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The effect of an α2δ calcium channel blocker on sleep parameters in women with chronic primary insomnia: A pragmatic study

By

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

Johannesburg, *2013*

DECLARATION

I declare that this dissertation is my own work, unaided except as specified. This dissertation is submitted for the Degree of Master of Science in the Faculty of Science at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination in this or any other University.



Naseem Ebrahim

Signed at Johannesburg on the 4th day of November 2013

ABSTRACT

Chronic neuropathic pain, epilepsy, depression and anxiety disorders have been treated successfully with pregabalin. Normal subjects, epileptics and patients with neuropathic pain to whom pregabalin was prescribed showed an improvement in objective and subjective sleep parameters. To determine if pregabalin's sleep enhancing effect is an independent process, it is necessary to test pregabalin in primary insomniacs who do not have conditions that could be treated by pregabalin. My study was designed as a double blind, randomised, crossover, placebo controlled trial, with 50 milligrams of pregabalin or placebo was administered for eight consecutive nights. I performed polysomnographic recordings on eight female chronic primary insomniacs on five nights. Sleep recordings were performed prior to the intervention, and on the first night and eighth night of each treatment. Subjects filled out subjective scales at baseline and night eight of every treatment. While polysomnography and subjective scales showed that my subjects were insomniac, sleep variables during the pregabalin or placebo period were unchanged when compared to baseline. A daily dose of 50 mg pregabalin did not have any significant effects on either sleep architecture or subjective sleep variables in female chronic primary insomniacs.

CONFERENCE PROCEEDINGS

I have presented part of the work in this dissertation orally, at the 36th meeting of The Physiology Society of Southern Africa (September 2008):

Ebrahim N, Bentley AJ, Mitchell D. *The effects of an alpha two delta calcium channel blocker on sleep parameters.*

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LIST OF ABBREVIATIONS

Alpha	α
Analysis of variance	ANOVA
Beta	β
Body mass index	BMI
Carbon	C
Delta	δ
Diagnostic and Statistical Manual IV	DSM IV
Electroencephalograph	EEG
Gabaaminobutyric acid	GABA
Gamma	γ
Milligram	mg
Nitrogen	N
Rapid eye movement	REM
Repeated measures	RM

1. LITERATURE REVIEW

There has been much emphasis placed on pregabalin's effectiveness in treating various neurological disorders including epilepsy, generalized anxiety disorder, neuropathic pain, and fibromyalgia. While various clinical trials have focused on the effects that pregabalin has on treating a primary condition, none has focused on the direct effects of pregabalin in patients with a sleep disorder, in spite of some studies showing that pregabalin does have sleep altering properties. In this literature review, I shall discuss the pharmacology of pregabalin as well as pregabalin's success in treating neuropathic pain, epilepsy and anxiety disorder. However, unlike other reviews I shall place special emphasis on the effects that pregabalin has on sleep as demonstrated in clinical and animal trials. I will also briefly discuss the prevalence and treatment options of insomnia and the possible advantages of testing pregabalin in this group of pathological sleepers.

1.1 Pregabalin

Pregabalin is an analgesic, anticonvulsant, and anxiolytic drug that is an analogue of the neurotransmitter gabaaminobutyric acid (GABA). Pregabalin has been studied as a treatment for various conditions, including diabetic peripheral neuropathy, post herpetic neuralgia and general anxiety disorder. Initially pregabalin was thought to have a mechanism similar to that of GABA, but it is now known that pregabalin has a novel mechanism of action.

1.1.1 Pharmacology

Pregabalin acts as a presynaptic inhibitor by binding to the α2δ sub unit of the N and P/Q voltage gated calcium channels (Davies et al., 2007, Sills, 2006). Voltage gated calcium channels control the movement of calcium ions across the cell membrane. The P/Q and N type voltage gated calcium channels have four sub units and six transmembrane helixes that can align to form a pore, which allows the influx of calcium ions (Davies et al., 2007) (Figure 1.1). The opening of the voltage gated calcium channels allow calcium ions to flow into the neuron causing vesicles to fuse to the cell membrane and release neurotransmitters into the synaptic cleft. When neurons are damaged or when neurons fire abnormally, excess influx of calcium ions can occur within the neuron, resulting in an excess release of neurotransmitters.

Excess calcium is prevented from entering the neuron when pregabalin binds to the α2δ site, as pregabalin changes the structural conformation of the channel. A reduction in calcium ions results in a decrease in neurotransmitter release into the synaptic cleft. Therefore, the stimulation of the postsynaptic receptor decreases and the neuron is restored to a normal physiological state. Pregabalin is also absorbed into the cell where it has additional calcium inhibiting effects as seen in rat spinal ligation studies (Bauer et al., 2010a).

