevent pain impulses from reaching the thalamus and therefore the cortex thus resulting in a decreased levels of pain (Malcangio & Bowery 1996).

1.3.4 Impact of sleep deprivation on physiological function

Sleep deprivation has been shown to affect cognitive ability, memory formation, immune function, hormones and the ability to perform psychomotor tasks. As measured by a Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT), sleep deprivation increases sleepiness during the day. In the long term, sleep deprivation is associated with a variety of medical problems such as coronary artery disease, heart failure, hypertension (Liu et al. 2013), obesity (Schmid et al. 2008; Orzeł-Gryglewska 2010), diabetes (Liu et al. 2013), depression (Cole & Dendukuri 2003) and an increased risk of injury from car accidents (McCartt et al. 2000).

A person is considered to be sleep deprived if they suffer from a lack of sleep, such as in the case of insomnia or sleep that is not restorative enough to be considered useful, as in the case of sleep fragmentation (Bonnet 1985; Levine et al. 1987). Experimentally the effects of sleep fragmentation on daytime performance, alertness and mood are indistinguishable from those occurring with sleep deprivation (Bonnet & Arand 2003); therefore fragmented sleep is as much a clinical problem as sleep deprivation or insomnia. The side effects of sleep fragmentation include increased daytime sleepiness, decreased cognitive ability, decreased motor performance and changes to mood (Bonnet 1985; Bonnet 1989; Stepanski 2002). Further explanation of the effect that sleep deprivation can have on mood will be given in the section on depression and sleep.

The main way sleep deprivation affects cognitive function is via its effect on the prefrontal cortex (Drummond et al. 1999; 2000). The prefrontal cortex is active during the day and uses sleep as a means of rest and repair (Horne 1988, 1993). If sleep is not achieved in sufficient quantity and quality the prefrontal cortex is deteriorated rather than repaired. The prefrontal cortex is the main part of the brain involved in decision making and an impaired prefrontal cortex results in decreased cognitive function (Milner & Petrides 1984).

The effect that sleep deprivation has on physical activity manifests in the form of fatigue. As described above, people who are sleep deprived i.e. insomnia patients, experience increased tiredness during the day and may find it difficult to maintain normal levels of physical activity. In many questionnaires developed to measure fatigue, physical activity and energy levels form a large part of the questionnaire such that low levels of energy and decreased physical activity are symptoms of fatigue (Chalder et al. 1993; Schaufeli & Van Dierendonck 1994; The WHOQOL Group 1998; Vercoulen et al. 1999; Michielsen et al. 2003). In patients

who are sleep deprived and are experiencing tiredness during the day i.e. fatigue, it may be possible to assume that they will have decreased physical activity.

1.3.5 The effect of sleep deprivation on pain

Aside from previously mentioned side effects of sleep deprivation, another consequence of disturbed sleep is increased pain sensitivity (hyperalgesia) (Moldosfsky & Scarsbrick 1976; Affleck et al. 1996; Onen et al. 2001a; Kunderman et al. 2004; Roehrs et al. 2006). In patients with chronic pain, a night of poor sleep predicts increased pain the next day (Affleck et al. 1996) and pre-existing sleep problems are good predictors of future pain (Raymond et al. 2001). Both REM and NREM sleep loss cause hyperalgesia, but in NREM sleep loss there are also bursts of alpha activity (working to increase pain sensitivity) in the EEG indicating lighter, less refreshing sleep, that is not seen following REM deprivation (Moldofsky & Scarsbrick 1976; Roehrs et al. 2006). One night of either REM or NREM sleep deprivation in healthy participants can cause decreased pain thresholds (Moldosfsky & Scarsbrick 1976; Roehrs et al. 2006) of both thermal pain (Kunderman et al. 2004) and pressure pain (Onen et al. 2001a) and there is evidence that the effects of sleep loss on pain perception can accumulate as the amount of sleep deprivation is inversely proportional to pain threshold (Roehrs et al. 2006). Similarly in rats, sleep disruption contributes to next day hyperalgesia (Onen et al. 2001b).

Sleep loss can affect the way in which pain is perceived but it does not have an effect on the ability to perceive sensations in general such as heat or cold (Kunderman et al. 2004). As shown in a study on healthy participants by Kunderman et al. (2004) sleep deprivation decreased heat and cold pain thresholds but had no effect on the perception of warm and cool sensations, i.e. sleep deprivation enhances the ability to feel pain but does not affect the ability to feel non-painful sensations.

1.4 Arthritis

1.4.1 Osteoarthritis

There are two different types of arthritis, Osteoarthritis (OA) and Rheumatoid Arthritis (RA). Osteoarthritis occurs in articular joints and can be present as either primary or secondary. Primary OA occurs where no previous underlying injury can be found, either due to ageing or alteration of the articular tissue. Secondary OA occurs where there is a pre-existing abnormality in joint structure and is also found as a result of other factors such as injury to the joint or pressure on the joints in cases of obesity. OA is caused by a combination of two processes. The first is when articular cartilage degenerates and bone damage and remodelling occurs as cartilage is no longer protecting the bone. The second cause of OA is based on the fact that the articular ends of bones undergo remodelling throughout life, but when the rate of remodelling exceeds the rate of cartilage repair, OA develops (Hough & Sokoloff 1989b).

The pain of OA is mechanical, triggered by effort, worse at the end of the day but with occasional short manifestations upon awakening. It is improved by rest and only leads to awakenings when associated with movements during the sleep episode. It is only found in the affected joints and can be caused by the bone itself (which experiences pain due to micro fractures or venous congestion during remodelling) or the muscles and ligaments surrounding the joint. Less common and at less severity than Rheumatoid Arthritis, pain can be caused by synovial inflammation (Brandt 1989). OA occurs in most articular joints. , one of the most common areas affected by OA is the knee, and OA can also be found in the hips and the spine (Moskowitz 1989). Osteoarthritis is the most common form of arthritis in elderly people and is the greatest cause of disability and limitation of activity (Louie et al. 2011).

1.4.2 Rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disorder characterised by the presence of specific auto-antibodies (rheumatoid factors) which mainly manifests itself through joint injury but may also target other organs (heart, lung, kidney). Joint injury starts with congestion and edema of the internal surface of the synovial joint (Hough & Sokoloff 1989a). T and B lymphocytes enter with the oedema fluid and initiate an inflammatory reaction. The cartilage in the joint undergoes erosion and the bone present, specifically the epiphyseal bone, also undergoes an inflammatory reaction, due to the fact that the bone has similar characteristics to synovial tissue, histologically.

Deformities of the joints occur with RA due to the destruction and remodelling of the articular surfaces during the inflammatory process (Hough & Sokoloff 1989a). The fingers, hands and wrists are the most affected, followed by the feet, knees and elbows, and, due to the disease being systemic, many joints can be affected simultaneously. The pain of RA is due to the inflammatory reaction and is present at rest and with movement. This pain leads to nocturnal awakenings (in the second half of the sleep episode) and reaches a maximum of intensity in the morning which leads to characteristic morning stiffness. RA is worsened by psychological stress, weather changes and excessive physical activity (McCarty 1989).

1.4.3 Epidemiology

In the general population in Canada and the United States, the prevalence of both rheumatoid and osteoarthritis varies from16.8% to 19.9% (Power et al. 2005; Ratcliffe et al. 2008; Louie et al. 2011). In the United States the prevalence of arthritis is higher in older individuals than the rest of the population; patients with arthritis are more likely to be women (58% vs. 49.5%); be overweight or obese (71.8% vs. 58.7%); have hypertension (53.7% vs. 20.3%) and have limitations due to their pain (42.8% vs. 3.7%) (Louie et al. 2011). In South Africa

24.7% of people over the age of 50 report problems with arthritis, 66.6% of these being women and 64.1% being black people. In a study by Wright (1985) in the United Kingdom, 67% of rheumatoid arthritis patients and 70% of osteoarthritis patients had sleep disturbances and in this same study 24% of rheumatoid arthritis patients and 18% of osteoarthritis patients reported taking sleeping aids at night. In another study by Taylor-Gjevre et al. (2011b) in Canada, 62% of rheumatoid arthritis patients and 67% of osteoarthritis patients had PSQI scores higher than five, indicating a sleep disturbance and Sariyildiz et al. (2014) have found the prevalence of sleep disturbances in Turkey in rheumatoid arthritis patients to be 64.1%. Pain severity is the main cause of sleep disturbances in arthritis patients (Wright 1985; Power et al. 2005).

1.4.4 Arthritis pain and sleep

OA and RA result in decreased physical activity during the day, depression and disrupted sleep caused by sleep fragmentation and alpha intrusion (Drewes et al. 1998b; Louie et al. 2011; Taylor-Gjevre 2011b). Actigraphy studies have found that RA patients have a high level of night-time activity, which confirms that they experience sirupted sleep (Lavie et al. 1992; Devins et al. 1993). Arthritis patients' disturbed sleep is caused by night-time pain and the severity of their pain is associated with the degree to which their sleep is disturbed (Lavie et al. 1992; Nicasso & Wallston 1992). Although cognitive and motor reactions to pain are usually suppressed during sleep, painful stimuli still affect the sleeping brain, causing micro-arousals and increasing body movement during sleep (Lavie et al. 1992). In studies where RA and OA patients are further deprived of sleep, arthritis patients show an exaggerated response to pain when compared to matched controls, thus arthritis patients are more sensitive to the effects of sleep deprivation than patients without chronic pain (Irwin et al. 2012).

Some patients with RA develop sleep apnea and periodic limb movements (Taylor-Gjevre 2011b), but the general problem with RA patients' sleep is sleep quality. Taylor-Gjevre (2011b) found that the sleep parameters that are affected by arthritis are the parameters used to diagnose insomnia: sleep latency longer than 30 minutes is experienced by 19.3% of RA patients 30.8% of OA patients (;sleep duration of less than 6 hours was reported in 20.7% of RA patients and 33.3% of OA patients ; sleep efficiency less than 74% was described in 25.5% of RA patients and 35.9% of OA patients and waking at night due to pain RA (33.1%) OA (44.9%), all of which contributes to decreased daytime functioning and increased joint stiffness and daily pain (Louie et al. 2011; Irwin et al. 2012; Sasaki et al. 2014). Thus despite having different causes and symptoms, RA and OA are comparable in terms of their effects on sleep. Alpha sleep patterns are usually seen in fibromyalgia patients but are present in the sleep of OA and RA patients due to arthritis causing chronic musculoskeletal pain (Drewes et al 1998b).

The effect that arthritic pain has on sleep can be severe enough that in a study done by Nicassio and Wallston (1992) pain was found to predict poor sleep two years later. Studies have shown that the decreased sleep efficiency and decreased sleep quality in arthritis contributes to hyperalgesia in patients (Moldofsky 2010). Patients with RA have higher levels of pro-inflammatory cytokines such as TNF alpha and IL-6 than matched controls which is associated with the increased amount of pain experienced by RA patients when compared to controls. Higher levels of pro-inflammatory cytokines may also be related to an impaired endogenous pain prevention system. (Lee et al. 2013). Pro-inflammatory cytokines cause pain by directly activating nociceptive fibers, and by causing nociceptive fibers to be more sensitive to other pain stimuli (Sommer & Kress 2004). Restless sleep is correlated with increased levels of disease activity (Devins et al.1993), and these increased levels of disease activity have been shown to contribute to poor sleep quality (Westhovens et al. 2014).

1.5 Confounders-depression

1.5.1 Depression and sleep

There is a confounding variable that can affect and worsen both the chronic pain and insomnia experienced by OA and RA patients and this is depression (Nicassio & Wallston 1992). In the DSM IV diagnostic criteria, depression is defined as a depressed mood that lasts at least two weeks and results in "clinically significant distress or impairment in social, occupational or other important areas of life (American Psychiatric Association) and 42% of patients with arthritis meet the diagnostic criteria for major depression (Frank et al. 1988). An important part of the DSM IV depression diagnosis is the presence of sleep disturbance (American Psychiatric Association).

Disturbed sleep can be a predictor of depression (Cole & Dendukuri 2003) in both young and elderly populations. In a study by Chang et al. (1997) reported that 12.2% of patients with insomnia have co morbid depression and Livingston et al. (1993) found that 30.1% of elderly patients with insomnia had co morbid depression. In another study by Buysse et al. (1994) the prevalence of a psychiatric disorder was present in 32%-61% of patients with insomnia. The presence of a psychiatric disorder in patients can predict insomnia (Katz & McHorney 1998; Foley et al. 1999) as shown in a study by Stewart et al. (2006) in which 41% of patients with depression had co morbid insomnia As far as I am aware there is only one study that has demographic information for depression in the South African population, Tomlinson et al. (2009) found that 9.7% of people have depression for life and 4.9% of people had depression in the year leading up to the interview with the investigators of the study.

PSG recordings in depressed patients show an increase in alpha waves during sleep (Hauri & Hawkins 1973), as well as increased time to fall asleep, multiple night-time awakenings, sleep fragmentation, decreased SWS and increased REM sleep (Walker & Van Der Helm

2009). These measures are similar to readings found with primary insomnia (aside from increased REM sleep). Severely fragmented sleep can cause decreased mood and the increase in REM sleep causes an over activation of the limbic system, causing depressed patients to have more intense and emotionally negative stimuli (Walker & Van Der Helm 2009). Subjectively, patients with depression can have an inaccurate perception of their sleep (Tsuchiyama et al. 2003). Thus treating depression involves not only relieving patients of depressive symptoms, but must also include regaining normal sleep patterns (Edge 2010).

The negative thoughts that are the main driving force behind depression can have a severe effect on arthritis in terms of both the amount of discomfort experienced by arthritis patients and the effectiveness of their treatment. As people have an increasingly negative way of thinking, their thoughts turn constantly to their illness and the effects of their illness which in the case of arthritis means a large amount of physical discomfort. People with arthritis and depression will pay more attention to the amount of pain they are in as well as their inability to do anything about their pain and discomfort. As people feel worse they may not adhere to their medication protocol and thus their treatment is affected which results in a further worsening of symptoms (Rathbun et al. 2013).

1.5.2 Depression and pain

Due to the fact that pain is multidimensional it has psychological effects (Stiefel 1993) and therefore depression is very strongly associated with chronic pain (Brown et al. 1989; Keefe et al. 1989; Kinney et al. 1993; Gureje et al. 1998; Ohayon & Schatzberg 2003; Von Korff et al. 2005), with a 65% co-occurrence rate for pain and depression (Edwards et al. 2008). In patients without chronic pain, the prevalence of psychiatric disorders is 10% (Gureje et al. 1998), in patients with chronic pain the prevalence increases to 35-46% (Kinney et al. 1993; Ohayon & Schatzberg 2003; Von Korff et al. 2005). Of patients who have had back pain for

less than 6 months, 8% have major depression and the prevalence of major depression in patients with back pain for more than 6 months is 46% (Kinney et al. 1993).

Patients with chronic pain and depression have higher pain intensities and functional impairment (Haythornwaite et al. 1991) and chronic pain is associated with an increase in attempted suicide (Ratcliffe et al. 2008). Therefore emotional wellbeing is an important consideration in treating chronic pain (Turk et al. 2008). Improved mood is an indication of efficacy of pain management (Turk et al. 2008) and depression is a predictor for worsening disability in chronic pain patients (Ericsson et al. 2002). A study by Keefe et al. (1989) on rheumatoid arthritis patients showed that in RA patients who catastrophize about their pain, a greater level of catastrophizing is related to increased amounts of pain, functional impairment and depression.

The link between pain and depression lies in shared neural pathways and neurotransmitters of the insular cortex, prefrontal cortex, anterior cingulated cortex, amygdale and hippocampus (Bair et al. 2003). Despite the importance of the interaction between pain, sleep disturbance and depression, there are few studies which focus on the effect these three conditions have together. Alfoldi et al (2013) found that 65.3% of chronic pain patients have insomnia, but there is a very low level of correlation between their insomnia, chronic pain and depression.

In a study done by Asih et al. (2013) patients with insomnia were separated into groups depending on the severity of their insomnia. The main outcome of the study was that as the severity of insomnia increases, so does the severity of depression, the amount of pain experienced and the amount of physical disability caused by the pain. Martinez et al. (2013) found that treating insomnia patients with CBT-I improved their levels of pain, physical functioning and depression and Wilson et al. (2002) found that although people with pain and depression have very high levels of pain related impairment, insomnia patients without

depression also had high levels of pain, thus despite the co-occurrence of pain and depression in insomnia, these conditions can be just as severe when present on their own.

In South Africa there are very few studies concentrating on pain, depression and insomnia. One study done by Peltzer & Phaswana-Mafuya (2013) found that among adults in South Africa 24.7% have arthritis, 8.9% have disturbed sleep and 60.5% have low levels of physical activity. Similarly, despite the prevalence of depression increasing with increased age, no depression studies have been done on older adults in South Africa with co-morbid insomnia or chronic pain (Peltzer & Phaswana-Mafuya 2013).

Due to the association between chronic pain, disrupted sleep and depression, many patients with depression use multiple over the counter pain medications and sleeping aids such as hypnotics (Mantyselka et al. 2002). Once again an inverse problem is created as analgesics are associated with depressive symptoms (Abbot & Fraser 1998) and hypnotics such as benzodiazepines cause depression (McLellan et al. 1979; Ashton 1991; Smith & Salzman 1991). In addition, many medications used to treat depression cause sleeping problems. SSRIs such as Fluoxetine decrease sleep efficiency, increase the number of awakenings at night, increase the number of arousals during NREM sleep, prolong REM latency and suppress REM sleep (Dorsey et al. 1996; Rush et al. 1998). Fluoxetine has also been found to cause periodic limb movements during sleep (Dorsey et al. 1996). Therefore in order to adequately treat depression, both daily pain and sleep must be taken into account.