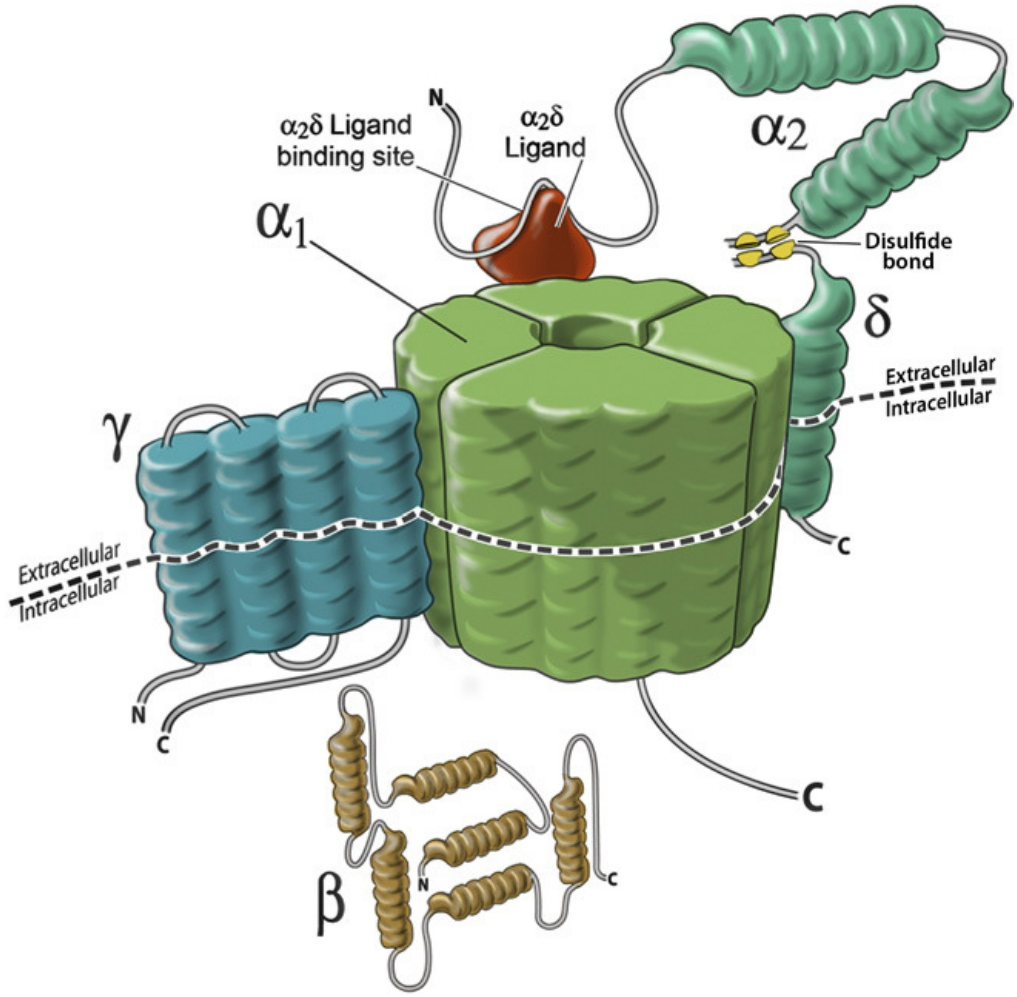

Figure 1.1 Structure of the voltage gated calcium channel. Voltage-gated calcium channels are composed of four subunits. There are 10 different types of alpha (α)1 pore forming sub units, however only the P/Q, N and, R types exist adjacent to neural synaptic vesicles. Symbols: β-Beta, γ-Gamma, C-carbon, N-nitrogen (Doan, 2010)

In a recent study that examined the effects of pregabalin in rats that had undergone spinal cord ligation in the ipsilateral nerves between T4 and T5, pregabalin had the ability to reduce the α2δ-1 expressed on the surface of the cell (Bauer et al., 2010). The α2δ-1 expression was reduced not by decreasing the expression of α2δ-1 mRNA within the cells, but by causing disruption of the traffic of the α2δ-1 from the endoplasmic reticulum to the cell surface (Bauer et al., 2010). Unlike other drugs that bind and have an effect at the cell surface, the effects of the gabapentinoid drugs (pregabalin and its predecessor gabapentin) are unique as they also act by disrupting traffic of α2δ-1 within the presynaptic cells (Bauer et al., 2010).

1.1.2 Pharmacokinetics

In healthy fasting patients who consumed single or multiple doses of pregabalin, the peak serum concentration was reached in approximately one hour (Taylor et al., 2007, Tassone et al., 2007). Food consumption does not affect the absorption or elimination half-life of pregabalin, but increases the time to peak serum concentration to three hours (Taylor et al., 2007, Tassone et al., 2007). Pregabalin does not bind to proteins and readily crosses the blood brain barrier (Taylor et al., 2007). Over 98% of pregabalin is excreted in the urine and 0.1 % is excreted in feces (Taylor et al., 2007, Tassone et al., 2007). Decreased renal function in elderly patients can result in lower clearance time of pregabalin (Taylor et al., 2007, Tassone et al., 2007). Regardless of the dose administered, the half-life of pregabalin is six hours.

1.1.3 Uses of pregabalin

The focus of this section is to highlight the efficacy of pregabalin when used to treat a primary condition as well as the effects that pregabalin has on sleep when treating the primary disorder. Conditions that pregabalin has been approved for include diabetic peripheral neuropathy, postherpetic neuralgia, generalized anxiety disorder (GAD) and as an adjunctive therapy in adults with partial-onset seizures (Tassone et al., 2007).

1.1.3.1 Neuropathic pain

Fifty to eighty percent of patients with chronic pain report sleep disturbances (Affleck et al., 1996). Over 70% of patients claim that pain is the sole reason for their sleep disturbance. (Argoff, 2007, Vinik, 2010) Pain results in an increased sleep latency, increased wakefulness after sleep onset, increased arousal, and reduced slow wave sleep (Chokroverty, 2000, Argoff, 2007). While it may seem intuitive that sleep and pain are related in an unidirectional manner with pain causing sleep impairment due to a physical discomfort, studies have found that the relationship is far more complex as depression and pain duration are both predictors of sleep disturbance (Lavigne et al., 2007). Studies also show that poor sleep the previous night can cause chronic pain sensations to be exacerbated the following day (Lavigne et al., 2007)

Nociceptive pain is a form of pain in which nerves responds to an external noxious stimulus, whereas neuropathic pain is caused by a lesion, dysfunction or damage to nerves within the central nervous system. Depending on the origin within the central nervous system, neuropathic pain can either be a central or peripheral condition. Various conditions can cause

neuropathic pain, with common causes being postherpetic neuralgia and diabetes mellitus and infection with the human immunodeficiency virus. Patients with chronic neuropathic pain are reported to have a higher incidence of depression, insomnia and psychological disturbances when compared to controls (Gormsen et al., 2010).

1.1.3.1.1 Consequences and treatment of neuropathic pain

While the pain experienced in a neuropathic pain condition is unpleasant, it also has an effect on patients' overall quality of life. In a study of 262 patients with painful diabetic peripheral neuropathy and 81 healthy controls, patients with neuropathy had a decreased quality of life: with the severity of the neuropathy correlated to a decrease in quality of life (Vinik et al., 2005). Other studies also showed that neuropathic pain has an impact on sleep (57.1% of patients), enjoyment of life (58.2%), recreational activities (56.1%), general activity (48.0%), mobility (57.0%), normal work (56.6%), and social activity (50.5%) (Galer et al., 2000).

Chronic neuropathic pain is often treated with medication such as opioid analgesics or sedative pain medications, such as tricyclic antidepressants or anticonvulsants or benzodiazepine receptor agonists (Smith and Haythornthwaite, 2004). As these drugs have both sleep inducing and pain reducing effects, drawing conclusions from clinical trials regarding the effects of the treatment on pain and sleep is therefore problematic as all these variables are interrelated (Smith and Haythornthwaite, 2004).

1.1.3.1.2 Postherpetic neuralgia

Postherpetic neuralgia is a condition that affects 10%-15% of people who have a herpes zoster infection (Frampton and Foster, 2005). Postherpetic neuralgia can cause substantial aching, itching, dysesthesia, paresthesia, hyperalgesia, hyperesthesia allodynia and psychological well-being (Frampton and Foster, 2005, Tassone et al., 2007). Over half of patients with postherpetic neuralgia have sleep disturbances and decreased daily activity (Engberg et al., 1995). Acute neuralgia is normally experienced for at least three months after the herpetic rash disappears. After one year, 50% of patients will continue to experience symptoms of postherpetic neuralgia (Tassone et al., 2007).

Postherpetic neuralgia is normally treated with opioids, tramadol, tricyclic antidepressants, gabapentin, capsaicin patches and lidocaine patches (Tassone et al., 2007). However these agents are not able to provide adequate relief with only 58-78% of patients on opioids or tramadol and 33% of patients on antidepressants experience a 50% reduction in pain and treatment is commonly discontinued due to adverse effects of treatments (Tassone et al., 2007). While capsaicin patches do provide a reduction in pain with minimal side effects, capsaicin patches are only 9% more effective then placebo (Backonja et al., 2008). As the current treatments for postherpetic neuralgia are not completely effective, pregabalin has been tested as an alternative treatment for postherpetic neuralgia in animal and clinical trials.

Clinical trials examining the effect that pregabalin has on pain in patients with postherpetic neuralgia highlight the pain reducing effects of pregabalin as the primary study outcome, and these studies also use subjective sleep measures as a secondary outcome (Dworkin et al., 2003, Sabatowski et al., 2004). In a double blind clinical trial,173 patients with postherpetic neuralgia received 300mg-600mg a day, in three divided doses of pregabalin or placebo (Dworkin et al., 2003). Patients were allowed to continue pre-study therapy with acetaminophen, non-steroidal anti-inflammatory drugs, antidepressants, opioids or tramadol. Patients using pregabalin had a decreased pain score after one day of treatment when compared to placebo and the decrease was maintained for the duration of the trial (Dworkin et al., 2003). Secondary outcomes such as total, sensory, and affective pain and sleep interference were improved with pregabalin when compared to placebo (Dworkin et al., 2003). Sleep was improved significantly after one week of using pregabalin and the sleep improvement was sustained until the end of the study when compared to placebo. More patients withdrew from the trial due to adverse events caused by pregabalin rather than placebo (32% vs 5%) (Dworkin et al., 2003). Somnolence was the highest reported adverse events and resulted in 11% of patient withdrawals (Dworkin et al., 2003).

In another double blind, randomised control trial testing the effectiveness of pregabalin on postherpetic neuralgia, somnolence was the second most commonly reported side effect, affecting 14% of the subjects who used pregabalin (Sabatowski et al., 2004). Pregabalin, however, was also noted to improve secondary outcomes, such as quality of life as well as sleep interference (Sabatowski et al., 2004). The authors note that sleep interference and neuropathic pain in patients with postherpetic neuralgia are interrelated and each of these factors can exacerbate the other (Sabatowski et al., 2004). Also noted by the authors is that the

improvement in sleep could be because pregabalin causes a reduction in pain, or because pregabalin causes an improvement in sleep (Sabatowski et al., 2004). While this study was unable to differentiate the cause of sleep improvement, patients in the pregabalin group showed reduction in sleep disturbances during the initial titration period and the sleep improvements were sustained for the duration of the study (Sabatowski et al., 2004).

1.1.3.1.3 Diabetic peripheral neuropathy

Diabetic peripheral neuropathy is a progressive disorder that affects 50% of diabetic sufferers at some point during their condition (Tassone et al., 2007). In addition to the pain, patients with diabetic peripheral neuropathy report a lower quality of sleep than healthy controls and diabetics who do not have peripheral neuropathy (Zelman et al., 2006). The pain in patients with diabetic peripheral neuropathy is treated with tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, anticonvulsants, gabapentin and opioids (Tassone et al., 2007).

Studies that examine the effect that pregabalin has on patients with diabetic peripheral neuropathy utilize pain intensity as the primary outcome measure, with secondary outcome measures varying between trials. One hundred to three hundred milligrams of pregabalin administered three times daily was effective in reducing pain intensity in patients with diabetic peripheral neuropathy (Lesser et al., 2004). Patients also had an improvement in the overall quality of life as detected on the Short Form Medical Outcome Questionnaire from as early as

week one. Other studies have shown similar results. Two hundred and forty six people with diabetic peripheral neuropathy pain received either 150mg or 600mg pregabalin or placebo daily for six weeks in a double blind randomized trial (Richter et al., 2005). Patients on 600mg/day pregabalin showed reductions in pain (visual analogue score 4.2/10 vs placebo 5.2/10) (Richter et al., 2005). Pregabalin was also well tolerated with the main side effects being dizziness and somnolence (Lesser et al., 2004).

In addition to pregabalin's pain relieving properties, it was found that pregabalin improves sleep in patients with diabetic peripheral neuropathy. One hundred milligrams of pregabalin three times daily had pain reducing properties when prescribed to a population of 146 adults with diabetic peripheral neuropathy in a randomized, double blind, placebo controlled clinical trial when compared to the placebo group (Rosenstock et al., 2004). There was an improvement in the McGill pain questionnaires and daily sleep interference score in the pregabalin group when compared to the group receiving placebo (Rosenstock et al., 2004). The mean daily sleep interference score decreased from 4.5 prior to pregabalin administration, to a score of 2.5 one week after administration of pregabalin, a reduction that was maintained for 7 weeks. Placebo scores remained higher than pregabalin scores and there was a significant reduction in sleep interference ($P=0.0001$) at the study end point, when pregabalin was compared to placebo. The two most common side effects experienced by patients on pregabalin were dizziness (36%) and somnolence (20%) (Rosenstock et al., 2004). Other studies have also confirmed the pain reducing and sleep improving properties of pregabalin in patients with diabetic peripheral neuropathy. The side effects, dosages of pregabalin and effects that pregabalin had on sleep and pain in patients with diabetic peripheral neuropathy were similar on the various trials (Frampton and Scott, 2004, Zin et al., 2010).