1.6 Physical activity

An important aspect in treating OA and RA patients, or treating anyone with chronic pain, is that of physical activity. The amount of activity performed day to day depends on a person's age, gender, physical fitness and mental health (Sadeh & Acebo 2002). In cases where a person has chronic daily pain, levels of physical activity decrease (Buckwalter et al. 2003;

Turk et al. 2008). Chronic pain decreases quality of life by impacting on work, social activities and any physical movement in general; sitting for too long, standing or walking can be very painful (Buckwalter et al. 2003; Turk et al. 2008). The severity of the pain is positively correlated with a decreased amount of physical activity (Smith et al. 2001a). A study by Tang & Sanborn (2014) showed that following a night of good sleep (measured using sleep quality), levels of physical activity during the day increased. In addition Wang et al. (2010) have shown that physical activity and exercise can be a way of treating pain. Moderate exercise done on a regular basis is a non-pharmacological way to improve sleep by improving physical fitness (Hauri 1993; Sherrill et al. 1998; Atkinson & Davenne 2007). Regular exercise improves subjective sleep quality, decreases the time taken to fall asleep and increases sleep duration (King et al. 1997; Sherrill et al. 1998), and is also useful in treating arthritis (Ettinger et al. 1997). The beneficial effect that exercise can have on sleep is comparable to the improvements in sleep caused by taking benzodiazepines (Morin et al. 1994).

Exercise changes the inflammatory response which occurs after glucocorticoids and catecholamines are released in response to stress. By decreasing pro inflammatory cytokines, exercise modulates pain and also improves sleep (Wang et al. 2010). Physical fitness is an important aspect of maintaining healthy sleep and a decreased amount of physical activity during the day contributes to sleep disruption (Moldofsky & Scarsbrick 1976; Sherrill et al. 1998). Studies have shown that physically fit people are less affected by sleep deprivation. Moldofsky and Scarsbrick (1976) showed that stage 4 sleep deprivation does not induce muscle soreness and hyperalgesia in fit people.

1.7 Treatment

1.7.1 Treating pain

The body's exogenous pain prevention pathway relies on the ability of opioids such as morphine to bind to mu and delta receptors in the limbic system (Ossipov et al. 1997). Studies in rats show that sleep deprivation not only deteriorates the analgesic properties of exogenous opioids, it also decreases the ability of opioids to bind to mu and delta receptors (Ukponmwan et al. 1984; Fadda et al. 1991).

Treating either pain or sleep is difficult due to the cyclical relationship between the two and is also hindered by the fact that pain medication such as non-opioid analgesics, opioids and adjuvant analgesics affects sleep. Non-opioid analgesics such as ibuprofen, aspirin and other Non Steroidal Anti Inflammatory drugs (NSAIDs) work by inhibiting the formation of prostaglandins (Horne 1989; Murphy et al. 1994). Prostaglandins exacerbate the immune response and lead to hyperalgesia and by inhibiting prostaglandins, NSAIDs decrease pain and inflammation. However, a suppression of prostaglandin also suppresses night-time melatonin synthesis and changes body temperature resulting in decreased SWS (Horne 1989), increased number of awakenings during the night, increased time spent in wake state, delayed onset of deeper sleep stages and decreased sleep efficiency (Murphy et al. 1994).

Opioid analgesics work by attaching to mu receptors. Opioids such as morphine contribute to poor sleep by decreasing SWS, decreasing REM sleep, increasing movement during sleep and causing alpha intrusion (Kay et al. 1979; Shaw et al. 2005). An increased use of opioid medication is a predictor of poor sleep the following night which will then result in an increased intake of opioids the next day (Raymond et al. 2004). Conversely other studies show that opioids such as morphine and oxymorphone can improve sleep by increasing the duration of sleep, decreasing the amount of time to sleep onset and increasing sleep quality

(Caldwell et al. 2002; Kivitz et al. 2006). In sleep deprived people the usefulness of opioid analgesics to treat chronic pain is limited due to the decreased ability for endogenous and exogenous opioids to bind to mu and delta receptors. Lastly there are the adjuvant analgesics such as antidepressants and anticonvulsants which, as has been explained in the section on depression and pain above, cause poor sleep.

1.7.2 Treating pain and insomnia in arthritis

The recommendations for diagnosing poor sleep and pain in patients include an evaluation of mental health state as well as a detailed history of past and present sleep and medical complaints in conjunction with a physical exam. This is done in order to diagnose co-morbid conditions as well as to allow full understanding of the degree of pain and sleep disturbance (Onen et al. 2005). In order to fully diagnose insomnia, a two week period of assessment is necessary in which the patient fills out a daily sleep diary which includes timing and severity of pain as well as all medications taken (Benca 2005).

Once insomnia and chronic pain have been diagnosed using actigraphy, sleep diaries and other subjective reports of symptoms, treatment can begin. Treating the simultaneous pain and sleep disturbance in arthritis patients is very difficult because treating sleep and pain in general is difficult. On average only 30% of patients have ever discussed sleep with a doctor and in these cases patients were the ones to raise the subject of sleep (Shochat et al. 1999). Of patients with chronic insomnia, 36% say that their doctor's advice was not effective (Shochat et al. 1999). In the US, 53% of doctors do not ask elderly patients about their sleep history (Everitt et al. 1990), a concern with the prevalence of sleep disorders increasing with age. When doctors do ask patients about sleep they only ask a mean of 2.5 questions and, in the absence of eliciting an adequate sleep history, 46% prescribe medication as the best treatment

option (Everitt et al. 1990). This implies that there is a deficit of physician training on the subject of sleep and sleep disturbances (Papp et al. 2002).

Another unhelpful factor is the lack of research on treating sleep disorders with co-morbid chronic pain, especially arthritic pain (Benca 2005); the few studies that have been done show that recovery from lost sleep can be analgesic. Kunderman et al. (2004) reported that despite a decreased thermal pain threshold after healthy participants underwent sleep deprivation, thermal thresholds increased to baseline levels after recovery sleep. Onen et al. (2001a) found a similar increase in pressure pain thresholds during recovery sleep after healthy volunteers underwent sleep deprivation, and this increase in pain thresholds was higher than baseline values indicating a hyperalgesic effect of recovery sleep. During REM sleep deprivation, the metabolism of serotonin is increased (Youngblood et al. 1997), serotonin, which plays a role in the descending modulation of pain, has analgesic properties (Hamon & Bourgoin 1999), thus the analgesic effect of recovery sleep could be due to an increased amount of serotonin released during recovery of REM sleep (Onen et al. 2001b).

As much as insomnia is under diagnosed and badly treated, pain is also inadequately managed. This is evidenced by the fact that many patients overmedicate for their pain, taking not only their prescription medication but also over the counter medication. In a study done by Mantyselka et al. (2002) in Finland on patients with musculoskeletal pain, 63% of patients used prescription medication and 46% used over the counter medication to treat pain. Of the study participants 28% used drugs daily for their pain and 29% used multiple medications to treat their pain. In the same study 16% of patients used additional sedatives in an attempt to treat pain despite the fact that sedatives do not benefit pain (Mantyselka et al. 2002).

King & Strain (1990) found that 38% of chronic pain patients take benzodiazepines to treat the sleep problems associated with their pain, yet still experience sleep disturbances. Fourteen

per cent of patients had been taking benzodiazepines for 1-2 years and 46% had been taking benzodiazepine for 2 years or longer. Simultaneous drug use by patients includes narcotics (58%), antidepressants (32%) and NSAIDs (26%) (King & Strain 1990). Twenty nine per cent of arthritis patients take benzodiazepines such as Temazepam, Nitrazepam, Triazolam and Clorazepate at night and once patients start taking sedatives they rarely stop, leading to problems with addiction and further overmedication (Hardo & Kennedy 1991).

The current treatment recommendations for arthritis in South African patients are a combination of physical therapy and medication such as NSAIDs, paracetamol, corticosteroids and methotrexate (Nam et al. 2010; Smolen et al. 2014). NSAIDs such as diclofenac decrease the activation of the inflammatory immune response that is typical of arthritis. Corticosteroids such as prednisone act as immunosuppressants and similarly inhibit the immune response. Paracetamol (along with NSAIDs) are useful in treating the pain experienced by arthritis patients however the main treatment prescribed for use by arthritis patients in South Africa is methotrexate. Methotrexate is an antimetabolite and antifolate drug, which stops cell growth and can suppress the immune system, thereby relieving symptoms of arthritis. Unfortunately in South Africa, as government hospitals are often under stocked in terms of medication, very often the only treatment arthritic patients can acquire is paracetamol and NSAIDs.

This review will be focusing on the treatment of insomnia. Treating insomnia, much like diagnosing insomnia, relies on the patient's subjective experience of either the improvement or worsening of daily sleepiness, sleep quality, daily pain severity and physical functioning (American Psychiatric Association 2000; Stiefel & Stagno 2004). When insomnia is co-morbid with physical and mental disorders, those disorders should be treated first (Holbrook et al. 2000). When treating insomnia non pharmacological therapy should be the first step

towards improving sleep and pain. If non pharmacological therapy is not effective or appropriate, then pharmacologic therapy is necessary (Holbrook et al. 2000).

1.7.3 Non – pharmacological treatment of insomnia

Non pharmacologic management of sleep disorders consists of cognitive behavioural therapy for insomnia (CBT-I) and the main aim of CBT-I is to improve attitudes towards sleep (Stiefel & Stagno 2004). The components of CBT-I involve stimulus control such as avoiding bright lights, noise and extreme variations in temperature before bed (Holbrook et al. 2000), imagery training such as counting sheep, as well as progressively tensing then relaxing different muscle groups (Stiefel & Stagno 2004). This distracts the mind from worrying about falling asleep and when people do not worry about sleep, they are better able to fall asleep (Stiefel & Stagno 2004).

CBT-I for primary insomnia has been shown to be superior to placebo and is superior to pharmacologic therapies in term of long term efficacy (Currie et al. 2000). Rybarczyk et al. (2011) found that CBT-I was effective in improving the self-reported sleep problems experienced by patients with co-morbid insomnia, and that these improvements were still present one year after the study had ended. Vitiello et al. (2009) found a similar long term effect of CBT-I in patients with co-morbid insomnia and osteoarthritis. In addition this study showed that CBTi also improved pain levels although it was an intervention that was not directed at pain alleviation. A later study by Vitiello et al. (2013) found that although CBT-PI (including both an insomnia and a pain focus) improved the poor sleep experienced by osteoarthritis patients, it was not effective at improving their levels of chronic pain.

1.7.4 Pharmacological treatment of insomnia

Pharmacologic therapies, although very effective immediately and short term, have not been shown to be useful long term due to health risks, iatrogenic effects (poor sleep quality and daytime function) and problems with tolerance and addiction (King & Strain 1990; Morin 1993; Lichstein & Riedel 1994). A 2012 study by Benca and Morin showed that a good compromise for treating chronic insomnia wasa combination of CBT-I and pharmacologic management. This would improve sleep and pain immediately and maintain the efficacy long term (Benca 2005). The general rules for pharmacological treatment are that the drug being administered be more effective than a placebo and should be prescribed at the lowest possible dose for the shortest amount of time (Holbrook et al. 2000). Over longer periods of time, discontinuing medication must be a gradual process (Holbrook et al. 2000).

The ideal medication should a. work immediately and be eliminated swiftly from the body and b. should not cause unwanted effects the next day (Weitzel et al. 2000; Morin 2003). Medication should also c. improve all aspects of sleep e.g. sleep duration; sleep architecture and daytime alertness. Medication should d. not interact with other drugs, e. should have few side effects and f. should have a low likelihood for tolerance, addiction, withdrawal and rebound (Weitzel et al. 2000; Morin 2003). Unfortunately such a medication does not exist although some get close on some of these variables. The two types of pharmacologic treatment used by insomnia patients are benzodiazepines and non-benzodiazepines.

1.7.4.1 Benzodiazepines

Benzodiazepines are a less preferred treatment due to their tendency towards dependency and withdrawal symptoms (Roy-Byrne & Hommer 1988; Kales et al. 1991). Benzodiazepines are frequently misused among arthritis patients (Hardo & Kennedy 1991). With long term abuse of benzodiazepines there is impaired cognitive and motor function (Morgan et al. 1980;

Petursson et al. 1983), deficits in short term memory (Subhan 1984) and a blunted emotional response (Lader & Petursson 1983).

Although benzodiazepines like triazolam, flurazepam and estazolam improve sleep in terms of night-time awakenings and sleep time, when compared to a placebo, they also change sleep architecture towards less SWS and REM and more stage 1 and 2 (Onen et al. 2005). Benzodiazepines cause next day impairments and thus lead to an increased risk for car accidents (Neutel 1995), falls and injuries (Ray et al. 1989) and, in the case of triazolam, odd behaviour and amnesia (Wysowski & Barash 1991).

1.7.4.2 Non - benzodiazepines

Non-benzodiazepines are currently the most popular sleeping aids (Huedo-Medina et al. 2012) and are preferred to benzodiazepines due to the fact that they have fewer next day side effects (Scharf et al. 1994; Walsh et al. 1998; Verster et al. 2002) and fewer drug interactions (Hesse et al. 2003). Non-benzodiazepines include Zopiclone, Eszopiclone, Zaleplon and Zolpidem. In a case-control study, rheumatoid arthritis patients treated with Eszopiclone for 4 weeks experienced improved sleep onset, maintenance, duration and quality as well as better daytime symptoms compared to the placebo control group (Roth et al. 2009). These patients also experienced a better quality of life with increased physical activity levels and a better ability to perform day to day activities but their pain levels were not modified (Roth et al. 2009). Animal studies have shown that Zopiclone has a weak antinociceptive effect (Pick et al. 2005). In another case-control study, rheumatoid arthritis patients treated with Zopiclone for 2 weeks did not have a change in pain levels, even though Zopiclone improved the quality of their sleep compared to the placebo control group (Drewes et al. 1998a).

1.7.4.2.1 Zolpidem

Zolpidem is a frequently prescribed non-benzodiazepine for treating insomnia and it improves sleep by binding to GABAa receptors, enhancing the inhibitory effect GABA has on neuronal excitation and thus acts as a sedative (Criswell et al. 1995; Lancel 1999; Holm et al. 2000). Huedo-Medina et al. (2012) found that although Zolpidem can improve sleep latency, this improvement is not clinically significant and is not significantly different to the effect produced by a placebo. In congruence with this theory is a study by Randal et al. (2012) where 10mg of Zolpidem nightly for eight months was found to increase total sleep time by 56.4 minutes; increase sleep efficiency by 12%; decrease sleep latency by 31.4 minutes and decrease wake time after sleep onset by 41.5 minutes. However all of these changes were no more significant than those observed by the placebo group in the study.

Disagreeing with the theory that Zolpidem is no better than a placebo is a study by Scharf et al. (1994) which found that 10mg of Zolpidem decreased sleep onset latency and increased total sleep time, a result also found by Besset et al. (1995) using 10mg doses of Zolpidem to treat poor sleep and Roth et al. (1995) when treating transient insomnia with 7.5mg and 10mg doses of Zolpidem. Similarly Uchimura et al. (2012) found that 10mg of Zolpidem improved total sleep time, sleep efficiency and wake time after sleep onset when compared to a placebo. In animal studies Zolpidem has an antinociceptive effect but only at very high, and therefore not clinically significant, doses (Pick et al. 2005). However there is very little research available on the effect that Zolpidem or any other non-benzodiazepine has on arthritis pain patients, or on pain and sleep in chronic pain patients in general.

Table 1. Table showing the effects of hypnotics on pain and sleep in painful disorders

Study	Population	Intervention	Outcome for sleep	Outcome for pain
Bayley & Haslock 1976	18 inpatients with RA; mean age = 43 years	Diazepam 10mg	No change to sleep	Decreased arthritic pain, increased morning stiffness
Gronblad et al. 1993	33 outpatients with fibromyalgia, mean age = 45 years	Zopiclone 7.5mg	No change to sleep	No change to pain
Moldofsky et al. 1996	16 outpatients with fibromyalgia; mean age = 42	Zolpidem 10mg	Decreased sleep latency and night-time awakenings, increased sleep time and improvement in daytime energy	No change to pain
Walsh et al. 1996	15 outpatients with RA; mean age = 53 years	Triazolam 0.25mg & 0.125mg	Increased total sleep time, decreased daytime sleepiness and morning stiffness	No change to pain
Drewes et al. 1998	40 outpatients with American Rheumatism Association criteria for RA; mean age = 51 years	Zopiclone 7.5mg	Increased sleep quality; decreased sleep onset latency and number of awakenings at night. Frequency analysis showed a shift to a higher EEG frequency	No change to pain
Tashjian et al. 2006	68 inpatients who had undergone knee arthroscopy	Zolpidem	Patients had less daily post-operative fatigue	Patients had less daily post-operative pain and took fewer analgesics
Roth et al. 2009	142 outpatients with American Rheumatism Association criteria for RA; on chronic stable RA meds for 90 days prior to study; mean age = 52 years	Eszopiclone 3mg	Increased sleep quality, total sleep time and depth of sleep; decreased sleep latency and wake time after sleep onset	Decrease in pain
Morillas-Arques et al. 2010	43 outpatients with fibromyalgia	Trazodone 25-50mg	Increased sleep duration, efficiency and quality; decreased sleep onset latency	Slight improvement in body pain; improvement in fatigue, morning stiffness and tiredness
Dimsdale et al. 2011	45 inpatients with mucositis; mean age = 46 years	Eszopiclone 3mg	Increased sleep quality, sleep time and depth of sleep; decreased night-time awakenings	Decreased amount of pain throughout the day
Tompkins et al. 2011	29 outpatients who had undergone ACL reconstruction, mean age = 36 years	Zolpidem 10mg	No sleep outcomes were measured	Patients took 28% fewer analgesics

Krenk et al. 2014	20 inpatients undergoing fast track hip and knee replacement	Zolpidem 10mg	Increased sleep quality; decreased fatigue	No change to pain

Although Zolpidem is effective in initiating sleep, it is not effective at maintaining sleep due to the fact that it has a short half-life. Therefore a longer lasting form of Zolpidem was developed called Zolpidem MR (modified release) (Greenblatt et al. 2006). Zolpidem MR is a two layer biphasic drug that binds to GABAa receptors (Kirkwood et al. 2007). The first layer of the drug is immediately released with a peak plasma concentration reached after 1.5 hours and is responsible for initiating sleep (Kirkwood et al. 2007). The second layer of Zolpidem MR is responsible for sleep maintenance via a controlled release during the night, maintaining a plasma concentration for 3-6 hours following administration (Kirkwood et al. 2007). Zolpidem MR has a half-life of 4.6 hours (Kirkwood et al. 2007).