1.1.3.1.4 Fibromyalgia

Fibromyalgia is a chronic pain disorder in which there is wide spread pain accompanied by a lowered pressure pain threshold (Goldenberg, 2009). In addition to pain, fibromyalgia is normally accompanied by, morning stiffness, affective disorders, chronic headaches, irritable bowel syndrome, irritable bladder, sleep disturbances and fatigue. Sleep disturbances in fibromyalgia patients is characterised by poor subjective sleep quality, lowered sleep duration and disrupted sleep (Goldenberg, 2009). The cause of fibromyalgia is unknown, but is it thought to be a result of biological as well as psychosocial factors. Treatment of fibromyalgia involves both pharmacological and non-pharmacological interventions that are geared to relieve the symptoms of the disorder.

Recent studies show that when pregabalin is prescribed to fibromialgia patients at doses of 300mg-450mg per day, there is reduced pain from as early as week one of treatment (Russell et al., 2009). In addition to pain reduction, pregabalin also improves fatigue levels, overall quality of life and sleep variables (Russell et al., 2009). Other studies in which pregabalin has been used to treat fibromyalgia have shown similar results, with doses of between 150mg-600mg per day effective in reducing pain (Hauser et al., 2009). Side effects reported when using pregabalin as a treatment to fibromyalgia at doses of 150mg of pregabalin were dizziness (23%), somnolence (16%), fatigue (5%) and weight gain (5%) (Hauser et al., 2009).

Pregabalin reduced subjective sleep disturbance and improved subjective sleep quality in fibromyalgia patients when prescribed at doses of 300mg, 450mg or 600mg per day when

compared to placebo (Arnold et al., 2008). The main side effects experienced by patients in this study were dizziness (35.8% in the pregabalin groups and 7.6% in the placebo group) and somnolence (18% in the pregabalin group and 3.8 in the placebo group) (Arnold et al., 2008).

A cross over designed study that used doses of 300-450mg pregabalin per day showed that in addition to reducing pain scores, pregabalin caused beneficial changes to objective sleep when compared to placebo (Roth et al., 2012). Pregabalin use resulted in a significant reduction in wake after sleep onset, and an improvement in total sleep time, sleep efficiency and the percentage of time spent in slow wave sleep when compared to placebo (Roth et al., 2012). Sixty five percent of participants suffered from adverse events while using pregabalin as opposed to thirty percent on placebo (Roth et al., 2012). The most common side effect in the pregabalin phase was dizziness (28.6%), followed by somnolence (4.5%) (Roth et al., 2012).

1.1.3.2 Epilepsy

Epilepsy is a neurological condition in which there are recurrent unprovoked seizures. There are about 90 million people worldwide who suffer from epilepsy, most of whom are in the developing world (Tassone et al., 2007). Treatment of epilepsy normally involves the administration on anticonvulsants administered either singularly or in a combination. In about 30% of cases epileptic attacks remain uncontrolled with medication (Tassone et al., 2007).

Epileptic patients have a twofold higher risk of suffering from a sleep disorder than healthy controls. Epileptics with sleep disorders also have lower quality of life scores than both healthy controls and epileptics without sleep disorders (de Weerd et al., 2004). Epileptics have higher levels of chronic sleep deficit and greater number of nocturnal awakenings when compared to normal controls. Impaired sleep in epileptics is not surprising as epileptic seizures during sleep cause a reduction in REM, stages 2 and 4 of sleep and an increase in REM latency and daytime somnolence (Placidi et al., 2000). Sleep efficiency is also negatively impacted when seizures occur during sleep (Placidi et al., 2000). Seizures can negatively impact sleep even if they only occur during the previous day, with patients showing a significant reduction in REM sleep but no changes occurred to sleep efficiency or drowsiness (Placidi et al., 2000). Disruptions to sleep can be reduced if seizure frequency is reduced (Bazil, 2003). Clinical studies indicated that pregabalin was able to reduce the occurrence of seizures when used as an adjunctive treatment for epilepsy with improvement rates between 17%-39.5% (Beydoun et al., 2005, French et al., 2003, Arroyo et al., 2004). Most studies examining the effects of pregabalin in patients with partial epilepsy have shown that doses of 150mg-600mg three times daily are effective in reducing seizure occurrences, with treatment being more effective at higher doses (Tassone et al., 2007). These studies indicate that pregabalin was well tolerated in epileptic patients, with the main side effects being dizziness and somnolence, weight gain and ataxia (French et al., 2003, Arroyo et al., 2004). Because pregabalin was noted to have sleep enhancing properties in non-epileptic patients, one study specifically investigated the effects that pregabalin has on sleep in epileptic patients (de Haas et al., 2007).

Seventeen patients with partial epilepsy and sleep disturbances (the group comprised of patients suffering from insomnia, periodic limb movements, excessive daytime sleepiness and

psychotic sleep disturbance according to the Sleep Diagnosis List) were randomly provided with 300mg twice daily doses of pregabalin or a placebo for four weeks (de Haas et al., 2007). Subjective sleep was evaluated using the Medical Outcomes Sleep Scale and The Groningen Sleep. The Medical Outcomes Sleep Scale consists of 12 questions on sleep during the past month with answers rated from one to six, with a lower score indicating worse sleep (de Haas et al., 2007). The Groningen Sleep Questionnaire evaluates subjective sleep from the previous night by asking 14 yes/no questions which are then scored according to a fixed set of rules, with lower scores indicating better sleep. The group of patients using pregabalin showed an improvement in the Groningen Sleep Questionnaire (pregabalin 11.6 vs 6.6 placebo; $P<0.03$), the Medical Outcomes Sleep Scale sections on sleep disturbance (pregabalin 44 vs placebo 20; $P<0.03$) and sleep quantity (pregabalin 7.6 vs placebo 5.4; $P<0.01$) scores when compared to placebo (de Haas et al., 2007). In addition to the subjective improvements pregabalin had on sleep, objective sleep was evaluated by polysomnographic recordings at home on baseline nights and after four weeks (de Haas et al., 2007). Subjects on pregabalin showed a decrease in the number of awakenings when compared to placebo. In addition, these subjects who used pregabalin also showed a reduction in the time spent awake after sleep onset when compared to placebo, implying that pregabalin may have sleep consolidating properties in epileptic patients with sleep disturbances (de Haas et al., 2007). However, this study failed to examine the effect of pregabalin on epileptic variables and cannot preclude that the sleep enhancing properties of pregabalin may be due to a direct effect that pregabalin has on epilepsy and sleep improvements might be a secondary effect.

1.1.3.3 Anxiety and pregabalin

Generalized anxiety disorder occurs when exaggerated worry and tension is experienced in the absence of provoking factors and the symptoms of generalized anxiety disorder is present for at least 6 months (Pounds, 1992). Generalized anxiety disorder often causes physical symptoms such as fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness and hot flashes (Pounds, 1992). Patients have difficulty relaxing, startle easily, have difficulty concentrating and these patients have trouble falling or staying asleep (Kessler, 2000).

Polysomnographic studies on patients with generalized anxiety disorder revealed that these patients took longer to fall asleep, had a smaller percentage of time spent in slow-wave sleep and more frequent transitions into stages one and two when compared to controls (Fuller et al., 1997). Generalized anxiety disorder patients also experienced a greater percentage of time in stage one and two sleep and had a lower rapid eye movement (REM) density relative to low-anxiety subjects (Fuller et al., 1997). In addition to objective changes, patients with generalized anxiety disorder also report lower sleep quality than controls as well as difficulty sleeping and difficulty remaining asleep. Polysomnographic changes in objective sleep combined with negative subjective sleep parameters in patients with generalized anxiety disorder are severe enough to produce a significant amount of sleep disturbance (Belanger et al., 2004, Saletu et al., 1997).

Pregabalin has been used to treat generalized anxiety disorder. Studies examining the effects that doses of 150-600mg pregabalin taken two or more times daily, in patients with generalised

and social anxiety disorder, showed that pregabalin reduced Hamilton anxiety scores when compared to placebo (Rickels et al., 2005, Pande et al., 2004, Pande et al., 2003, Feltner et al., 2003, Pohl et al., 2005). The main side effects of pregabalin use in these studies were dizziness (affecting 30% of subjects using pregabalin) and somnolence (affecting 29% of subjects using pregabalin) with the dropout rates of subjects on pregabalin being similar to that of placebo (11% pregabalin group vs 9% placebo) (Tassone et al., 2007). Patients with an anxiety disorder who used 300-600mg pregabalin daily had an improvement in the Medical Outcomes Sleep Scale and a reduction in anxiety when compared to patients who used placebo (Herman et al., 2009).

1.1.3.4 Normal sleep

As pregabalin was observed to have sleep enhancing effects on patients with neuropathic pain, rats were given pregabalin to observe if pregabalin had any effect on sleep. Ninety-eight rats were given doses of 3-100mg/kg of pregabalin either before light or dark onset. Rats given pregabalin before the dark phase and rates given pregabalin before the phase showed similar results: pregabalin caused an increase in duration of non-rapid eye movement (NREM) sleep and a decrease in REM sleep (Kubota et al., 2001). The authors indicated that pregabalin's effects were similar to that of triazolam, but pregabalin better mimicked sleep after sleep deprivation, implying that pregabalin has sleep consolidating properties (Kubota et al., 2001). Despite evidence that pregabalin may have an impact on sleep, no study has examined the effect of pregabalin on patients with a sleep disorder. However one study has examined the impact that pregabalin has on normal sleepers. Hindmarch *et al* (2005) tested the effect that

150mg pregabalin three times daily had on three nights of sleep in normal human subjects. Their results showed that after one night subjects had a significant increase in slow wave sleep (pregabalin 127.76 min vs placebo 77.94 min), total sleep time (pregabalin 465.78 min vs placebo 440.64 min), a reduction in sleep onset latency (pregabalin 9.24 min vs placebo13.63 min) and the number of one minute awakenings (Hindmarch et al., 2005), and all of the indicated changes were sustained for three nights.

Taken together the studies examining the effect of pregabalin on various conditions, rats and normal subjects imply that pregabalin may have the ability to improve sleep as a primary effect. An internet search revealed that pregabalin is being prescribed as an off label treatment for insomnia (ASENT, n.d., Paxilprogress, 2005) even though there is no data showing that pregabalin has an independent sleep enhancing effect. When pregabalin is prescribed as a sleep aid there is no fixed doses of pregabalin being used; doctors prescribe a dose of 15mg (by dividing up 50mg tablets) before bed time and increase the dose weekly until subjects experience better sleep. In order to show the direct effect that pregabalin has on sleep, it is necessary to test pregabalin in a group of individuals where poor sleep is the primary complaint.

1.1.4 Insomnia

Insomnia is defined as the difficulty sleeping or the difficulty remaining asleep. Regardless of the criteria used, most studies agree that the prevalence of insomnia in the general population is about 33-40% (Edinger et al., 2004, Breslau et al., 1996, Kim et al., 2000, Ohayon, 1996, Ohayon, 2002, Ohayon and Caulet, 1996, Roth and Roehrs, 2003, Ohayon and Shapiro, 2002).

Differences in the prevalence of insomnia arise depending on the definition of insomnia that is used. For example according to studies that have used the DSM-IV criteria of insomnia 10-20% of the adult population suffers from chronic insomnia with 25% of them suffering from primary insomnia (American Psychiatric Association, 2004). Fifty percent of responders to the National Sleep Foundations sleep poll in the United Stated had at least one symptom of insomnia present for at least a year (Budur et al., 2007). These symptoms included having difficulty falling asleep, remaining asleep or not having a refreshing sleep.

Ohayon reviewed epidemiological studies of insomnia and divided the studies into three groups: studies that used no restrictive criteria, studies that used the frequency that poor sleep or symptoms associated with poor sleep, or studies that examined the severity of poor sleep and insomnia symptoms (Ohayon, 2002). Studies with no restrictive criteria normally report on the presence of insomnia symptoms regardless of frequency or severity of the symptoms and indicated prevalence ranges of symptoms from 25% in males and 36% in females (Ohayon, 2002).