Zolpidem MR is available in two doses, 6.25mg and 12.5mg (Ambien CR Prescribing information 2007). The recommended dose is 6.25mg for women and 6.25mg or 12.5mg for men taken nightly directly before sleep. If 6.25mg is not effective for women, they can take 12.5mg; however, neither women nor men should take more than 12.5mg per day (Ambien CR Prescribing information 2007).The recommended clinical dose for patients in South Africa is 12.5mg. Less than 4% of elderly patients stop taking Zolpidem MR due to side effects, the most common of which are headaches (14%), drowsiness (8%) and dizziness (6%)(Ambien CR prescribing information 2007). Disorientation, visual disturbances and hallucinations are also mentioned as rare side effects (Ambien CR prescribing information 2007).

In healthy males 12.5mg of Zolpidem MR taken over an average of 26 days increased sleep efficiency and decreased the percentage of stage 1 sleep compared to a placebo (Kleykamp et

al. 2012). Roth et al. (2006) showed that in a population of primary insomniacs, 12.5mg of Zolpidem MR taken nightly for 3 weeks decreases wake time after sleep onset and number of night-time awakenings, as well as increases sleep duration and sleep efficiency when compared to a placebo.

Aside from the sleep improving abilities of Zolpidem MR, there may also be antinociceptive properties to Zolpidem MR in humans. GABA agonists have been shown to be antinociceptive in animal studies. Lee et al. (2011) showed that Zolpidem given to rats experiencing formalin induced inflammatory pain decreased nociceptive behaviour. In rats with spinal cord injuries that cause neuropathic pain, GABA agonists have shown anti-allodynic and anti-hyperalgesic properties (Rode et al. 2005; Munro et al. 2008; Di Lio et al. 2011). Conversely in a study by Malan et al. (2002), rats with neuropathic pain that were given GABA antagonists showed signs of allodynia and hyperalgesia. As Zolpidem MR works on GABA receptors in rats it might also decrease pain levels in another mammal species i.e. human patients with chronic pain.

There are no studies on the effect of Zolpidem MR on pain and sleep in patients with arthritis therefore the aim of this project was to determine if treating insomnia accompanying chronic pain in OA and RA patients with Zolpidem MR would have a beneficial effect on the amount of daytime pain as well as physical activity.

1.8 Literature review conclusion and objectives of this study

The reciprocal relationship between sleep and pain suggests that treating either sleep or pain will have a positive effect on the other condition, thus by treating pain during the day sleep would improve that night and improved sleep at night would lead to less pain during the day (Affleck et al. 1996; Edwards et al. 2008; Fine 2011). The hypothesis of this study is that pain levels of arthritis patients can be decreased by improving sleep via administration of

hypnotics i.e. Zolpidem MR The reason that this is expected to work in a South African population when past studies have not conclusively shown that improving sleep can lessen pain, is due to the fact that in previous studies patients were already treated as much as possible for their pain, thus the impact from improving sleep would be very minimal. In contrast the participants in my study do not have optimal treatment (as described towards the end of section 1.7.2) and I wanted to explore whether improving sleep can have an effect on the pain levels of this sub-optimally treated population.

Through this literature review, I have shown that chronic pain has an impact on sleep quality and conversely, I have seen that sleep disruption may decrease thresholds to pain stimuli. I have also reviewed the importance of depression and physical activity when treating disorders involving poor sleep and chronic pain. In spite of these interrelationships, I have found only a few studies investigating the effect of a hypnotic on sleep, pain levels, and physical activity in arthritis patients. Surprisingly, none of these studies took into account depression symptoms and none of these studies used a crossover design. Therefore the objectives of my randomized double blind crossover design study were:

- to compare sleep patterns, daily pain, depression and physical activity levels both before and after drug intervention and placebo

- to determine whether one week of Zolpidem MR has an effect on sleep in chronic pain patients

- to determine whether one week of Zolpidem MR has an effect on daily pain in chronic pain patients

CHAPTER TWO

Materials and methods

2.1 Materials and methods

2.1.1 Participants

The study included patients between 35-75 years of age from the arthritis clinic of Chris Hani Baragwanath Hospital in Johannesburg, South Africa. The women and men were initially briefed by the doctor in charge of the arthritis clinic and thereafter were interviewed by myself while in the waiting room. Based on this informal interview, the patients were selected if they had fulfilled the inclusion criteria.

The inclusion criteria for the study included: chronic musculoskeletal pain in the form of osteoarthritis and rheumatoid arthritis both at night as well as during the day, as well as insomnia-like symptoms The arthritis needed to have been present for longer than a year and arthritis secondary to trauma was also included.. The insomnia-like symptoms needed to be present for a sufficient amount of time (>1 month) that the insomnia was considered a problem to the patient.

The exclusion criteria for the study included: presence of fibromyalgia, restless legs syndrome, sleep apnea and severe depression. Participants were not excluded for illnesses such as diabetes or hypertension. Participants were not tested for other physical ailments such as liver failure; illnesses such as HIV or psychological disorders thus these were not used as exclusion criteria. In terms of pain conditions other than arthritis such as headaches or neuropathy, the pain from these disorders was regarded as contributing to the pain related insomnia and participants were not excluded. Participants were excluded if they were taking hypnotics or antidepressants however other medications which may affect the absorption of Zolpidem were not assessed. None of the patients were working shifts during the period of the study.

2.1.2 Study design

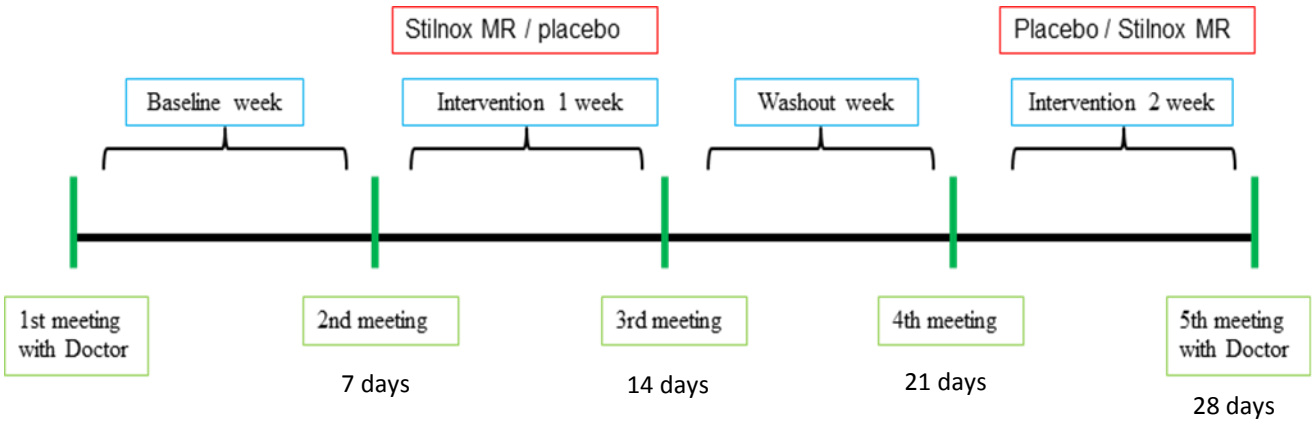


Figure 1. A diagram of the study design shown along a timeline.

The study lasted four weeks and included five meetings with myself and the participants- before, during and after the four weeks. The four weeks consisted of a seven day baseline period followed by a seven day intervention week; a seven day washout week and another seven day intervention week respectively (Figure 2).

2.1.2.1 First meeting with Doctor

After selection a meeting was arranged between the patient, myself and a medical doctor experienced in pain and sleep disorders who is my supervisor Dr Alison Bentley. At this first meeting details of the study were explained and participants were questioned about their sleep and pain, as well as presence of sleep problems. A thorough medical history was taken to ensure that the patients met the inclusion criteria, participants were also questioned about whether they suffered from any other severe co-morbidities. For those who met the inclusion criteria details of informed consent (Appendix A) were explained to the subject with special mention of the fact that they could withdraw from the study at any time and participants signed an informed consent form. Participants were advised to continue taking all analgesic medication that they were prescribed prior to the study and were asked to avoid hypnotic

medication. Participants were not asked to avoid things that would interfere with sleep such as caffeine as it was important for participants to maintain a normal routine.

2.1.2.2 Baseline week

During the baseline week data was obtained for all participants prior to any interventions. These data included demographic and anthropometric data and a general health questionnaire (Appendix B). Participants then filled out weekly questionnaires and were given the Hobo data loggers, that they would wear for the duration of the study. Participants were also given daily diaries for sleep and pain and were instructed on recording their daily sleep and pain information. Participants were allowed to choose their own bed and wake times throughout the duration of the study. Participants then returned home for their baseline week.

2.1.2.3 Washout week

The washout week lasted seven days and took place between the intervention weeks. The structure of the washout week in terms of questionnaires and daily data collection was similar to the baseline week, and the washout week allowed the intervention to be completely removed from the participants so that their sleep quality and levels of pain could return to those measured during baseline.

2.1.2.4 Intervention 1/ intervention 2

After either the baseline or washout week participants returned to Baragwanath hospital for their second (or fourth) meeting with me in which they filled out the weekly questionnaires and were reminded to continue wearing their data loggers and continue filling out the daily sleep diary. At this meeting participants were given the intervention that they would be taking for the next week.

After the baseline week, participants were randomly assigned to either a Zolpidem MR group or a placebo group. The participants were assigned by one of my supervisors, Dr Karine Scheuermaier, so that both the participants and myself were blinded. The participants were instructed to take the medication every night just before they got into bed to go to sleep regardless of whether they felt sleepy or not. The participants then received the other medication during intervention week two, so that whoever had received Zolpidem MR during intervention week one, received a placebo during intervention week two and vice versa.

2.1.2.5 Fifth meeting

The fifth and final meeting took place at the end of intervention week two. Participants met with both me and the medical doctor who specialises in sleep and pain, my supervisor Dr Bentley, to fill out weekly questionnaires and return their data loggers and daily sleep diaries. This meeting also had an informal component to discuss the study with participants, to determine their subjective experience of the study in general and to inform the participants as to which medication (Zolpidem MR or placebo) they had received in intervention weeks one and two. Participants were also advised on what to do in future should they wish to continue taking Zolpidem MR or another hypnotic. Participants were referred back to the doctor they usually saw at the arthritis clinic for further hypnotic use.

2.1.3 Weekly Questionnaires

The weekly questionnaires consisted of a McGill pain inventory (Appendix C), a Pittsburgh Sleep Quality Index (PSQI) (Appendix D), a Beck's Depression Inventory (BDI) (Appendix E) and a physical activity questionnaire (Appendix F). The McGill pain inventory is a questionnaire used to record patients' subjective experience of pain The pain rating index (PRI) of the McGill questionnaire consists of twenty groups of words with seventy eight words in total, each with a numerical value patients select the appropriate word from each

group and the values, when totalled, allow for a description of patients' pain experience (Appendix C). The severity of the patient's pain is correlated with the score such that lower scores indicate less severe pain and higher scores indicate more severe pain. The McGill also contains a present pain intensity (PPI) scale which rates the subjects pain level from one to five with one being 'mild' and five being 'excruciating' (Melzack 1975). The McGill has been validated as a pain measure (Byrne et al. 1982) and has also been validated in a language other than English (Mystakidou et al. 2002)..

The PSQI consists of seven components which ask about sleep quality, duration, maintenance, efficiency and sleep disturbance as well as the use of sleeping aids and daytime dysfunction (Buysse et al. 1989). The PSQI assesses sleep over a period of one month prior to taking the test and is regarded as non-specific as it asks a variety of questions about sleep during the night, daytime consequences of sleep, symptoms of insomnia as well as symptoms of sleep apnea. The PSQI can assign a global score in the range of 0 to 21, but a global score greater than 5 is indicative of a sleep disruption.

The PSQI has been well validated repeatedly as a test of sleep quality, not only after its conception in 1989 by Buysse, but repeatedly since then to assess sleep disruption in varying cohorts (primary insomnia patients, patients with osteoporosis, Rheumatoid arthritis) (Backhaus 2002; Beaudreau 2012; Nicassio 2014) as well as in languages other than English (Bertolazi et al. 2011; Moghaddam et al. 2012; Tzeng et al. 2012; Hashmi et al. 2014) a PSQI score greater than 5 indicates a sleep disturbance (Buysse et al. 1989). The PSQI score has also been used successfully in a number of epidemiology studies (Taylor-Gjevre 2011a; Ulus 2011; Sariyildiz et al. 2014; Sasaki et al. 2014; Westhovens et al. 2014) and intervention/ treatment studies involving sleep and both osteoarthritis and rheumatoid arthritis (Rybarczyk et al. 2011; Taylor-Gjevre 2011b; Irwin et al. 2012). In these cases the PSQI is used to determine the presence of sleep problems as well as the effect of treatment on sleep problems.

The PSQI and McGill tests were done weekly to assess any changes that may have taken place in regard to sleep quality and daily pain respectively.

The BDI consists of twenty one multiple choice questions which allow patients to describe their mood state in terms of emotions, behaviour and somatic symptoms (Beck et al. 1961). Each of the twenty one questions has four possible answers scored 0, 1, 2, or 3 and patients must choose one answer for each question. When added together the total score from the questionnaire is used to determine the severity of the depression with 0-9 minimal depression; 10-18 mild depression; 19-29 moderate depression and 30-63 severe depression (Beck et al. 1961). The BDI has been validated in a language other than English (Gorenstein & Andrade 1996).

The physical activity questionnaire contains questions about the activity performed during the past week by participants. The questionnaire was developed based on a paper by Ainsworth et al. (1993) and was chosen for this study (despite it not being validated) due to the fact that it had been used before in the Wits Sleep Laboratory as well as by the exercise unit in the School of Physiology at the University of the Witwatersrand. Questions are asked regarding sporting activities; walking either as transport or for leisure; informal activities (such as housework and gardening); sedentary activities (such as reading or watching TV) and transport (by car/bus/taxi or train) during the week and weekend. For each of the questions participants are asked to indicate the number of minutes per day spent doing the activity as well as the level of exertion they felt while doing the activity from very low to very high.

2.1. Actigraphy

Participants were asked to wear Hobo data loggers – HOBO® Pendant G acceleration Data Logger (Part # UA-004-64, Doc #: 10872-A, Patent #: 6,826,664) ©2006 Onset Computer Corporation- to gather data on all movement and physical activity during the day and night.

The data loggers were placed into a pouch and were worn by the participants on their non-dominant wrist.

2.1.5 Daily sleep diary

Participants were asked to fill out a daily diary which recorded their bed and wake times, number of hours slept, sleep onset latency, sleep quality, daily sleepiness and fatigue, morning pain level and evening pain level (Appendix G). Sleep quality was measured on a one to five scale with one being extremely poor and five being extremely good. Daily sleepiness and fatigue was measured each morning on a visual analogue scale as a line 100mm long with the anchors "Awfully sleepy & lacklustre" and "Marvellously alert and energetic" on the left and right respectively. Morning and evening pain levels were measured on similar visual analogue scales with the anchors "no pain" and "worst pain ever felt". The VAS scales were measured using a standard ruler and the length of the scales in millimetres from the left hand anchor was recorded.

2.1.6 Medication

Two types of medication were used in the study, Zolpidem MR 12.5mg and placebo. Zolpidem MR is manufactured by Sanofi-Aventis in Australia and is available in 6.25mg and 12.5mg dosages. The 12.5mg dose was chosen as this is the most widely used dose in South Africa. In South Africa Zolpidem MR is sold under the name 'Stilnox CR'. The placebo was a generic calcium supplement bought from a local pharmacy. Both medications were placed by me into similar empty capsules. Seven capsules with the same contents were then placed into similar containers with no identifying markings. As described above, the placebo and Zolpidem were randomised for each participant by a person external to the studyBoth the participant and myself were blinded to the order. The external randomisation person kept a record of which patient received placebo or Zolpidem MR in week 2 and 4 which was given

to me at the end of data analysis. Patients were instructed to take the medication immediately before bed each night and to not mix it with alcohol. The time of taking was left up to each participant. During the weekly meetings participants were asked about any side effects they may have experienced and if a participant had felt any adverse side effects they would immediately be removed from the study and told to stop taking the medication. Participants were also given my contact number should they need to discuss the way they felt after taking medication when in between meetings.

2.1.7 Data analysis

All data was analysed using GraphPad Prism 5 statistical package (GraphPad Software, San Diego, CA, USA). A two-tailed probability of $P < 0.05$ was considered statistically significant. Data was analysed according to either weekly or daily measurements.

2.1.7.1 Weekly measurements

In order to obtain the baseline measurements for the weekly tests presented in Table 1, a mean was calculated between all the participants for each test at meetings 1 and 2.

For weekly measurements of McGill pain questionnaire, PPI, PSQI and BDI, scoring was assigned based on previously established guidelines. For the scores of these four tests as well as the Physical activity score, a Wilcoxon signed rank test was done to compare baseline and placebo weeks, and where no significant difference was found, a mean was calculated for baseline and placebo weeks. A Friedman test, with a Dunns multiple comparison post hoc, was done to compare between the baseline week and intervention weeks for each of the five tests. For the PPI test three participants were excluded for missing data points and for the BDI one participant was excluded for missing data points.

After the weekly tests across baseline/washout, intervention 1 and intervention 2 had been compared, the weekly tests were re-analysed using all patients' scores placed in the order of weeks 1-4 that they had completed them, not in the order of placebo vs. Zolpidem MR. This was done using a Friedmans test with a Dunns post hoc comparing all columns to each other.

After the total PSQI score was analysed, I isolated specific questions from the questionnaire to see whether the interventions had any effect on individual questions rather than the PQSI score as a whole. The questions chosen were: Q5a - cannot get to sleep within 30 minutes; Q5b - woke up during the night or early morning; Q5c - have to get up to use the bathroom; Q5i - pain at night; Q6 - overall sleep quality and Q9 - a problem working up enthusiasm to get things done. These six items were first tested with a Wilcoxon signed rank test to ensure a mean could be calculated for baseline and washout and then a Friedmans test with a Dunns post hoc test was done.