Frequency studies usually define insomnia by a frequency of symptoms occurring for more than three times a week to qualify as insomnia and showed that 17%-23% of the population have insomnia (Ohayon, 2002).

Severity studies examine the impact that insomnia symptoms have on patient quality of life. Eighteen to twenty percent of people from Sweden, the United Kingdom, the United States of

America, Belgium and Germany experience insomnia symptoms with daytime consequences (Hoffmann, 1999, Ford and Kamerow, 1989, Ohayon, 1997, Ohayon, 2002, Breslau et al., 1996). Ohayon showed that dissatisfaction with sleep quality and quantity affects 15% of the population in Canada, United Kingdom, France and Germany (Ohayon, 2002).

Variability in the prevalence statistics for insomnia exists because of the differences in the definition used as well as external factors like the political, social or economic period the study was conducted in. Even with the variability between studies, it is agreed that chronic primary insomnia affects about 10% of the population although epidemiological studies have also shown that certain risk factors increase the likelihood of individuals to develop insomnia (Buysse et al., 2006, Edinger et al., 2004, Budur et al., 2007, Drake et al., 2003).

1.1.4.1 Risk factors for insomnia

Age, gender, income, education, pain or psychiatric disease have been highlighted as the leading risk factors for the development of insomnia (Ohayon, 2007, Chevalier et al., 1999, Ohayon, 1996, Drake et al., 2003, Roth and Roehrs, 2003). As age increases, females are at a higher risk of developing insomnia than their male counterparts, with the female male ratio also increasing with age (Voderholzer et al., 2003).

Even though females are one and a half times more likely than males to suffer from insomnia, gender differences in the prevalence of insomnia exist between men and women only after the

onset of puberty (Voderholzer et al., 2003). Divorced women, separated couples, widows, housewives, retired males and males who have received less education are all at a higher risk of developing insomnia (Ohayon, 2002). Increased levels of insomnia in the elderly have been explained by high rates of prescription drug use, somatic disorders, neurological decline, decreased exposure to sunlight, a reduction in daytime activity and an altered biological sleep wake pattern (Ohayon, 2002).

Psychological conditions (mainly anxiety and depression) are the strongest correlates associated with insomnia followed by conditions that cause pain (Riedel and Lichstein, 2000). Almost 80% of people suffering with major depression and 90% of people with anxiety disorders have insomnia. Depressed patients who concurrently suffer with insomnia are more likely to commit suicide and are also more likely to suffer from depressive relapses (Roth et al., 2007). Forty percent of subjects with depression experience insomnia prior to a depression episode (Dombrovski et al., 2008). Whether insomnia is a result of the psychological condition or the insomnia causes the psychological impairment is still unknown.

Other factors that affect insomnia include education level and income. Some studies have shown that lower income states and education levels are correlated with a higher incidence of insomnia; however other studies have shown no correlation (Breslau et al., 1996, Newman et al., 1997, Ancoli-Israel and Roth, 1999, Henderson et al., 1995, Kim et al., 2000). Ohayon has suggested that an index that takes age, household income and household size into consideration may cause the relationship between insomnia, education and income state to become clearer

(Ohayon, 2002). Regardless of the risk factors involved, most insomniacs experience some negative consequence the next day.

1.1.4.2 Daytime repercussions of insomnia

Insomnia patients report emotional, social and physical impairments as well as reduced subjective reasoning, memory, concentration and attention skills (Riedel and Lichstein, 2001). Insomniacs also complain about daytime fatigue when compared to good sleepers (Guilleminault et al., 2006, Åkerstedt et al., 2004, Lichstein et al., 1997).

Studies examining daytime fatigue normally use the Fatigue Severity Scale to compare subjective fatigue levels of subjects (Appendix 1). Sleepiness and fatigue are often synonymous concepts; however, it is possible to be fatigued but not sleepy. People with insomnia often experience daytime fatigue but not daytime sleepiness (Riedel and Lichstein, 2000). While studies do show that people with chronic primary insomnia have higher scores on the Fatigue Severity Scale when compared to controls, these results are not always statistically significant (Means et al., 2000, Bonnet and Arand, 1995, Seidel et al., 1984, Lichstein et al., 1997). Objective measures between insomniacs and controls have failed to find differences in psychomotor, cognitive and memory tasks however, insomniacs under rated self-performance and overestimate the degree of their impairment (Riedel and Lichstein, 2000).

Even though insomniacs have no objective signs of daytime impairment, the effects of insomnia permeate other aspects of patient's life. The areas which insomnia has an effect on include higher work related errors, higher levels of absenteeism, lower productivity, lower work satisfaction, lower work performance and higher levels of accidents when compared to controls (Leger et al., 2006, Sivertsen et al., 2009, Riedel and Lichstein, 2000, Leger et al., 2002).

The reason for higher absenteeism and heath care visits, lower perceived health and job productivity among insomniacs is not clear. It is possible that lower subjective perceptions of quality of life among insomniacs maybe due to negative perceptions about their health, leading to higher levels of absenteeism. Because insomnia affects a large proportion of the population and because it has a serious effect on the daytime functioning of individuals, effective treatment options are needed to adequately manage the impact of insomnia.

1.1.4.3 Treatment of insomnia

Two main approaches for treating insomnia are currently used: cognitive and pharmacological options. Proponents of each treatment option are able to cite data proving their favored treatment option is superior to the other. It is thus useful to assess the various parameters examined in insomnia studies and whether these parameters are useful as measures of insomnia treatment outcomes.

1.1.4.3.1 What should you measure?

The effectiveness of insomnia treatment needs to be assessed as a combination of subjective and objective measures that affect sleep, mood and daytime functioning. In order to standardize assessment techniques, a panel of 25 experts in insomnia research compiled a standard list of questionnaires and screening tools (Buysse et al., 2006).

If an insomnia treatment caused changes to objective sleep variables without changing subjective sleep, patients would not use the treatment option, as there is no change in quality of life. Alternatively, if treatments change perceived sleep without changing objective sleep variables, the treatment would be effective in improving patient's perceived quality of life and would likely be used by patients. The problem with relying purely on subjective scales is the large discrepancy that exists between insomniac's perceived impairment and their actual impairment. All recommended tools in the paper have been used in previous trials and consist of validated techniques. These recommendations comprise of screening procedures of insomnia patients, qualitative measures, questionnaires used to monitor daytime fatigue, mood, depression, quality of life and performance

In order to measure objective sleep variables researchers suggest that studies use a combination of polysomnography and actigraphy (activity monitors) (Buysse et al., 2006). Polysomnography is regarded as the gold standard in sleep research as it allows for an accurate measurement of the time spent in all stages of sleep, time taken to fall asleep (sleep onset

latency), total sleep time and time awake. The disadvantage of polysomnography is that it is extremely expensive to perform and it can disrupt the normal routine that of subjects before bedtime and the requirement of trained personnel.

The subjective parameters usually measured in insomnia studies include fatigue, depression, overall sleep quality and insomnia symptoms, using questionnaires that have been validated in insomniac populations.

The Fatigue Severity Scale (Appendix 1) is a validated and recommended test to use in sleep impaired individuals (Bastien et al., 2001) which consists of answering a short questionnaire that requires the subject to rate his or her own level of fatigue. As both depression and fatigue share some similar symptoms, the Fatigue Severity Scale is designed to differentiate fatigue from clinical depression.

Sleep deprived individuals often display depression and anxiety symptoms (Buysse et al., 2006). The Becks Depression Inventory (Appendix 2) was developed to provide a quantative assessment of the intensity of depression. It is designed to reflect the depth of depression and it can monitor changes over time. Extreme mood fluctuations will most likely have an effect on sleep.

The Pittsburgh Sleep Quality Index (Appendix 3) is a useful tool in evaluating subjective aspects of sleep and can be used for weekly intervals (Buysse et al., 1989, Buysse et al., 2006). The Pittsburgh Sleep Quality Index was developed to measure sleep quality and to discriminate between good and poor sleepers. Sleep involves several components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction; each of which is covered by the Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index has been shown to be effective in insomnia control studies and changes that occur during an intervention (Buysse et al., 1989).

The Insomnia Severity Index (Appendix 4) is a brief self-report questionnaire used to measure the patient's perception of insomnia (Bastien et al., 2001). The questionnaire comprises of seven items that include the severity of sleep-onset, sleep maintenance difficulties, the satisfaction with current sleep patterns, the impact insomnia has on day time functioning, notice ability of impairment attributed to the sleep problem and the degree of distress caused by the sleep problem.

The advantage of questionnaires is that they are cheap, quick and easy to use. Questionnaires however, rely heavily on patient’s honesty, integrity and patients may not always complete it accurately. Most studies utilize a combination of objective and subjective measures of sleep at different time points.

1.1.4.5 Treatments for insomnia

All insomnia treatments seek to improve the duration and quality of sleep while reducing the awakenings during the night. Insomnia is treated either by changing the patients behavior (cognitive behavioral therapy), or by prescribing hypnotics. Both treatment options are expensive and treatment success is not guaranteed in all patients. Cognitive behavioral therapy for insomnia is less invasive as it involves altering perceptions and behavior associated with sleep (Smith and Neubauer, 2003). However, not all patients respond well to cognitive behavioral therapy for insomnia and frequent visits to a health care provider are needed to change behavior (Smith and Neubauer, 2003). The advantage of a hypnotic approach is that drugs can be carefully selected to address the primary sleep complaint, such as low total sleep time or increased awakenings (Wilson and Nutt, 2004).

While much progress has been made with prescription hypnotics, hypnotics still fail to improve all criteria associated with subjective and objective sleep that are affected by insomnia. Because of this, there is a large amount of interest in new drugs that can be used as a treatment in insomnia as the current insomnia treatments have many negative side effects, can be addictive, are unable to adequately improve sleep architecture and there is a lack of data on the safety of long-term hypnotic use. Medications that are found to have sleep enhancing properties with negligible side effects have been proposed as future treatments for insomnia (Winkelman, 2005).

2. AIM

Pregabalin is effective in the treatment of chronic neuropathic pain, epilepsy and generalized anxiety disorder. These conditions affect sleep quality and pregabalin has the ability to improve the primary condition. Whether the sleep enhancing effects seen in these studies are a direct result of pregabalin on sleep, or the effect of improving the primary condition is not known.

However, experiments in normal subjects and rats have shown an improvement in objective sleep variables when administering large doses of pregabalin multiple times a day, implying that pregabalin may have sleep consolidating properties. In order to test the effectiveness of pregabalin in enhancing and consolidating sleep, pregabalin needs to be tested in a group of patients that primarily suffer from poor sleep and who do not suffer from epilepsy, generalized anxiety disorder, or neuropathic pain.

The first aim of my study was to examine whether any of the sleep enhancing effects of pregabalin are a direct result of pregabalin on sleep mechanisms as opposed to pregabalin providing relief to conditions that affect sleep. The group of patients in which pregabalin's sleep enhancing effect were studied are patients with chronic primary insomnia. The advantage of using primary insomniacs is that sleep patterns and psychological characteristics in primary insomniacs are similar to that of patients with pain related insomnia (Tang et al., 2012). Female chronic primary insomniacs were used, as chronic primary insomnia is more common in this group.

As pregabalin is already being prescribed as an off label hypnotic used in the treatment for insomnia, the second aim of my study was to examine if the sleep enhancing effects of pregabalin can be harnessed to improve sleep in patients with chronic primary insomnia. If pregabalin did have hypnotic effects, insomniac subjects would have been unwilling to use the drug at high does or multiple times a day, therefore pregabalin was prescribed to patients once daily, prior to bed time.

Pregabalin has been found to affect subjective sleep within a one week period, and the effect on subjective sleep has been maintained for the study period, hence my study examined the effects that pregabalin had after being consumed once daily for eight consecutive nights.

Unlike other studies, the patients in this study were allowed to pick their own wake and sleep times, because allowing subjects to choose their own sleep and wake times is similar to how subjects will use the medication outside the laboratory environment. Similarly, if subjects were unable to sleep they were allowed to get out of bed and do what they would normally have done in their home environment.

A pilot study was done examining the best once daily doses that are tolerated by healthy controls. The insomniac patients were given the highest dose that has with the least side effects.

Objective 1: Does pregabalin have a primary sleep enhancing effect and is the effect sustained after one week of use?

Objective 2: Can pregabalin be used as an off label treatment for insomnia?