For the weekly physical activity tests I established my own method of analysis by assigning scores for each patient activity. I established my own method of analysis as there was no available set method for analysing the questionnaire which I used. The scores for each activity were taken from the original paper on which the physical activity questionnaire was based and higher scores indicate increased physical activity (Ainsworth et al. 1993). Each activity that the participants did during the week was allocated a specific score or number of points (Appendix H). I grouped the scores into three levels based on the exertion produced by participants. The first level of sedentary activity included any activity in which the participants were immobile such as watching TV or riding in a taxi. The second level included light to moderate activity and this included informal activities done around the house such as cooking and cleaning. The last level was used to classify high exertion activity such as dancing or any sporting activities. I calculated the number of 'activity points' patients had per week, at each of the three levels and a Friedman test was done to analyse data. For

this and all other tests done on data obtained from the physical activity questionnaire five subjects were excluded for insufficient data. An example of the scoring for activity points has been provided in Appendix F.

The total number of minutes spent physically active at all levels of exertion during each week were calculated and a Wilcoxon signed rank test performed to determine any difference between the baseline and washout week. Where no difference was found, a mean was calculated for baseline and washout weeks. A Friedman test with a Dunns multiple comparison post hoc test was done to compare physical activity from baseline/washout to intervention week 1 and 2. Thereafter each activity exertion level (i.e. sedentary; light to moderate and high exertion) was tested individually from week to week in terms of minutes spent in that activity. Baseline/washout was compared to intervention weeks 1 and 2 using a Friedman test. An example of the scoring for minutes has been provided in Appendix F.

2.1.7.2 Daily measurements

For the daily VAS measurements for daily sleep and fatigue; morning pain and evening pain, a mean was calculated from results from days five, six and seven to assess maximal effect on the last three days of every week. A Wilcoxon signed rank test was done to compare baseline and placebo weeks, and, if no significant difference was found, a mean was calculated for each of the three descriptors for baseline and placebo weeks. A Friedman test, with a Dunns multiple comparison post hoc, was done to compare between weeks for each of the three descriptors with two participants excluded for missing data points.

2.1.7.3 Actigraphy measurements

For each patient for each day analysed the number of hours from wake time to bedtime was calculated and time from wake time to midpoint of the day was defined as morning activity

and from the midpoint to bedtime was defined as afternoon activity. The hours from bedtime to wake time defined the night-time activity. Results from the last three days of every week were used to assess maximal effect. If bed times and wake times were not indicated in sleep diaries by the patient, bed and wake times were inferred from the mean bed and wake times that the patient had indicated for the rest of the month. This HOBO® data logger recorded activity every 5 minutes in 3 dimensions (x, y and z) and derived a sum vector which was expressed in function of gravity (g). A typical display would be datapoint 1. sum vector activity = 1.05 (times g), datapoint 2. sum vector activity =-1.1 (times g) etc. As all data recorded included gravity (g=1), 1 was subtracted from each data point and then the absolute value was recorded for each data point. For each of the three periods of the day a mean, median, standard deviation and range were calculated in order for normality to be tested. As the data did not meet the normality criteria due to skewing of much of the data, non-parametric tests were chosen for the analysis. A Wilcoxon signed rank test was done to compare between baseline and washout values for each of the three time periods and, where no differences were found, a mean was calculated for baseline and washout weeks. A Friedman test was then done to compare between weeks for each of the three time periods.

2.1.8 Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (ethics clearance no: M110633) (Appendix I).

CHAPTER THREE

Results

3.1 Results

Eleven participants took part in this study and their demographic and baseline characteristics are presented in Table 2. As per the inclusion criteria, all participants had sleeping problems as demonstrated by a mean PSQI of 11.3±2; all participants had daily pain. Participants also had mild depression (BDI 16.2±5.7). The majority of the participants were overweight, had hypertension and were middle aged to elderly. In intervention week 1, 8 of the participants took placebo and 3 took Zolpidem MR and the opposite was true for intervention week 2.

Table 2. Demographic, anthropometric and baseline data for all study participants

Demographics and anthropometry	n=11
Age (years)	59.0 ± 8.1
Male	2
BMI (n=8)	31.1 ± 6.3
Smokers	3
OA:RA	7 : 4
Controlled hypertension	9
Diabetes	5
Mean baseline population characteristics	
PSQI	11.3 ± 2.8
BDI	16.2 ± 5.7
McGill - PRI	30.8 ± 17.4
PPI	3.0 ± 0.9
Physical activity	14.8 ± 7.7

Data are mean ± SD. BMI – body mass index; OA – osteoarthritis; RA – rheumatoid arthritis; PSQI – Pittsburgh Sleep Quality Index; BDI – Beck Depression Inventory; McGill – PRI (pain rating index) by rank; PPI – Present pain intensity.

3.1.1 Weekly measurements

The tests done to compare baseline and washout weeks for the McGill (PRI), PPI, global PSQI, BDI and physical activity score showed no differences between baseline and washout for all but the BDI score (Table 3), therefore data were combined and a mean was calculated for the two weeks to be used in subsequent analysis for all but the BDI score.

Table 3. Weekly McGill (PRI) and PPI tests; PSQI total test, BDI and physical activity questionnaire scores after baseline and washout weeks

	Baseline	Washout	p Value
McGill (PRI)	30.5 (10.0: 60.5)	30.0 (15.0: 68.0)	0.06
PPI	3.0 (2.0: 5.0)	3.0 (1.0: 5.0)	0.83
PSQI total	11.5 (7.5: 15.5)	11.0 (6.0: 15.0)	0.14
BDI	18.5 (8.0:24.5)	10.0 (2.0:15.0)	0.01 *
Phys activity score	17.8 (10.9: 42.1)	16.8 (10.3: 40.8)	0.31

Data are expressed as median (min:max). Data were analysed using a Wilcoxon signed rank test with a significance level of $p<0.05$. PRI – pain rating index; PPI – present pain intensity; PSQI – Pittsburgh Sleep Quality Index; BDI – Beck Depression Inventory; Phys act score – physical activity questionnaire score.

Tests done to compare intervention weeks to baseline for the McGill (PRI), PPI, global PSQI and physical activity score found no differences between any of the weeks (Table 4).

Table 4. Comparison of weekly McGill (PRI) and PPI tests; PSQI total test and physical activity questionnaire scores between baseline and intervention weeks

	Base	Placebo	Zolpidem MR	p Value
McGill	30.3 (10: 68)	34 (10:66)	34 (7:70)	0.84
PPI	3 (1:5)	3 (1:5)	2 (1:5)	0.29
PSQI	11.3 (6: 15.5)	10 (4:13)	9 (4:13)	0.12
Phys act score	17.3 (10.3: 42.1)	14.4 (10.3:40.8)	15.6 (9.3:40.8)	0.30

Data are expressed as median (min:max). Friedman test with a Dunns multiple comparison post hoc test. Baseline represents the mean of baseline and washout weeks. PRI – pain rating index; PPI – present pain intensity; PSQI – Pittsburgh Sleep Quality Index; Phys act score – physical activity questionnaire score.

A Wilcoxon signed rank test done on individual questions taken from the PSQI questionnaire to compare baseline and washout weeks found no differences for any of the questions data were combined and a mean was calculated for baseline and washout to be used in subsequent analysis (Table 5).

Table 5. Values for selected individual PSQI questions during baseline and washout weeks

	Baseline	**Washout**	**p Value**
Q 5a - cannot get to sleep within 30 minutes	4.0 (2.5:4.0)	4.0 (1.0:4.0)	0.59
Q 5b - wake up during the night	4.0 (1.5:4.0)	4.0 (2.0:4.0)	0.46
Q 5c - get up to use the bathroom	3.5 (1.5:4.0)	4.0 (1.0:4.0)	1.00
Q 5i - have pain during the night	4.0 (3.5:4.0)	4.0 (3.0:4.0)	0.09
Q 6 - overall sleep quality	3.0 (2.0:4.0)	3.0 (2.0:4.0)	0.42
Q 9 - enthusiasm to get things done	2.0 (1.5:4.0)	2.0 (1.0:4.0)	0.52

Data are expressed as median (min:max). Comparison done with Wilcoxon signed rank test with a significance level of $p<0.05$.

A Friedmans test with a Dunns post hoc test to compare between baseline and intervention weeks for the individual PSQI questions showed a significant difference for the question regarding overall sleep quality (Q6) where Zolpidem MR was found to have improved sleep quality compared to baseline (Table 6).

Table 6. Values for individual PSQI questions during baseline and intervention weeks

	Base	**Placebo**	**Zolpidem MR**	**p Value**
Q 5a - cannot get to sleep within 30 minutes	4.0 (2.0:4.0)	4.0 (1.0:4.0)	4.0 (1.0:4.0)	0.63
Q 5b - wake up during the night	3.8 (2.3:4)	4.0 (1.0:4.0)	4.0 (1.0:4.0)	0.47
Q 5c - get up to use the bathroom	3.8 (2.3:4.0)	4.0 (2.0:4.0)	3.0 (1.0:4.0)	0.26
Q 5i - have pain during the night	4.0 (3.3:4.0)	4.0 (2.0:4.0)	4.0 (2.0:4.0)	0.12
Q 6 - overall sleep quality	3.0 (2.0:4.0)	3.0 (2.0:4.0)	2.0 (1.0:3.0)	0.007 *
Q 9 - enthusiasm to get things done	2.0 (1.5:3.5)	2.0 (1.0:4.0)	2.0 (1.0:3.0)	0.22

Data are expressed as median (min:max). Data were analysed using a Friedman test with a Dunns multiple comparison post hoc test. Baseline represents the mean of baseline and washout weeks.

The first test done on BDI was to compare the intervention weeks to baseline and washout, and the Zolpidem MR week was found to have a significantly improved score compared to the baseline week (*p<0.05 , Figure 2a). Analysis was redone to compare BDI scores week to week regardless of intervention and a definite decrease in BDI scores was found as the weeks progressed with the scores for washout week lower than baseline week (*p<0.05, Figure 2b) and the scores for the 4th week lower than both baseline week and week 2. This decrease in BDI regardless of condition but steadily across weeks was labelled the 'hands on' effect.

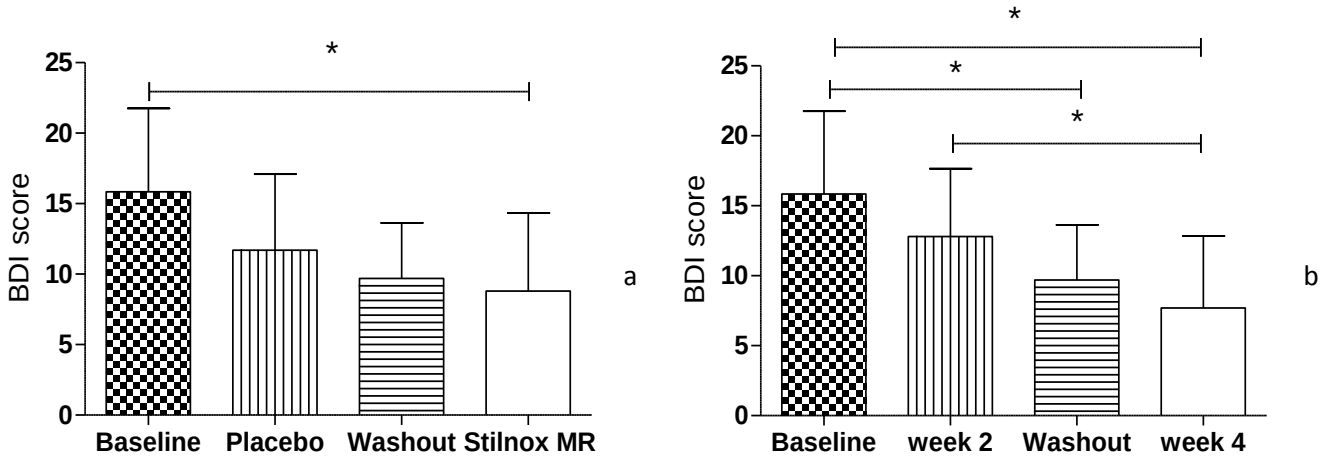


Figure 2. The BDI score before (Figure 2a) and after (Figure 2b) testing for the 'hands on' effect. Figure 2a shows the BDI score when tested by week of intervention. Figure 2b shows the 'hands on' effect on the BDI score from week 1 to week 4 of the study independent of intervention. All data are expressed as Mean ± SD * p<0.05 Friedman test with a Dunns multiple comparison post hoc.

Analysis comparing the McGill, PPI and PSQI was also redone to compare scores week to week regardless of intervention (Figure 3). No differences were found for the McGill or PPI tests but the test comparing PSQI scores from week to week showed that the PSQI score at baseline was significantly higher than the PSQI score at the end of the study (Figure 3c).

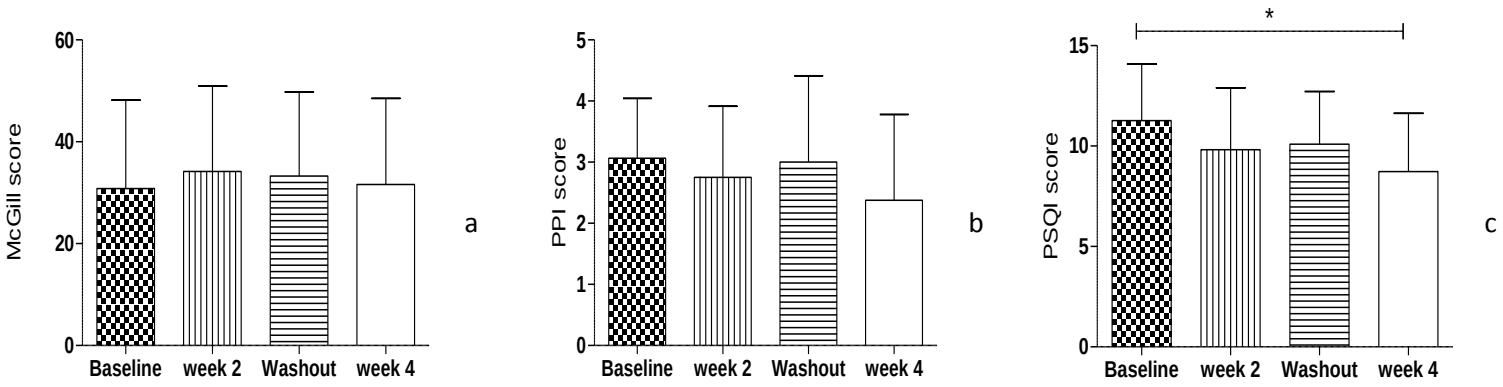


Figure 3. The McGill (Figure 3a), PPI (Figure 3b) and PSQI (Figure 3c) scores after testing for the 'hands on' effect. All data are expressed as Mean ± SD * p=0.0106 Friedman test with a Dunns multiple comparison post hoc.

The results for the tests done on the overall physical activity score are indicated in Table 2 and Table 3. When comparing the number of minutes physically active between the baseline week and washout week there were no differences and thus data were combined and a mean was calculated for baseline and washout weeks (Figure 4).

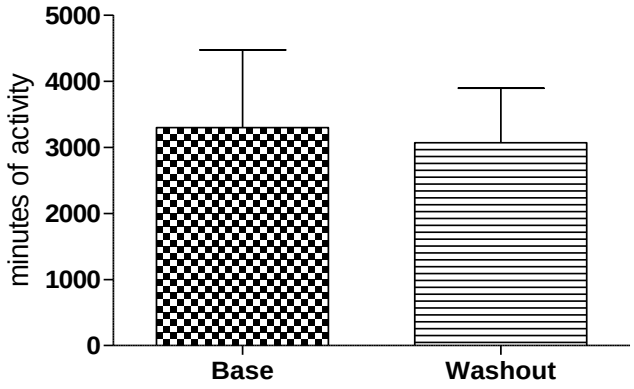


Figure 4. Total minutes of physical activity of all intensities during baseline and washout weeks. All data are expressed as Mean ± SD. Wilcoxon signed rank test.

When comparing baseline to intervention weeks for total minutes spent physically active there were no differences between intervention weeks and the baseline week, nor were any differences found when the placebo week was compared to the Zolpidem MR week (Figure

5). A similar lack of differences between weeks was found when the number of minutes spent at each 'level' of physical activity was analysed (Figures 6, 7, 8).

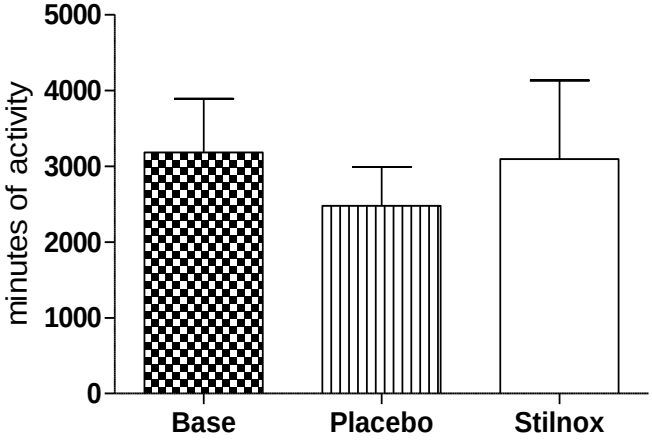


Figure 5. A comparison between baseline week, placebo week and Zolpidem MR week for the combined number of minutes for the week. In all Figures the week labelled as "baseline" represents a mean of both the baseline and washout weeks. All data are expressed as Mean ± SD. Friedman test used for comparisons

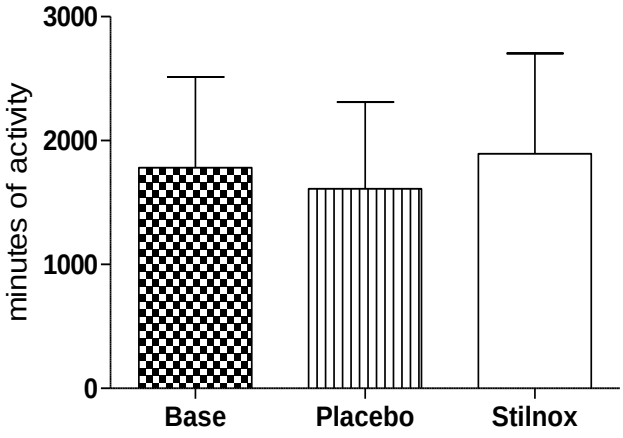


Figure 6. A comparison between baseline week, placebo week and Zolpidem MR week for the number of minutes spent in sedentary activities. In all Figures the week labelled as "baseline" represents a mean of both the baseline and washout weeks. All data are expressed as Mean ± SD. Friedman test used for comparisons

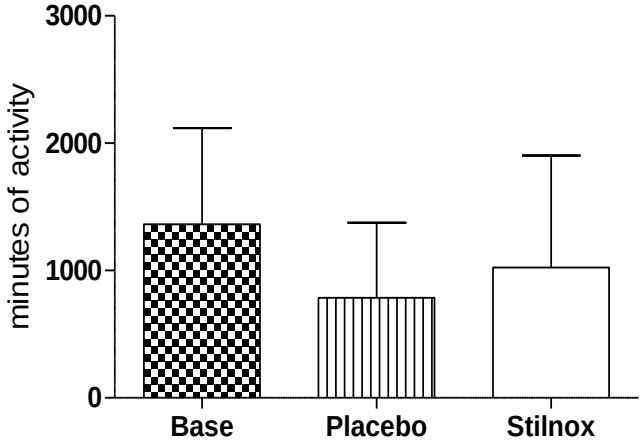


Figure 7. A comparison between baseline week, placebo week and Zolpidem MR week for the number of minutes spent in light to moderate intensity activities. In all Figures the week labelled as "baseline" represents a mean of both the baseline and washout weeks. All data are expressed as Mean ± SD. Friedman test used for comparisons

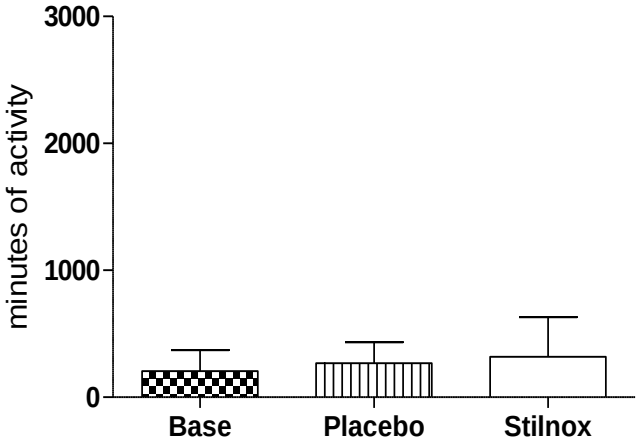


Figure 8. A comparison between baseline week, placebo week and Zolpidem MR week for the number of minutes spent in high intensity activities. In all Figures the week labelled as "baseline" represents a mean of both the baseline and washout weeks. All data are expressed as Mean ± SD. Friedman test used for comparisons

3.1.2 Daily measurements

For the daily VAS scores of daily sleepiness and fatigue; morning pain and evening pain no difference was found between the baseline and washout weeks and the data were combined and a mean was calculated for subsequent analysis (Table 7).

Table 7. Values for the daily VAS scores of combined sleepiness and fatigue; morning pain and evening pain during baseline and washout weeks

	Baseline	**Washout**	**p Value**
Daily sleepiness and fatigue	51.0 (37.3:77.3)	54.0 (31.7:100.0)	0.81
Morning pain	60.8 (6.0:100.0)	52.7 (10.7:93.7)	0.22
Evening pain	58.7 (42.5:100.0)	55.3 (35.5:93.3)	0.58

Data are expressed as median (min:max). Data were analysed using a Wilcoxon signed rank test. VAS – visual analogue scale.

When comparing intervention weeks to baseline for the daily VAS scores there were no differences between intervention weeks and baseline week, nor were there any differences when the placebo week was compared to the Zolpidem MR week (Table 8).

Table 8. Values for the daily VAS scores of combined sleepiness and fatigue; morning pain and evening pain during baseline and intervention weeks

	Baseline	**Placebo**	**Zolpidem MR**	**p Value**
Daily sleepiness and fatigue	52.5 (34.5:88.7)	55.5 (32.7:100.0)	69.8 (24.7:100.0)	0.28
Morning pain	56.8 (8.3:96.8)	55.3 (7.0:100.0)	52.3 (1.0:94.7)	0.57
Evening pain	57.0 (39.0:96.7)	58.7 (4.7:95.3)	38.7 (7.3:94.7)	0.69

Data are expressed as median (min:max). Data were analysed using a Friedman test with a Dunns multiple comparison post hoc test. The baseline shown in this table represents a mean of both the baseline and washout weeks. VAS – visual analogue scale.

3.1.3 Actigraphy

For the three periods of the 24 hour day i.e. morning, afternoon and night-time, no differences were found between baseline and washout weeks and data were combined and a mean was calculated (Figures 9a, b and c). A Friedmans test comparing intervention weeks to baseline for the three time periods showed no differences between intervention weeks and baseline week, nor were any differences found when the placebo week was compared to the Zolpidem MR week (Figures 9d, e and f).

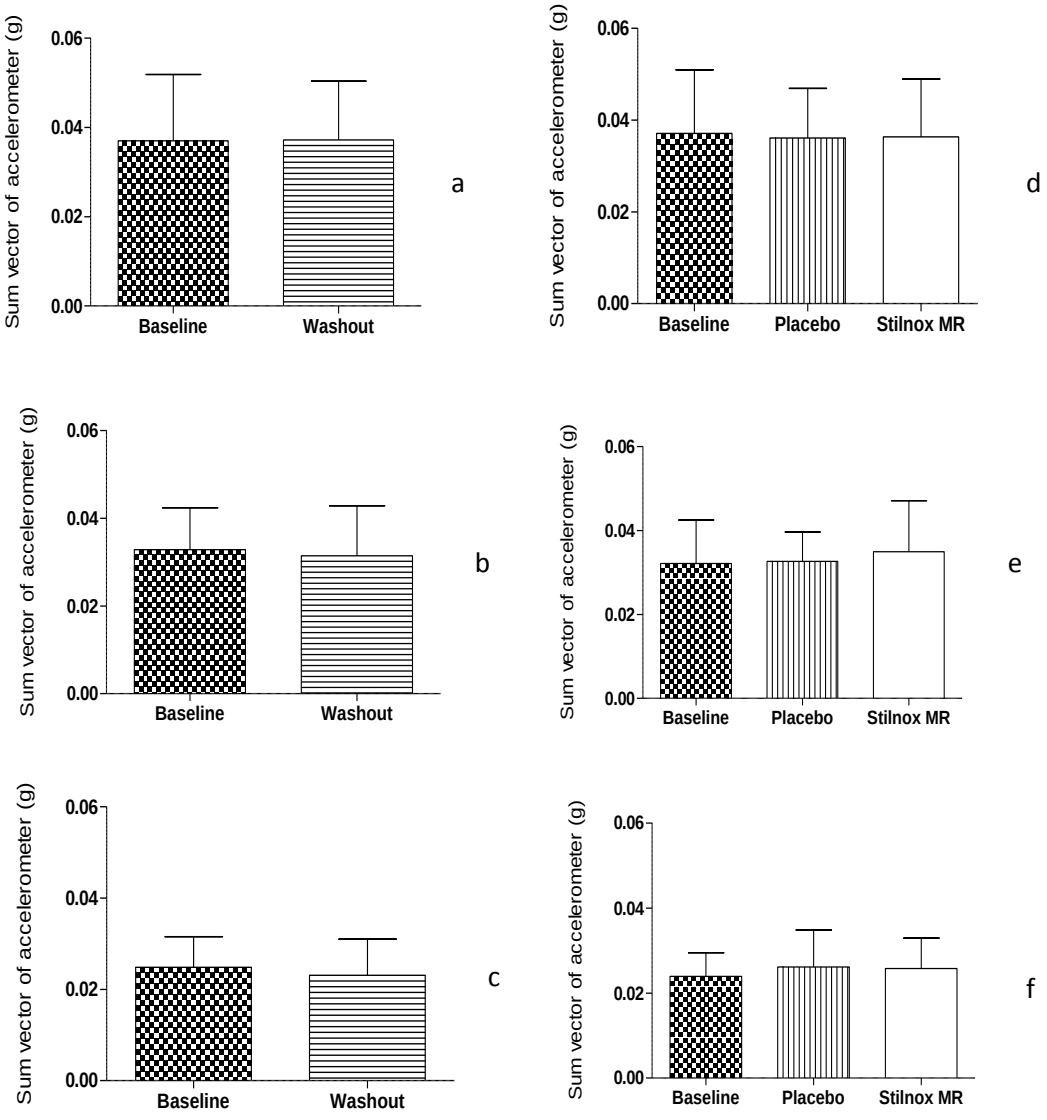


Figure 9. Sum vector data taken from actigraphy represented as units of gravity (g). Figure 9a + d represents the sum vectors for the morning i.e. from wake time to midday; Figure 9b + e represents the sum vectors for the afternoon i.e. from midday to bedtime and Figure 9c + f represents the sum vectors for the night-time i.e. from bedtime to wake time. Figures 9a – c are compared using a Wilcoxon signed rank test and Figures 9d - f are compared using a Friedman test with the "baseline" representing a mean of the baseline and washout weeks. All data are expressed as Mean ± SD.

3.1.4 Anecdotal report back from participants

Although not directly measured in this study, participants were very keen to talk about their experience of taking part in the study. Participants were usually correct in assessing which week they took Zolpidem MR and which week they took placebo:

> "*I preferred week four's tablets"* – M008

One participant felt that neither Zolpidem MR nor a placebo makes any difference:

> *"Both kinds of tablets felt the same, I still had pain during the day"* – M005

Participants were also very keen to continue taking Zolpidem MR after the study had ended:

> "*I would like to keep taking week two's tablets*" – M003

The most important comments that the participants made were about how they felt after the study. Despite a lack of a significantly measured decrease in pain or increase in physical activity, participants said things such as:

> *"I still have pain but its better. Before the study I was always sleepy but now I am more awake and its easier to move around and walk"* – M006

Other participants said that they felt so much better they no longer felt the need to use physical aids such as crutches or walkers:

> *"I have been able to do work around the house and I have stopped using my walking stick unless I go to work, but even then I don't really need it."* – M012

> *"I feel so much better, I have more energy, everything is easier now, I can walk without crutches"* – M010

One participant went on to say that:

> *"I hardly wake up at night and I feel better during the day as well, I have less pain. Because I feel better I can carry on with my day almost as if I did not have arthritis"* – M008

CHAPTER FOUR

Discussion

4.1 Discussion

This was a crossover design study comparing Zolpidem MR to placebo on the pain, physical activity, sleep quality and depression levels of chronic arthritis patients who complained both of pain and sleep disruption.

The two main findings in this study were the lack of improvement of general sleep and pain measures, as well as the improvement in BDI and PSQI scores from week to week. Despite starting with poor sleep and significant pain, the 11 participants showed no improvement on the weekly PSQI and daily sleepiness and fatigue measures after taking a hypnotic for seven days. There was one indication that sleep had improved after taking Zolpidem MR with the isolated PSQI question of sleep quality as a whole compared to baseline measures. For both weekly and daily pain measurements there was no decrease found in the amount of pain the patients experienced. Similarly no changes were found in the overall amount of physical activity done by participants as well as time spent on activity at different intensities both as self-report measures and as measured via actigraphy. There was an improvement of depression scores and PSQI scores but this was found to occur as a result of the length of the study rather than as an effect of administration of either the placebo or Zolpidem MR.

The majority of participants in this study were black, elderly, female and obese with hypertension. All of the participants had very poor sleep as determined by a high baseline PSQI and as a group were mildly depressed. The participants in this study were different from participants in other clinical studies reporting on the pain and sleep relationship.

The trend with experimental studies on sleep, pain, depression and physical activity is that participants are usually healthy, young, white participants (Moldofsky 1976; Bonnet 1989; Martin 1999; Onen et al. 2001a; Roehrs 2006). For clinical trials using medication, patients are also older, female and obese and often suffering from diabetes and hypertension (Lavie

1992; Affleck 1996; Moldofsky 1996; Currie et al. 2000; Turk 2008; Edwards 2008; Chung & Tso 2010; Moldofsky 2010; Louie et al. 2011; Tang et al. 2012). The majority of clinical studies investigating sleep, pain, depression and physical activity in arthritis patients used educated white patients as participants and who were younger than the participants in this study, with a mean age of 45-50 years (Affleck 1996; Turk 2008; Edwards 2008; Louie et al. 2011; Tang et al. 2012). Not only were the demographics of the participants in this study different to those of other studies, they also attended government hospitals, which has restricted treatment regimens and this may also be the cause of some of the discrepancies found in this study when compared to other literature.

The results of both the weekly and daily tests for sleep quality and quantity showed that there were no improvements in sleep during either placebo or Zolpidem MR intervention weeks. There are two possibilities that can account for these results, either the tests used were not good measures for an improvement in sleep quality in this study or Zolpidem MR did not improve sleep at all. The lack of a placebo effect for both sleep and pain is interesting as well.

The results from the PSQI test show that there was no improvement in sleep quality following administration of Zolpidem MR. Past studies using PSQI as a measuring tool found that the PSQI was able to detect changes to sleep caused by taking hypnotics (Rybarczyk et al. 2011; Taylor Gjevre et al. 2011b; Irwin et al. 2012). A reason for the lack of improvement in this study may be that Zolpidem MR did not improve sleep.

The PSQI is a reliable and tested method of determining sleep quality (Backhaus 2002; Beaudrau 2012; Nicassio 2014), however, after performing data analysis I realised that the final PSQI score can be altered depending on the manner in which one interprets a few questions, specifically the one regarding medication taken in the week prior to filling out the questionnaire. As participants differed in their answers to this question, even though they

were all taking medication to help them sleep, this resulted in variations between patients which affected analysis of the results and was the reasoning behind separating specific questions from the PSQI for re-analysis.

When the PSQI test was separated into individual questions and then analysed separately, improvements in sleep quality were found following a week of Zolpidem MR use, which is in agreement with previous research which indicates that Zolpidem MR does improve sleep.. However the PSQI had to be separated into individual questions for this improvement to be seen so it may be that the PSQI was not the correct questionnaire for this study.

Alternatively it might be considered that the PSQI was an accurate measuring tool, but sleep was not improved. As previous research indicates that both Zolpidem and Zolpidem MR improve parameters of sleep (Scharf et al. 1994, Besset et al. 1995; Roth et al. 1995;). Roth et al. (2006) found that 12.5mg of Zolpidem MR (Zolpidem MR) increased sleep efficiency and decreased sleep onset latency as well as number of awakenings at night as measured by a PSG and sleep diaries. Using the Leeds Sleep Evaluation Questionnaire, Hindmarch et al. (2006) found a decreased sleep onset latency and improved sleep quality when 12.5mg of Zolpidem MR was administered to healthy volunteers; it was expected that Zolpidem MR would have improved sleep in this study. However, not only did the results of the PSQI confirm this not to be the case, but there were also no improvements in daytime sleepiness and fatigue i.e. not only was the quality of sleep not improved but the negative effects of sleep disorders such as sleepiness and fatigue were not lessened. The structure of the sleep diaries used in this study, specifically the VAS scales for daily sleepiness and fatigue, was similar to sleep diaries used in other sleep research (Walsh et al. 1996; Drewes et al. 1998b; Kushida et al. 2001; O'Donnel et al. 2009; Roth et al. 2009; Krystal et al. 2012) but a lack of improvement in sleep was found which contrasts previous studies.

The reason for Zolpidem MR not improving sleep in this study, when it has been proven to be effective in other studies may be the difference between the baseline data for participants in this study compared to other studies. Generally clinical studies done to test the efficacy of hypnotics start with patients whose baseline data point to severe problems with sleep. This would include long sleep onset latencies and low levels of sleep efficiency or sleep quality (Walsh et al. 1996; Drewes et al. 1998a). As levels of sleep problems are very high to begin with, a decrease in sleep problems would be more apparent. Although the participants in this study had sleep problems, their PSQI scores and levels of sleepiness and fatigue were moderately high, maybe not severe enough that changes would be apparent. Another reason for Zolpidem MR not improving sleep might be due to the differences in demographics found in this study when compared to other studies.

An interesting and surprising result was the lack of any of placebo effect on either sleep or pain measures. In past studies that utilised a hypnotic treatment versus a placebo for treating sleep an improvement was seen in sleep with administration of the placebo. This improvement was not as great as the improvement found after administration of the hypnotic (Moldofsky et al. 1996; Roth et al. 2009). The same placebo effect occurs in studies that used an analgesic versus a placebo for treating pain (Chappell et al. 2009; Abou-Raya et al. 2012; Brown et al. 2012; Paulsen et al. 2014) although these studies generally do not report on whether the placebo effect is significant or not. Thus it would be expected that in this study, after the placebo intervention week, there would be a small increase in sleep quality.

In a review article published in Nature Medicine in 2010, Tracey explains that in order for a placebo effect to occur i.e. in order for analgesia to occur in chronic pain patients, expectation of a positive outcome is one of the main deciding factors. If a patient does not believe that the placebo will work to relieve pain then no analgesia will occur. The lack of a placebo effect in this study begs the question of whether correct blinding procedures were maintained. For this

study the correct blinding procedures were in place so the lack of a placebo effect would correlate with the idea that the study design was too short and had too few participants for any changes to be noticed in terms of sleep and pain. However, looking at the data there is no trend towards a placebo effect, which would be expected if the number of participants is too small.

The results of both the weekly and daily tests for pain showed that there were no improvements in pain levels following both placebo and Zolpidem MR intervention weeks, despite the fact that more than one method of measuring pain was used. There could be three reasons for the fact that pain did not decrease: pain did not decrease because sleep was not improved or if we assume that sleep has improved based on the single question of the PSQI, pain did not decrease because the relationship between sleep and pain is not as bidirectional as assumed i.e. either these data prove the reciprocal relationship or they do not. A third option is also present, that the changes in sleep quality and the daytime effects of decreased pain and increased physical activity were too mild for changes to be noticed. Due to the small sample size of the participants and the low baseline levels of PPI it is possible that there was not enough statistical power in any of the tests to indicate an improvement in sleep or a decrease in pain.

The hypothesis of this study was that pain levels of arthritis patients could be decreased by improving sleep via administration of hypnotics i.e. Zolpidem MR. However, if administration of Zolpidem MR did not improve sleep then there would not be a decrease in hyperalgesia and patients would not experience less pain.

If the second option is considered, that Zolpidem MR did improve sleep, then the lack of a decrease in pain levels means that the bidirectional relationship between sleep and pain is not as strong as previously thought. It may very well be that the pain of arthritis causes sleep

fragmentation and alpha intrusion and this results in poor sleep (Lavie et al. 1992; Walsh et al. 1996; Drewes et al. 1998b), but it is possible that poor sleep does not contribute to hyperalgesia in arthritis patients, and that treating sleep will have no impact on the daytime pain as previously thought.

The lack of an improvement in pain levels is further supported by a lack of improvement in physical activity levels. Physical activity was used as a surrogate to understand whether a person has more or less pain, due to the fact that pain decreases physical activity levels (Turk et al. 2008), As physical activity levels did not increase this would mean that the pain levels of the participants had not changed to allow participants to increase their activity and to move more comfortably and perform more day to day tasks such as cooking and walking. An alternative explanation could be that the participants were used to living their lives a certain way and even though they felt better, they did not change their activity patterns. It may be too short a study period to expect a behaviour change to be evident and a longer follow up on Zolpidem MR may be needed to notice any effect.

Studies that investigate the level of physical activity present among patients with arthritis have found that, when compared to healthy controls, patients with arthritis have lower levels of physical activity, both in terms of minutes of activity and the level of intensity at which activity is done (Tierney et al. 2012; Dos Santos et al. 2014; Hernández-Hernández et al. 2014). These results have been found despite studies using different methods of measurement. Unfortunately, due to the fact that the questionnaires used in this study differed from physical activity questionnaires used in other arthritis studies, a quantitative comparison could not be made between the activity levels of arthritis patients in this study and the activity levels of other arthritis patients, however it may be assumed that, just as in other studies, the levels of physical activity found in this study's participants are lower than in people without arthritis.

The only significant changes across the interventions were the decreases in BDI and PSQI from the start to the end of the study. The decrease in BDI at the end of the study could be due to the fact that eight of the eleven participants received Zolpidem MR in the final week of the study, but a more likely explanation the decrease in BDI was the interaction the participants had each week with the researcher. A precedent for this can be found in a study done by Brown et al. (1989) in which decreased amounts of perceived emotional support was associated with depression; as well as in studies regarding the use of empathy when treating a patient. Steinhausen et al. (2014) found that trauma surgery patients who receive greater empathy from their attending doctors were more likely to have better treatment outcomes than trauma surgery patients with less empathetic doctors. Ogle et al. (2013) found that medical students who were empathetic were more likely to have positive reactions from patients and were more likely to be clinically competent.

A review by Derksen et al. (2013) shows that empathy among doctors is correlated with more positive and less anxious patients. The participants recruited for the study are patients at a government hospital where the high volume of patients means that doctors have very short consulting times and patients have to wait for a long time in queues. This means that patients often feel overlooked and not cared for, so the fact that the principal investigator spent an hour each week talking to the participants allowed them to feel cared for. Thus participants who felt more emotional support had fewer depressive symptoms.

Emotional wellbeing is important in clinical trials as patients will consider the way they feel as an indication of whether the treatment is working (Turk et al. 2008). It was the' hands on' effect that made a difference in how the participants felt and caused their BDI scores to decrease, not the presence of an intervention, which may be an indication that Zolpidem MR does not affect emotional state (Hyland 2003). Relatively few studies have been done looking at the effect that Zolpidem or Zolpidem MR can have on depression; Ji et al. (2007) found

that the addition of Zolpidem with an antidepressant to treat depression improved sleep and depressive symptoms versus an antidepressant alone, while Fava et al. (2011) found that Zolpidem MR taken with an antidepressant improved sleep but not depression. Thus there is no way to be sure that the finding in this study that Zolpidem MR has no effect on depression is correct. The reason behind the fact that PSQI scores decreased across the four weeks may be due to the decrease in BDI scores as a higher PSQI score is associated with greater psychiatric problems (Katz & McHorney 1998; Foley et al. 1999).

Another aspect of the study which could not be quantified are the comments of the participants during the weekly meetings and during the final meeting at the end of intervention week 2. The majority of the participants reported feeling better at the conclusion of the study than at its start. The majority of the participants preferred taking Zolpidem MR to placebo even thought they were blinded to the contents of the capsules. Participants felt that the placebo had no effect, and one participant felt that neither intervention was effective. The majority of participants, when asked at the final meeting, said that they would be willing to continue taking Zolpidem MR as they felt that it had helped them. Another three participants reported that they no longer felt the need to use physical aids such as crutches or walkers when moving about by the end of the study. Thus it is important that even though the data suggests a lack of improvement of sleep and pain, subjectively the participants may feel an improvement in their sleep and their levels of pain and discomfort. .

Even though it is not a proper qualitative measure, the anecdotes from participants suggest that a quality of life questionnaire would have been useful in this study. It was expected that any change in sleep and pain would be measureable; but perhaps for this study, improvements in pain and sleep are very minor and cannot be measured. Essentially the participants did find the study useful in improving their daily pain levels and sleep disruption i.e. their quality of life, it was just unfortunately not measured.

The anecdotes commenting on improved energy levels and easier physical movement may give support to the theory that decreasing depression can increase levels of energy and physical activity. Camacho et al. (1991) found that people with lower levels of physical activity were more likely to develop depression than people with high levels of physical activity. Similarly Strawbridge et al (2002) found that physical activity was a deterrent to depression. Commenting on the effect that depression can have on physical activity, Roshanaei-Moghaddam et al. (2009) found in their review of the relevant literature that people with depression were more likely to have lower physical activity levels. Thus the decreased BDI score may be the reason behind the participants feeling more energised.

The limitations of this study included a small number of participants and a short study timeframe. Better results may have been found if the study design included a longer period of time and if there were more participants. Unfortunately it was difficult to recruit participants for this study. Everyone who attended the arthritis clinic was approached and although this was a large number of people, many patients at the clinic were uncomfortable with the idea of using sleeping aids and of those patients that were interested initially in doing the study, many patients did not want to do the study when contacted later. One of the participants that did initially begin the study fell and broke her arm and she did not continue and that participant was the only dropout. There were only two men in the study but it was decided that they would remain in the study due to the scarcity of available participants. Including both osteoarthritis and rheumatoid arthritis patients in the study was also due to the scarcity of available participants. Although OA and RA have different disease origins and outcomes, and the pain of OA and RA have different origins with OA pain not having the immunological component that RA pain has, it was assumed that the effect that pain had on GABA pathways would be a determining factor of the efficacy of treatment and thus including both OA and RA patients would not be cause for concern.

The patients who did participate in the study may represent only a small percentage of the population, being from one hospital, similar sociodemographic backgrounds, the same ethnic group and similar body composition. The results of this study may not apply to people in the private sector, people of different sociodemographic backgrounds, ages and ethnicities. A limitation that was discovered at the end of the study was that 8 out of 11 patients received Zolpidem MR in the second intervention week but despite this imbalanced randomisation it did not change the fact that Zolpidem MR did not improve sleep or pain and still cannot explain the weak 'hands on' effect.

An unintended limitation found after data analysis, whilst interpreting the results was that the PSQI score could be greatly affected by the manner in which a few questions are answered. No indication has been given in past studies that this is a problem with the PSQI. If I was aware of the problem prior to starting the study I would have been more precise at the first interview when explaining the questionnaire to the participants, giving examples on how to best answer the question.

Another limitation could be that inadequate measures and questionnaires were used and other types of questionnaires such as the quality of life questionnaire would have achieved better results. A further limitation was that the questionnaires used in this study are tailored for English-as a first language speaking participants. Although participants in this study were fluent in English, it was not their first language, which may have resulted in some interpretation difficulties which may explain the missing data. It would have been useful to have an interpreter present, at least for the first meeting to help explain the questionnaires. Also of added help in a non-English speaking population would be questionnaires that do not require words, for example, the Faces Scale (Wong & Baker 1988) measures pain using pictures of six faces moving from a smiling face with no pain up to a very sad and crying face which represents worst pain imaginable and could be better suited for this population.

Finally the study may have benefited from a PSG component, an objective measure to determine whether or not sleep quality improved, although, if the patients did not perceive any changes, the relevance of changes on a PSG is questionable.

Conclusion

Thus despite having participants with chronic pain and poor sleep, and giving them a sleeping tablet, I showed no major impact on sleep using global measures, but some minor effects using more precise measures, however this had no impact on pain or physical activity using multiple measures.

The most important effects found during the study are that giving Zolpidem MR or a placebo for a week does not cause an improvement in sleep, pain or depression scores in these patients. Participants felt less depressed at the end of the study but the reason for this effect was not due to Zolpidem MR. Instead, because these effects were found at the end of the 4-week study period, regardless of the order of the interventions, we interpreted this effect as due to the fact that every week for a month or longer participants felt as though someone cared about them. This 'hands on' effect, or bedside manner, is a very important part of treatment for any illness. If patients feel that they and their disease are not important, they are less likely to recover as quickly or as well than they would if nurses and doctors were able to give them more time. Unfortunately, in an environment where the sheer number of patients forces doctors to have very short consulting times, giving patients more time is not always possible.

In future studies that are similar to this one it would be beneficial to have a longer time period for the study and perhaps follow up interview after the study to asses long term improvements. Another important addition would be a quality of life questionnaire or something similar to properly measure the subtle subjective improvements that participants

experience. It would also be useful to include other types of questionnaires that more subtly measure sleep quality and pain levels such as the Insomnia Severity Index (Bastien et al. 2001) or the Faces Scale (Wong & Baker 1988).

In conclusion this study has shown that an important aspect of treatment for patients is bedside manner and time spent showing appropriate care and attention to patients. There is no placebo effect for an improvement in sleep and giving patients a placebo will not change their sleep quality. Finally, administering a hypnotic is not guaranteed to improve the sleep or pain levels of arthritis patients but it may cause them to feel more energised and able to live life more comfortably.

References

Abbott FV, Fraser MI (1998) Use and abuse of over-the-counter analgesic agents. *J Psychiatry Neurosci.* 23(1):13-34

Abou-Raya S, Abou-Raya A, Helmii M (2012) Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age Ageing*. 41(5):646-52

Affleck G, Urrows S, Tennen H, Higgins P, Abeles M (1996) Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. *Pain.* 68(2-3):363-8

Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr (1993) Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 25(1):71-80

Alföldi P, Wiklund T, Gerdle B (2013) Comorbid insomnia in patients with chronic pain: a study based on the Swedish quality registry for pain rehabilitation (SQRP). *Disabil Rehabil* Dec 9 [Epub ahead of print]

Ambien CR Prescribing Information. 2007. Ambien CR (zolpidem tartrate extended release). Bridgewater, NJ: Sanofi –Aventis

American Academy of Sleep Medicine. The International Classification of Sleep Disorders, Second Edition (ICSD-2): Diagnostic and Coding Manual. Second Edition. 2005.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IVTR). Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.

Ashton H (1991) Protracted withdrawal syndromes from benzodiazepines. *J Subst Abuse Treat.* 8(1-2):19-28

Asih S, Neblett R, Mayer TG, Brede E, Gatchel RJ (2013) Insomnia in Chronic Disabling Musculoskeletal Pain Disorders is Independent of Pain and Depression. *Spine J.* Dec 9 [Epub ahead of print]

Atkinson, J. H.; Ancoli-Israel, Sonia; Slater, Mark A.; Garfin, Steven R.; Gillin, Christian (1988) Subjective Sleep Disturbance in Chronic Back Pain. *Clin J Pain*. 65:225-232

Atkinson G, Davenne D (2007) Relationships between sleep, physical activity and human health. *Physiol Behav*. 90(2-3):229-35

Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F (2002) Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res*. 53(3):737-40

Bair MJ, Robinson RL, Katon W, Kroenke K (2003) Depression and pain comorbidity: a literature review. *Arch Intern Med*. 163(20):2433-45

Bastien CH, Vallières A, Morin CM (2001) Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2(4):297-307

Bayley TR, Haslock I (1976) Night medication in rheumatoid arthritis. *J R Coll Gen Pract*. 26(169):591-4

Beaudreau SA, Spira AP, Stewart A, Kezirian EJ, Lui LY, Ensrud K, Redline S, Ancoli-Israel S, Stone KL; Study of Osteoporotic Fractures (2012) Validation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older black and white women. *Sleep Med*. 13(1):36-42

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. *Arch Gen Psychiatry.* 4:561-71

Benca RM (2005) Diagnosis and treatment of chronic insomnia: a review. *Psychiatr Serv* 56(3):332-43

Bentley AJ, Newton S, Zio CD (2003) Sensitivity of sleep stages to painful thermal stimuli. *J Sleep Res.* 12(2):143-7

Besset A, Tafti M, Villemin E, Borderies P, Billiard M (1995) Effects of zolpidem on the architecture and cyclical structure of sleep in poor sleepers. *Drugs Exp Clin Res*. 21(4):161-9

Bertolazi AN, Fagondes SC, Hoff LS, Dartora EG, Miozzo IC, de Barba ME, Barreto SS (2011) Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. *Sleep Med*. 12(1):70-5

Bomholt SF, Harbuz MS, Blackburn-Munro G, Blackburn-Munro RE (2004) Involvement and role of the hypothalamo-pituitary-adrenal (HPA) stress axis in animal models of chronic pain and inflammation. *Stress*. 7(1):1-14

Bonnet MH (1985) Effect of sleep disruption on sleep, performance, and mood. *Sleep*. 8(1):11-9

Bonnet MH (1986) Performance and sleepiness as a function of frequency and placement of sleep disruption. *Psychophysiology*. 23(3):263-71

Bonnet MH (1989) Infrequent periodic sleep disruption: effects on sleep, performance and mood. *Physiol Behav*. 45(5):1049-55

Bonnet MH, Arand DL (2003) Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Med Rev*. 7(4):297-310

Brandt KD (1989) Treatment of Osteoarthritis. In *Arthritis and Allied Conditions, a textbook of Rheumatology*, 11th edn, ed. McCarty DJ, pp. 1631-1641. Lea & Febiger, Philadelphia

Brown GK, Nicassio PM, Wallston KA (1989) Pain coping strategies and depression in rheumatoid arthritis. *J Consult Clin Psychol*. 57(5):652-7

Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR (2012) Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. *J Pain*. 13(8):790-8

Buckwalter JA, Heckman JD, Petrie DP; AOA (2003) An AOA critical issue: aging of the North American population: new challenges for orthopaedics. *J Bone Joint Surg Am.* 85(4):748-58

Budhiraja R, Roth T, Hudgel DW, Budhiraja P, Drake CL (2011) Prevalence and polysomnographic correlates of insomnia comorbid with medical disorders. *Sleep*. 34(7):859-67

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 28(2):193-213

Buysse DJ, Reynolds CF 3rd, Kupfer DJ, Thorpy MJ, Bixler E, Manfredi R, Kales A, Vgontzas A, Stepanski E, Roth T, et al (1994) Clinical diagnoses in 216 insomnia patients using the International Classification of Sleep Disorders (ICSD), DSM-IV and ICD-10 categories: a report from the APA/NIMH DSM-IV Field Trial. *Sleep*. 17(7):630-7

Buysse DJ (2013) Insomnia. *JAMA*. 309(7):706-16

Byrne M, Troy A, Bradley LA, Marchisello PJ, Geisinger KF, Van der Heide LH, Prieto EJ (1982) Cross-validation of the factor structure of the McGill Pain Questionnaire. *Pain*. 13(2):193-201

Caldwell JR, Rapoport RJ, Davis JC, Offenberg HL, Marker HW, Roth SH, Yuan W, Eliot L, Babul N, Lynch PM (2002) Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage*. 23(4):278-91

Camacho TC, Roberts RE, Lazarus NB, Kaplan GA, Cohen RD (1991) Physical activity and depression: evidence from the Alameda County Study. *Am J Epidemiol.* 134(2):220-31

Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace EP (1993) Development of a fatigue scale. *J Psychosom Res*. 37(2):147-53

Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, Bennett RM, Collins H (2009) Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain*. 146(3):253-60

Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ (1997) Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. *Am J Epidemiol*. 146(2):105-14

coleChung KF, Tso KC (2010) Relationship between insomnia and pain in major depressive disorder: A sleep diary and actigraphy study. *Sleep Med*. 11(8):752-8

Cole MG, Dendukuri N (2003) Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry*. 160(6):1147-56

Criswell HE, Simson PE, Knapp DJ, Devaud LL, McCown TJ, Duncan GE, Morrow AL, Breese GR (1995) Effect of zolpidem on gamma-aminobutyric acid (GABA)-induced inhibition predicts the interaction of ethanol with GABA on individual neurons in several rat brain regions. *J Pharmacol Exp Ther*. 273(1):526-36

Currie SR, Wilson KG, Pontefract AJ, deLaplante L.(2000) Cognitive-behavioral treatment of insomnia secondary to chronic pain. *J Consult Clin Psycho.* 68(3):407-16

Derksen F, Bensing J, Lagro-Janssen A (2013) Effectiveness of empathy in general practice: a systematic review. *Br J Gen Pract*. 63(606):76-84

Devins GM, Edworthy SM, Paul LC, Mandin H, Seland TP, Klein G, Costello CG, Shapiro CM (1993) Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. *J Psychosom Res*. 37(2):163-70

Di Lio A, Benke D, Besson M, Desmeules J, Daali Y, Wang ZJ, Edwankar R, Cook JM, Zeilhofer HU (2011) HZ166, a novel GABAA receptor subtype-selective benzodiazepine site ligand, is antihyperalgesic in mouse models of inflammatory and neuropathic pain. *Neuropharmacology*. 60(4):626-32

Dorsey CM, Lukas SE, Cunningham SL (1996) Fluoxetine-induced sleep disturbance in depressed patients. *Neuropsychopharmacology*.14(6):437-42

Dos Santos WT, Rodrigues Ede C, Mainenti MR (2014) Muscle performance, body fat, pain and function in the elderly with arthritis. *Acta Ortop Bras*. 22(1):54-8

Drewes AM, Bjerregård K, Taagholt SJ, Svendsen L, Nielsen KD (1998 a) Zopiclone as night medication in rheumatoid arthritis. *Scand J Rheumatol.* 27(3):180-7

Drewes AM, Svendsen L, Taagholt SJ, Bjerregård K, Nielsen KD, Hansen B (1998 b) Sleep in rheumatoid arthritis: a comparison with healthy subjects and studies of sleep/wake interactions. *Br J Rheumatol*. 37(1):71-81

Drummond SP, Brown GG, Stricker JL, Buxton RB, Wong EC, Gillin JC (1999) Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *Neuroreport*. 10(18):3745-8

Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB (2000) Altered brain response to verbal learning following sleep deprivation. *Nature*. 403(6770):655-7

Edge LC (2010) The role of emotional brain processing during sleep in depression. *J Psychiatr Ment Health Nurs.* 17(10):857-61

Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT (2008) Duration of sleep contributes to next-day pain report in the general population. *Pain* 137(1):202-7EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. (1992) 15(2):173-84

Ericsson M, Poston WS, Linder J, Taylor JE, Haddock CK, Foreyt JP (2002) Depression predicts disability in long-term chronic pain patients. *Disabil Rehabil.* 24(6):334-40

Ettinger WH Jr, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, Shumaker S, Berry MJ, O'Toole M, Monu J, Craven T (1997) A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). *JAMA*. 277(1):25-31

Everitt DE, Avorn J, Baker MW (1990) Clinical decision-making in the evaluation and treatment of insomnia. *Am J Med*. 89(3):357-62

Fadda P, Tortorella A, Fratta W (1991) Sleep deprivation decreases mu and delta opioid receptor binding in the rat limbic system. *Neurosci Lett.* 129(2):315-7

Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, Roth T (2011) Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. *J Clin Psychiatry.* 72(7):914-28

Fine PG (2011) Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med*. 12(7):996-1004

Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG (1999) Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. *Sleep*. 22 Suppl 2:366-72

Foo H, Mason P (2003) Brainstem modulation of pain during sleep and waking. *Sleep Med Rev*. 7(2):145-54

Ford DE, Kamerow DB (1989) Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 262(11):1479-84

Frank RG, Beck NC, Parker JC, Kashani JH, Elliott TR, Haut AE, Smith E, Atwood C, Brownlee-Duffeck M, Kay DR (1988) Depression in rheumatoid arthritis. *J Rheumatol.* 15(6):920-5

Friedman L, Benson K, Noda A, Zarcone V, Wicks DA, O'Connell K, Brooks JO 3rd, Bliwise DL, Yesavage JA (2000) An actigraphic comparison of sleep restriction and sleep hygiene treatments for insomnia in older adults. *J Geriatr Psychiatry Neurol*. 13(1):17-27

Gallopin T, Fort P, Eggermann E, Cauli B, Luppi PH, Rossier J, Audinat E, Mühlethaler M, Serafin M (2000) Identification of sleep-promoting neurons in vitro. *Nature*. 404(6781):992-5

Gorenstein C, Andrade L (1996) Validation of a Portuguese version of the Beck Depression Inventory and the State-Trait Anxiety Inventory in Brazilian subjects. *Braz J Med Biol Res*. 29(4):453-7

Granges G, Littlejohn G (1993) Pressure pain threshold in pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia syndrome. *Arthritis Rheum.* 36(5):642-6

Greenblatt DJ, Legangneux E, Harmatz JS, Weinling E, Freeman J, Rice K, Zammit GK (2006) Dynamics and kinetics of a modified-release formulation of zolpidem: comparison with immediate-release standard zolpidem and placebo. *J Clin Pharmaco.* 46(12):1469-80

Gureje O, Von Korff M, Simon GE, Gater R (1998) Persistent pain and well-being: a World Health Organization Study in Primary Care. *JAMA*. 280(2):147-51

Hamon M, Bourgoin S (1999) Serotonin and its receptors in pain control. In *Novel Aspects of Pain Management: Opioids and Beyond*, ed Sawynok J, Cowan A, pp. 203–228. Wiley–Liss, New York

Hardo PG, Kennedy TD (1991) Night sedation and arthritic pain. *J R Soc Med*. 84(2):73-5

Hashmi AM, Khawaja IS, Butt Z, Umair M, Naqvi SH, Jawad-Ul-Haq (2014) The pittsburgh sleep quality index: validation of the urdu translation. *J Coll Physicians Surg Pak*. 24(2):123-6

Hauri P, Hawkins DR (1973) Alpha-delta sleep. *Electroencephalogr Clin Neurophysiol*. 34(3):233-7

Hauri PJ (1993) Consulting about insomnia: a method and some preliminary data. *Sleep*. 16(4):344-50

Haythornthwaite JA, Sieber WJ, Kerns RD (1991) Depression and the chronic pain experience. *Pain*. 46(2):177-84

Hernández-Hernández V, Ferraz-Amaro I, Díaz-González F (2014) Influence of disease activity on the physical activity of rheumatoid arthritis patients. *Rheumatology (Oxford)*. 53(4):722-31

Hesse LM, von Moltke LL, Greenblatt DJ (2003) Clinically important drug interactions with zopiclone, zolpidem and zaleplon. *CNS Drugs*. 17(7):513-32

Hindmarch I, Legangneux E, Stanley N, Emegbo S, Dawson J (2006) A double-blind, placebo-controlled investigation of the residual psychomotor and cognitive effects of zolpidem-MR in healthy elderly volunteers. *Br J Clin Pharmacol*. 62(5):538-45

Holbrook AM, Crowther R, Lotter A, Cheng C, King D (2000) The diagnosis and management of insomnia in clinical practice: a practical evidence-based approach. *CMAJ*. 162(2):216-20

Holm KJ, Goa KL (2000) Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs*. 59(4):865-89

Horne JA (1989) Aspirin and nonfebrile waking oral temperature in healthy men and women: links with SWS changes? *Sleep*. 12(6):516-21

Horne JA (1993) Human sleep, sleep loss and behaviour. Implications for the prefrontal cortex and psychiatric disorder. *Br J Psychiatry*. 162:413-9

Horoszok L, Baleeiro T, D'Aniello F, Gropper S, Santos B, Guglietta A, Roth T (2014) A single-dose, randomized, double-blind, double dummy, placebo and positive-controlled, five-way cross-over study to assess the pharmacodynamic effects of lorediplon in a phase advance model of insomnia in healthy Caucasian adult male subjects. *Hum Psychopharmacol*. 29(3):266-73

Hough AJ, Sokoloff L (1989a) Pathology of Rheumatoid Arthritis and Allied Disorders. In *Arthritis and Allied Conditions, a textbook of Rheumatology*, 11th edn, ed. McCarty DJ, pp. 674-697. Lea & Febiger, Philadelphia

Hough AJ, Sokoloff L (1989b) Pathology of Osteoarthritis. In *Arthritis and Allied Conditions, a textbook of Rheumatology*, 11th edn, ed. McCarty DJ, pp. 1571-1594. Lea & Febiger, Philadelphia

Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN (2012) Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ*. 345:e8343

Hyland ME (2003) Using the placebo response in clinical practice. *Clin Med*. 3(4):347-50

Jungquist CR, O'Brien C, Matteson-Rusby S, Smith MT, Pigeon WR, Xia Y, Lu N, Perlis ML (2010) The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. *Sleep Med.* 11(3):302-9

Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Fitzgerald JD, Ranganath VK, Nicassio PM (2012) Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. *Sleep*. 35(4):537-43

Ji JL, Liu WJ, Zhang N, Chen ZQ, Zheng AL, Mei QY, Pan JY, Zhao ZX, Tao M, Wang YP, Wei J (2007) Effects of paroxetine with or without zolpidem on depression with insomnia: a multi-center randomized comparative study. *Zhonghua Yi Xue Za Zhi*. 87(23):1585-9

Jungquist CR, O'Brien C, Matteson-Rusby S, Smith MT, Pigeon WR, Xia Y, Lu N, Perlis ML (2010) The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. *Sleep Med.* 11(3):302-9

Kales A, Manfredi RL, Vgontzas AN, Bixler EO, Vela-Bueno A, Fee EC (1991) Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. *Clin Pharmacol Ther*. 49(4):468-76

Katz DA, McHorney CA (1998) Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med.* 158(10):1099-107

Kay DC, Pickworth WB, Neidert GL, Falcone D, Fishman PM, Othmer E (1979) Opioid effects on computer-derived sleep and EEG parameters in nondependent human addicts. *Sleep*. 2(2):175-91

Keefe FJ, Brown GK, Wallston KA, Caldwell DS (1989) Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. *Pain*. 37(1):51-6

King SA, Strain JJ (1990) Benzodiazepine use by chronic pain patients. *Clin J Pain* 6(2):143-7

King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL (1997) Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. *JAMA*. 277(1):32-7

Kinney RK, Gatchel RJ, Polatin PB, Fogarty WT, Mayer TG (1993) Prevalence of psychopathology in acute and chronic low back pain patients. *J Occup Rehabil.* 3(2):95-103

Kirkwood C, Neill J, Breden E (2007) Zolpidem modified-release in insomnia. *Neuropsychiatr Dis Treat*.3(5):521-6

Kivitz A, Ma C, Ahdieh H, Galer BS (2006) A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clin Ther.* 28(3):352-64

Kleykamp BA, Griffiths RR, McCann UD, Smith MT, Mintzer MZ (2012) Acute effects of zolpidem extended-release on cognitive performance and sleep in healthy males after repeated nightly use. *Exp Clin Psychopharmacol*. 20(1):28-39

Krenk L, Jennum P, Kehlet H (2014) Postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement. *J Clin Sleep Med*. 10(3):321-6

Krystal AD, McCall WV, Fava M, Joffe H, Soares CN, Huang H, Grinell T, Zummo J, Spalding W, Marshall R (2012) Eszopiclone treatment for insomnia: effect size comparisons in patients with primary insomnia and insomnia with medical and psychiatric comorbidity. *Prim Care Companion CNS Disord*. 14(4)

Kundermann B, Spernal J, Huber MT, Krieg JC, Lautenbacher S (2004) Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med*. 66(6):932-7

Kuppermann M, Lubeck DP, Mazonson PD, Patrick DL, Stewart AL, Buesching DP, Fifer SK (1995) Sleep problems and their correlates in a working population. *J Gen Intern Med*. 10(1):25-32

Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC (2001) Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med*. 2(5):389-96

Lader MH, Petursson H (1981) Benzodiazepine derivatives--side effects and dangers. *Biol Psychiatry*. 16(12):1195-201

Lancel M (1999) Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. *Sleep*. 22(1):33-42

Lavie P, Epstein R, Tzischinsky O, Gilad D, Nahir M, Lorber M, Scharf Y (1992) Actigraphic measurements of sleep in rheumatoid arthritis: comparison of patients with low back pain and healthy controls. *J Rheumatol*. 19(3):362-5

Lavigne G, Zucconi M, Castronovo C, Manzini C, Marchettini P, Smirne S (2000) Sleep arousal response to experimental thermal stimulation during sleep in human subjects free of pain and sleep problems. *Pain*. 84(2-3):283-90

Lee AT, Ariffin MZ, Zhou M, Ye JZ, Moochhala SM, Khanna S (2011) Forebrain medial septum region facilitates nociception in a rat formalin model of inflammatory pain. *Pain*. 152(11):2528-42

Lee YC, Lu B, Edwards RR, Wasan AD, Nassikas NJ, Clauw DJ, Solomon DH, Karlson EW (2013) The role of sleep problems in central pain processing in rheumatoid arthritis. *Arthritis Rheum.* 65(1):59-68

Levine B, Roehrs T, Stepanski E, Zorick F, Roth T (1987) Fragmenting sleep diminishes its recuperative value. *Sleep*. 10(6):590-9

Lichstein KL, Riedel BW (1994) Behavioral assessment and treatment of insomnia: A review with an emphasis on clinical application. *Behavior Therapy.* 25(4):659-688

Lichstein KL, Stone KC, Donaldson J, Nau SD, Soeffing JP, Murray D, Lester KW, Aguillard RN (2006) Actigraphy validation with insomnia. *Sleep*. 29(2):232-9

Liu Y, Croft JB, Wheaton AG, Perry GS, Chapman DP, Strine TW, McKnight-Eily LR, Presley-Cantrell L (2013) Association between perceived insufficient sleep, frequent mental distress, obesity and chronic diseases among US adults, 2009 behavioral risk factor surveillance system. *BMC Public Health*. 13:84

Litwack K (2009) Somatosensory function, pain, and headache. In *Pathophysiology: Concepts of altered health states*, 8th edn, ed. Porth CM and Matfin G, pp. 1225-1259. Wolters Kluwer Health, Lippincott Williams & Wilkins, Philadelphia

Livingston G, Blizard B, Mann A (1993) Does sleep disturbance predict depression in elderly people? A study in inner London. *Br J Gen Pract*. 43(376):445-8

Louie GH, Tektonidou MG, Caban-Martinez AJ, Ward MM (2011) Sleep disturbances in adults with arthritis: prevalence, mediators, and subgroups at greatest risk. Data from the 2007 National Health Interview Survey. *Arthritis Care Res (Hoboken)*. 63(2):247-60

Lu J, Greco MA, Shiromani P, Saper CB (2000) Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J Neurosci*. 20(10):3830-42

Lunde LH, Pallesen S, Krangnes L, Nordhus IH (2010) Characteristics of sleep in older persons with chronic pain: a study based on actigraphy and self-reporting. *Clin J Pain.* 26(2):132-7

Malcangio M, Bowery NG (1996) GABA and its receptors in the spinal cord. *Trends Pharmacol Sci*. 17(12):457-62

Mäntyselkä P, Ahonen R, Viinamäki H, Takala J, Kumpusalo E (2002) Drug use by patients visiting primary care physicians due to nonacute musculoskeletal pain. *Eur J Pharm Sci*. 17(4-5):201-6

Martin JL, Hakim AD (2011) Wrist actigraphy. *Chest*. 139(6):1514-27

Martin SE, Brander PE, Deary IJ, Douglas NJ (1999) The effect of clustered versus regular sleep fragmentation on daytime function. *J Sleep Res*. 8(4):305-11.

Martínez MP, Miró E, Sánchez AI, Díaz-Piedra C, Cáliz R, Vlaeyen JW, Buela-Casal G (2013) Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. *J Behav Med*. Jun 7 [Epub ahead of print]

Marty M, Rozenberg S, Duplan B, Thomas P, Duquesnoy B, Allaert F; Section Rachis de la Société Française de Rhumatologie (2008) Quality of sleep in patients with chronic low back pain: a case-control study. *Eur Spine J.* 17(6):839-44

McCartt AT, Rohrbaugh JW, Hammer MC, Fuller SZ (2000) Factors associated with falling asleep at the wheel among long-distance truck drivers. *Accid Anal Prev*. 32(4):493-504

McCarty DJ (1989) Clinical Picture of Rheumatoid Arthritis. In *Arthritis and Allied Conditions, a textbook of Rheumatology*, 11th edn, ed. McCarty DJ, pp. 715-742. Lea & Febiger, Philadelphia

McCracken LM, Iverson GL (2002) Disrupted sleep patterns and daily functioning in patients with chronic pain. *Pain Res Manag*. 7(2):75-9

Mc Lellan AT, Woody GE, O'Brien CP (1979) Development of psychiatric illness in drug abusers. Possible role of drug preference. *N Engl J Med*. 301(24):1310-4

Mellinger GD, Balter MB, Uhlenhuth EH (1985) Insomnia and its treatment. Prevalence and correlates. *Arch Gen Psychiatry*. 42(3):225-32

Melzack R (1975) The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1(3):277-99

Merskey H, B Bogduk N (ed.) (1994) *Classification of chronic pain: Description of chronic pain and definition of pain terms*, 2nd edn, IASP Publications, Seattle

Michielsen HJ, De Vries J, Van Heck GL (2003) Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. *J Psychosom Res*. 54(4):345-52

Milner B, & Petrides M (1984). Behavioural effects of frontal lobe lesions in man. *Trends in Neuroscience, 7,* 403-407.

Moffitt PF, Kalucy EC, Kalucy RS, Baum FE, Cooke RD (1991) Sleep difficulties, pain and other correlates. *J Intern Med*. 230(3):245-9

Moldofsky H, Scarisbrick P (1976) Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med*. 38(1):35-44

Moldofsky H, Lue FA, Mously C, Roth-Schechter B, Reynolds WJ (1996) The effect of zolpidem in patients with fibromyalgia: a dose ranging, double blind, placebo controlled, modified crossover study. *J Rheumatol*. 23(3):529-33

Moldofsky H (2010) Rheumatic manifestations of sleep disorders. *Curr Opin Rheumatol*. 22(1):59-63

Morgan H, Borg S, Holm L (1980) Neuropsychological impairment and exclusive abuse of sedatives or hypnotics. *Am J Psychiatry*. 137:215-17

Morillas-Arques P, Rodriguez-Lopez CM, Molina-Barea R, Rico-Villademoros F, Calandre EP (2010) Trazodone for the treatment of fibromyalgia: an open-label, 12-week study. *BMC Musculoskelet Disord*. Sep 10;11:204

Morin CM, Stone J, Trinkle D, Mercer J, Remsberg S (1993) Dysfunctional beliefs and attitudes about sleep among older adults with and without insomnia complaints. *Psychol Aging*. 8(3):463-7

Morin CM, Culbert JP, Schwartz SM (1994) Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry.* 151(8):1172-80

Morin CM, Gibson D, Wade J (1998) Self-reported sleep and mood disturbance in chronic pain patients. *Clin J Pain*. 14(4):311-4

Morin CM (2003) Measuring outcomes in randomized clinical trials of insomnia treatments. *Sleep Med Rev*. 7(3):263-79

Morin CM, LeBlanc M, Bélanger L, Ivers H, Mérette C, Savard J (2011) Prevalence of insomnia and its treatment in Canada. *Can J Psychiatry.* 56(9):540-8

Moskowitz RW (1989) Clinical and Laboratory findings in Osteoarthritis. In *Arthritis and Allied Conditions, a textbook of Rheumatology*, 11th edn, ed. McCarty DJ, pp. 1605-1630. Lea & Febiger, Philadelphia

Munro G, Lopez-Garcia JA, Rivera-Arconada I, Erichsen HK, Nielsen EØ, Larsen JS, Ahring PK, Mirza NR (2008) Comparison of the novel subtype-selective GABAA receptor-positive allosteric modulator NS11394 [3'-[5-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-biphenyl-2-carbonitrile] with diazepam, zolpidem, bretazenil, and gaboxadol in rat models of inflammatory and neuropathic pain. *J Pharmacol Exp Ther.* 327(3):969-81

Murphy PJ, Badia P, Myers BL, Boecker MR, Wright KP Jr (1994) Nonsteroidal anti-inflammatory drugs affect normal sleep patterns in humans. *Physiol Behav.* 55(6):1063-6

Mystakidou K, Parpa E, Tsilika E, Kalaidopoulou O, Georgaki S, Galanos A, Vlahos L (2002) Greek McGill Pain Questionnaire: validation and utility in cancer patients. *J Pain Symptom Manage.* 24(4):379-87

Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, Worthy G, Landewé R, Smolen JS, Emery P, Buch MH (2010) Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis*. 69(6):976-86

Neutel CI (1995) Risk of traffic accident injury after a prescription for a benzodiazepine. *Ann Epidemiol.* 5(3):239-44

Nicassio PM, Wallston KA (1992) Longitudinal relationships among pain, sleep problems, and depression in rheumatoid arthritis. *J Abnorm Psychol*. 101(3):514-20

Nicassio PM, Moxham EG, Schuman CE, Gevirtz RN (2002) The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *Pain*. 100(3):271-9

Nicassio PM, Ormseth SR, Custodio MK, Olmstead R, Weisman MH, Irwin MR (2014) Confirmatory factor analysis of the Pittsburgh Sleep Quality Index in rheumatoid arthritis patients. *Behav Sleep Med*. 12(1):1-12

O'Brien EM, Waxenberg LB, Atchison JW, Gremillion HA, Staud RM, McCrae CS, Robinson ME (2011) Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. *Clin J Pain*. 27(5):425-33

O'Donnell D, Silva EJ, Münch M, Ronda JM, Wang W, Duffy JF (2009) Comparison of subjective and objective assessments of sleep in healthy older subjects without sleep complaints. *J Sleep Res*. 18(2):254-63

Ogle J, Bushnell JA, Caputi P (2013) Empathy is related to clinical competence in medical care. *Med Educ*. 47(8):824-31

Ohayon M (1996) Epidemiological study on insomnia in the general population. *Sleep*. 19(3 Suppl):S7-15

Ohayon MM, Schatzberg AF (2003) Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 60(1):39-47

Onen SH, Alloui A, Gross A, Eschallier A, Dubray C (2001 a) The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res*. 10(1):35-42

Onen SH, Alloui A, Jourdan D, Eschalier A, Dubray C (2001 b) Effects of rapid eye movement (REM) sleep deprivation on pain sensitivity in the rat. *Brain Res*. 900(2):261-7

Onen SH, Onen F, Courpron P, Dubray C (2005) How pain and analgesics disturb sleep. *Clin J Pain.* 21(5):422-31

Orzeł-Gryglewska J (2010) Consequences of sleep deprivation. *Int J Occup Med Environ Health*. 23(1):95-114

Ossipov, M.H., Malan, T.P., Lai, J. Porreca, F (1997) Opioid pharmacology of acute and chronic pain, In *The Pharmacology of Pain* ed. Dickenson A, Besson JM, pp. 305-333. Springer, Berlin

Papp KK, Penrod CE, Strohl KP (2002) Knowledge and attitudes of primary care physicians toward sleep and sleep disorders. *Sleep Breath*. 6(3):103-9

Peltzer K, Phaswana-Mafuya N (2013) Depression and associated factors in older adults in South Africa. *Glob Health Action*. 18(6):1-9

Petursson H, Gudjonson G, Lader MH (1983) Psychometric performance during chronic benzodiazepines treatment and withdrawal. *Psychopharmacology*. 81:345

Subhan Z (1984) Benzodiazepines and memory. *Psychiatry in Practice*. 319:15-20

Phaswana-Mafuya N, Peltzer K, Chirinda W, Musekiwa A, Kose Z, Hoosain E, Davids A, Ramlagan S (2013) Self-reported prevalence of chronic non-communicable diseases and associated factors among older adults in South Africa. *Glob Health Action.* Sep 19;6:20936

Pick CG, Chernes Y, Rigai T, Rice KC, Schreiber S (2005) The antinociceptive effect of zolpidem and zopiclone in mice. *Pharmacol Biochem Behav*. 81(3):417-23

Pilowsky I, Crettenden I, Townley M (1985) Sleep disturbance in pain clinic patients. *Pain*. 23(1):27-33

Porth CM (2009) Sleep and sleep disorders. In *Pathophysiology: Concepts of altered health states*, 8th edn, ed. Porth CM and Matfin G, pp.1338-1356. Wolters Kluwer Health, Lippincott Williams & Wilkins, Philadelphia

Power JD, Perruccio AV, Badley EM (2005) Pain as a mediator of sleep problems in arthritis and other chronic conditions. *Arthritis Rheum.* 53(6):911-9

Radecki SE, Brunton SA (1993) Management of insomnia in office-based practice. National prevalence and therapeutic patterns. *Arch Fam Med.* 2(11):1129-34

Randall S, Roehrs TA, Roth T (2012) Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study. *Sleep*. 35(11):1551-7

Ratcliffe GE, Enns MW, Belik SL, Sareen J (2008) Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. *Clin J Pain*. 24(3):204-10

Rathbun AM, Reed GW, Harrold LR (2013) The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. *Rheumatology (Oxford*). 52(10):1785-94

Ray WA, Griffin MR, Downey W (1989) Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA.* 262(23):3303-7

Raymond I, Nielsen TA, Lavigne G, Manzini C, Choinière M (2001) Quality of sleep and its daily relationship to pain intensity in hospitalized adult burn patients. *Pain.* 92(3):381-8

Raymond I, Ancoli-Israel S, Choinière M (2004) Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries. *Sleep Med*. 5(6):551-9

Rechtschaffen A & Kales AA (1968) *A Manual of Standardized Terminology: Techniques and Scoring System for Sleep Stages of Human Subjects*. Brain Information Service, Brain Research Institute, Los Angeles

Rode F, Jensen DG, Blackburn-Munro G, Bjerrum OJ (2005) Centrally-mediated antinociceptive actions of GABA(A) receptor agonists in the rat spared nerve injury model of neuropathic pain. *Eur J Pharmacol*. 516(2):131-8

Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T (2006) Sleep loss and REM sleep loss are hyperalgesic. *Sleep*. 29(2):145-51

Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S (2001) Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum*. 44(1):222-30

Roshanaei-Moghaddam B, Katon WJ, Russo J (2009) The longitudinal effects of depression on physical activity. *Gen Hosp Psychiatry*. 31(4):306-15

Roth T, Roehrs T, Vogel G (1995) Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. *Sleep*. 18(4):246-51.

Roth T, Price JM, Amato DA, Rubens RP, Roach JM, Schnitzer TJ (2009) The effect of eszopiclone in patients with insomnia and coexisting rheumatoid arthritis: a pilot study. *Prim Care Companion J Clin Psychiatry*. 11(6):292-301

Roth T, Soubrane C, Titeux L, Walsh JK; Zoladult Study Group (2006) Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. *Sleep Med.* 7(5):397-406

Roy-Byrne PP, Hommer D (1988) Benzodiazepine withdrawal: overview and implications for the treatment of anxiety. *Am J Med*. 84(6):1041-52

Rush AJ, Armitage R, Gillin JC, Yonkers KA, Winokur A, Moldofsky H, Vogel GW, Kaplita SB, Fleming JB, Montplaisir J, Erman MK, Albala BJ, McQuade RD (1998) Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. *Biol Psychiatry*. 44(1):3-14

Rybarczyk B, Mack L, Harris JH, Stepanski E (2011) Testing two types of self-help CBT-I for insomnia in older adults with arthritis or coronary artery disease. *Rehabil Psychol.* 56(4):257-66

Sadeh A, Acebo C (2002) The role of actigraphy in sleep medicine. *Sleep Med Rev*. 6(2):113-24

Sánchez-Ortuño MM, Edinger JD, Means MK, Almirall D (2010) Home is where sleep is: an ecological approach to test the validity of actigraphy for the assessment of insomnia. *J Clin Sleep Med*. 6(1):21-9

Saper CB, Chou TC, Scammell TE (2001) The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci*. 24(12):726-31

Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 437(7063):1257-63

Sariyildiz MA, Batmaz I, Bozkurt M, Bez Y, Cetincakmak MG, Yazmalar L, Ucar D, Celepkolu T (2014) Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. *J Clin Med Res*. 6(1):44-52

Sasaki E, Tsuda E, Yamamoto Y, Maeda S, Inoue R, Chiba D, Okubo N, Takahashi I, Nakaji S, Ishibashi Y (2014) Nocturnal knee pain increases with the severity of knee osteoarthritis, disturbing patient sleep quality. *Arthritis Care Res (Hoboken).* Jan 27 [Epub ahead of print]

Scharf MB, Roth T, Vogel GW, Walsh JK (1994) A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. *J Clin Psychiatry*. 55(5):192-9

Schaufeli W, Van Dierendonck D (1994) Burnout, the measurement of a concept. The Dutch version of the Maslach Burnout Inventory (MBI-NL). *Gedrag Gezondheid*.22:153–72

Schmid SM, Hallschmid M, Jauch-Chara K, Born J, Schultes B (2008) A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *J Sleep Res*. 17(3):331-4

Sherrill DL, Kotchou K, Quan SF (1998) Association of physical activity and human sleep disorders. *Arch Intern Med*. 158(17):1894-8

Shaw IR, Lavigne G, Mayer P, Choinière M (2005) Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. *Sleep*. 28(6):677-82

Shochat T, Umphress J, Israel AG, Ancoli-Israel S (1999) Insomnia in primary care patients. *Sleep*. 22 Suppl 2:359-65

Simon GE, VonKorff M (1997) Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry*. 154(10):1417-23**.**

Smith BD, Salzman C (1991) Do benzodiazepines cause depression? *Hosp Community Psychiatry*. 42(11):1101-2

Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K (2001a) The impact of chronic pain in the community. *Fam Pract*. 18(3):292-9

Smith MT, Haythornthwaite JA (2004) How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev*. 8(2):119-32

Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, de Wit M, Aletaha D, Betteridge N, Bijlsma JW, Boers M, Buttgereit F, Combe B, Cutolo M, Damjanov N, Hazes JM, Kouloumas M, Kvien TK, Mariette X, Pavelka K, van Riel PL, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, Sokka-Isler T, Wong JB, van der Heijde D (2014) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 73(3):492-509

Sommer C, Kress M (2004) Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci Lett*. 361(1-3):184-7

Spielman AJ, Caruso LS, Glovinsky PB (1987) A behavioral perspective on insomnia treatment. *Psychiatr Clin North Am*. 10(4):541-53

Staud R, Spaeth M (2008) Psychophysical and neurochemical abnormalities of pain processing in fibromyalgia. *CNS Spectr*. 13(3 Suppl 5):12-7

Steele MT, Ma OJ, Watson WA, Thomas HA Jr, Muelleman RL (1999) The occupational risk of motor vehicle collisions for emergency medicine residents. *Acad Emerg Med*. 6(10):1050-3

Steinhausen S, Ommen O, Thüm S, Lefering R, Koehler T, Neugebauer E, Pfaff H (2014) Physician empathy and subjective evaluation of medical treatment outcome in trauma surgery patients. *Patient Educ Couns*. 95(1):53-60

Stepanski E, Lamphere J, Badia P, Zorick F, Roth T (1984) Sleep fragmentation and daytime sleepiness. *Sleep*. 7(1):18-26

Stepanski EJ (2002) The effect of sleep fragmentation on daytime function. *Sleep*. 25(3):268-76

Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, Singleton N, Meltzer H (2006) Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. *Sleep*. 29(11):1391-7

Stiefel F (1993) Psychosocial aspects of cancer pain. *Support Care Cancer*. 1(3):130-4

International Association for the Study of Pain (1986) Classification of chronic pain. *Pain*. (suppl 3):s1-s226

Stiefel F, Stagno D (2004) Management of insomnia in patients with chronic pain conditions. *CNS Drugs*. 18(5):285-96

Strawbridge WJ, Deleger S, Roberts RE, Kaplan GA (2002) Physical activity reduces the risk of subsequent depression for older adults. *Am J Epidemiol*. 156(4):328-34

Sutton DA, Moldofsky H, Badley EM (2001) Insomnia and health problems in Canadians. *Sleep*. 24(6):665-70

Tang NK, Goodchild CE, Hester J, Salkovskis PM (2012) Pain-related insomnia versus primary insomnia: a comparison study of sleep pattern, psychological characteristics, and cognitive-behavioral processes. *Clin J Pain*. 28(5):428-36

Tashjian RZ, Banerjee R, Bradley MP, Alford W, Fadale PD (2006) Zolpidem reduces postoperative pain, fatigue, and narcotic consumption following knee arthroscopy: a prospective randomized placebo-controlled double-blinded study. *J Knee Surg*. 19(2):105-11

Task force on Taxonomy for the International Association for the Study of Pain (1994) Classification of pain: Descriptions of chronic pain syndromes and definitions of pain terms, 2nd edn, ed Merskey &, Bogduk N, IASP Seattle

Taylor-Gjevre RM, Gjevre JA, Nair BV, Skomro RP, Lim HJ (2011a) Improved Sleep Efficiency after Anti-Tumor Necrosis Factor α Therapy in Rheumatoid Arthritis Patients. *Ther Adv Musculoskelet Dis*. 3(5):227-33

Taylor-Gjevre RM, Gjevre JA, Nair B, Skomro R, Lim HJ (2011b) Components of Sleep Quality and Sleep Fragmentation in Rheumatoid Arthritis and Osteoarthritis. *Musculoskeletal Care.* 9(3):152-159

Tierney M, Fraser A, Kennedy N (2012) Physical activity in rheumatoid arthritis: a systematic review. *J Phys Act Health.* 9(7):1036-48

Tompkins M, Plante M, Monchik K, Fleming B, Fadale P (2011) The use of a non-benzodiazepine hypnotic sleep-aid (Zolpidem) in patients undergoing ACL reconstruction: a randomized controlled clinical trial. *Knee Surg Sports Traumatol Arthrosc*. 19(5):787-91

Tracey I (2010) Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nature Medicine.* 16: 1277-1283

Tsuchiyama K, Nagayama H, Kudo K, Kojima K, Yamada K (2003) Discrepancy between subjective and objective sleep in patients with depression. *Psychiatry Clin Neurosci.* 57(3):259-64

Turk DC, Dworkin RH, Revicki D, Harding G, Burke LB, Cella D, Cleeland CS, Cowan P, Farrar JT, Hertz S, Max MB, Rappaport BA (2008) Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain*. 137(2):276-85

Tzeng JI, Fu YW, Lin CC (2012) Validity and reliability of the Taiwanese version of the Pittsburgh Sleep Quality Index in cancer patients. *Int J Nurs Stud*. 49(1):102-8

Uchimura N, Kamijo A, Kuwahara H, Uchiyama M, Shimizu T, Chiba S, Inoue Y (2012) A randomized placebo-controlled polysomnographic study of eszopiclone in Japanese patients with primary insomnia. *Sleep Med.* 13(10):1247-53

Ukponmwan OE, Rupreht J, Dzoljic MR (1984) REM sleep deprivation decreases the antinociceptive property of enkephalinase-inhibition, morphine and cold-water-swim. *Gen Pharmacol*. 15(3):255-8

Ulus Y, Akyol Y, Tander B, Durmus D, Bilgici A, Kuru O (2011) Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol.* 29(6 Suppl 69):S92-6

Vallières A, Morin CM (2003) Actigraphy in the assessment of insomnia. *Sleep*. 26(7):902-6

Vercoulen JHMM, Alberts M, Bleijenberg G (1999) De Checklist Individual Strength. *Gedragstherapie*.32:131–6.

Verster JC, Volkerts ER, Schreuder AH, Eijken EJ, van Heuckelum JH, Veldhuijzen DS, Verbaten MN, Paty I, Darwish M, Danjou P, Patat A (2002) Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*. 22(6):576-83

Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ (2009) Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. *J Clin Sleep Med*. 5(4):355-62

Vitiello MV, McCurry SM, Shortreed SM, Balderson BH, Baker LD, Keefe FJ, Rybarczyk BD, Von Korff M (2013) Cognitive-behavioral treatment for comorbid insomnia and osteoarthritis pain in primary care: the lifestyles randomized controlled trial. *J Am Geriatr Soc*. 61(6):947-56

Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, Stang P, Brandenburg N, Kessler R (2005) Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain*. 113(3):331-9

Walker MP, van der Helm E (2009) Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull*. 135(5):731-48

Walsh JK, Muehlbach MJ, Lauter SA, Hilliker NA, Schweitzer PK (1996) Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. *J Rheumatol*. 23(2):245-52

Walsh JK, Erman M, Erwin CW, Jamieson A, Mahowald M, Regestein Q, Scharf M, Tigel P, Vogel G, Catesby Ware J (1998) Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII–R primary insomnia. *Human Psychopharmacology: Clinical and Experimental*. 13(3):191-198

Wang H, Ahrens C, Rief W, Schiltenwolf M (2010) Influence of comorbidity with depression on interdisciplinary therapy: outcomes in patients with chronic low back pain. *Arthritis Res Ther*. 12(5):R185

Weitzel KW, Wickman JM, Augustin SG, Strom JG (2000) Zaleplon: a pyrazolopyrimidine sedative-hypnotic agent for the treatment of insomnia. *Clin Ther*. 22(11):1254-67

Westhovens R, Van der Elst K, Matthys A, Tran M, Gilloteau I (2014) Sleep problems in patients with rheumatoid arthritis. *J Rheumatol*. 41(1):31-40

The WHOQOL Group (1998) Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med*. 28(3):551-8

Willis WD, Westlund KN (1997) Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol.* 14(1):2-31

Wilson KG, Watson ST, Currie SR (1998) Daily diary and ambulatory activity monitoring of sleep in patients with insomnia associated with chronic musculoskeletal pain. *Pain*. 75(1):75-84

Wilson KG, Eriksson MY, D'Eon JL, Mikail SF, Emery PC (2002) Major depression and insomnia in chronic pain. *Clin J Pain*. 18(2):77-83

Wittig RM, Zorick FJ, Blumer D, Heilbronn M, Roth T (1982) Disturbed sleep in patients complaining of chronic pain. *J Nerv Ment Dis*. 170(7):429-31

Wong DL, Baker CM (1988) Pain in children: comparison of assessment scales. *Pediatr Nurs.* 14(1):9-17

World Health Organization. The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992

Wright V (1985) Measurement of outcome in rheumatic diseases. *J R Soc Med*. 78(12):985-94

Wysowski DK, Barash D (1991) Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's Spontaneous Reporting System. *Arch Intern Med*. 151(10):2003-8

Youngblood BD, Zhou J, Smagin GN, Ryan DH, Harris RB (1997) Sleep deprivation by the "flower pot" technique and spatial reference memory. *Physiol Behav.* 61(2):249-56