3. MATERIALS AND METHODS

3.1 Pregabalin dose

As there is limited published literature available on the side effects of pregabalin when used once a day, the possible side effects experienced when taking a once off dose of pregabalin at 150mg, 75mg, 50mg and 25mg was tested in five normal subjects before bedtime, with a week washout period between each dose .

Subjects were healthy with no reported sleep conditions or other diagnosed medical conditions. The subjects in the pilot study were between the ages of 21-30 years, and four were female. Subjects were asked to take a dose of pregabalin one hour before bedtime. They were asked to report any side effects that they had experienced the next day. After a week wash out period, subjects were given a new dose and the process was repeated.

When used once off daily, taken in the evenings 150mg of pregabalin caused dizziness, nausea, moodiness, irritability, vertigo, extreme daytime sleepiness, muscle soreness and muscle weakness in four out of five subjects on awakening. Seventy-five milligrams of pregabalin caused sleepiness, irritability and vertigo in three subjects. The five subjects did not report any adverse side effects on awakening after using the 50mg and 25mg dose of pregabalin.

Therefore, a dose of 50mg pregabalin was decided upon as this was the highest dose that, when taken the previous night, was not followed by distressing symptoms in the five pilot study subjects. Two 25mg pregabalin capsules were placed into an opaque gelatine capsule. The capsules were tightly packed and any spaces with sugar, ensuring that no rattling noise could be heard. An identical gelatin capsule tightly filled with white sugar (Huletts, South Africa) was used as the placebo.

For the final study a staff member of the sleep laboratory was responsible for randomising participants, storing the medication and for distributing the gelatine capsules. The staff member unblinded the treatment groups to the investigator only once the study was completed and the results had been analysed.

3.2 Subject selection

Eligible non-pregnant female subjects between the ages of 18-55, with chronic primary insomnia were recruited from the general population by advertising in the local Gauteng newspapers, via the Johannesburg Insomnia Facebook group and via electronic mailing lists. Subjects were excluded from this study if they were on any chronic medications, were depressed or experiencing high levels of anxiety, were experiencing any form of pain, and epilepsy or had any other sleep disorders. Chronic insomnia was defined as difficulty falling asleep or difficulty remaining asleep at least three times a week for a period of more than three months that was not caused by any existing medical condition, psychological condition or sleep disorder (Buysse et al., 2006). Insomniacs were categorized as having at least 1 sleep complaint

(non refreshing sleep, early awakening, and difficulties initiating or maintaining sleep) at least three times a week for at least three months and the insomnia had consequences on daytime functioning. Six of the subjects were previously diagnosed with primary insomnia by their general practitioner and the diagnosis of primary insomnia in the remaining two subjects was confirmed by a sleep specialist.

Over 50 people responded to the advertisements, with only 12 subjects fulfilling the study criteria of insomnia (Figure 3.1). Four subjects dropped out of the study before the treatment nights; three due to transport problems and one who was unhappy with the study procedures. Besides having insomnia subjects reported no other health related problems, with no subjects taking any medication other than sleep aids.

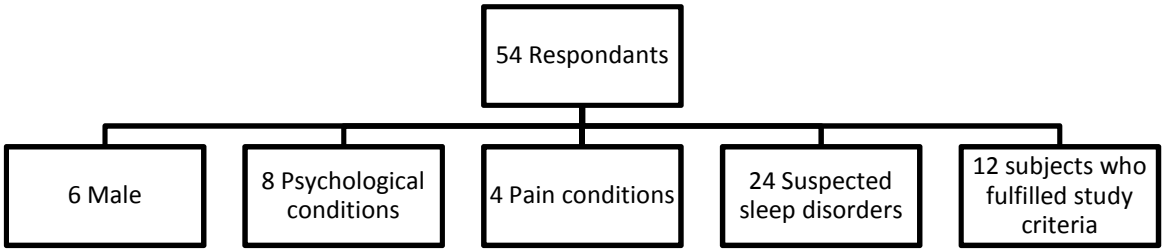

Figure 3.1 Pictorial representation of the subjects who were excluded from this study

3.2.1 Screening

Sleep diaries were used to evaluate sleep patterns, the frequency of daytime naps as well as the presence of circadian rhythm disorders. Sleep diaries were collected from potential subjects for at least seven days before baseline recordings. A detailed sleep and medical history was collected (Stood, 2001) (Appendix 5).The sleep history questionnaire was used to exclude subjects who did not fulfill the inclusion criteria. One subject who was suspected of suffering from a sleep disorder underwent an additional interview with a sleep specialist to confirm the diagnosis of chronic primary insomnia. Subjects who were taking medications to assist with sleep were asked to stop all sleeping aids for at least one week before the adaptation night recording.

3.3 Study design

This study was designed as a double blind, randomized, crossover, placebo controlled trial. Subjects spent six nights in the sleep laboratory; an adaptation night was performed before any recording nights, followed by five polysomnography recordings (Figure 3.2). In addition to the 'mock' polysomnography performed on the adaptation night, subjects also had their body mass index (BMI) assessed, as a high BMI is a possible indicator for sleep apnoea. Adaptation and baseline recordings were performed at least three days apart with all recording nights performed during the luteal phase of the menstrual cycle. Hormonal changes can affect sleep during different phases of the menstrual cycle. In order to remove possible changes to sleep

that could have been caused by menstrual events, the subjects were asked about their menstrual cycle before each visit and if they felt that they were too close to the end of the luteal phase, sleep recordings were delayed until the next luteal phase occurred. If sleep recordings were delayed, the adaptation night was repeated prior to continuing the study sleep recordings. The five polysomnography recordings were performed at baseline, after consuming pregabalin on the first night , after the eight dose of pregabalin administration, after consuming placebo on the first night and after the eight dose of placebo. Subjects were randomised to receive either placebo or pregabalin first with a minimum of a two week "wash out" between treatments. Both pregabalin and placebo were taken for 8 consecutive nights an hour and a half prior to bed time. Subjects were asked to fill out a battery of questionnaires (Section 3.5) on recording nights prior to drug administration. Our study is designed differently from hypnotic studies, as we allowed subjects to go to bed and wake at their own pre chosen times. The subjects and the researcher were kept blind as to the assigned treatment group until all sleep records had been scored.

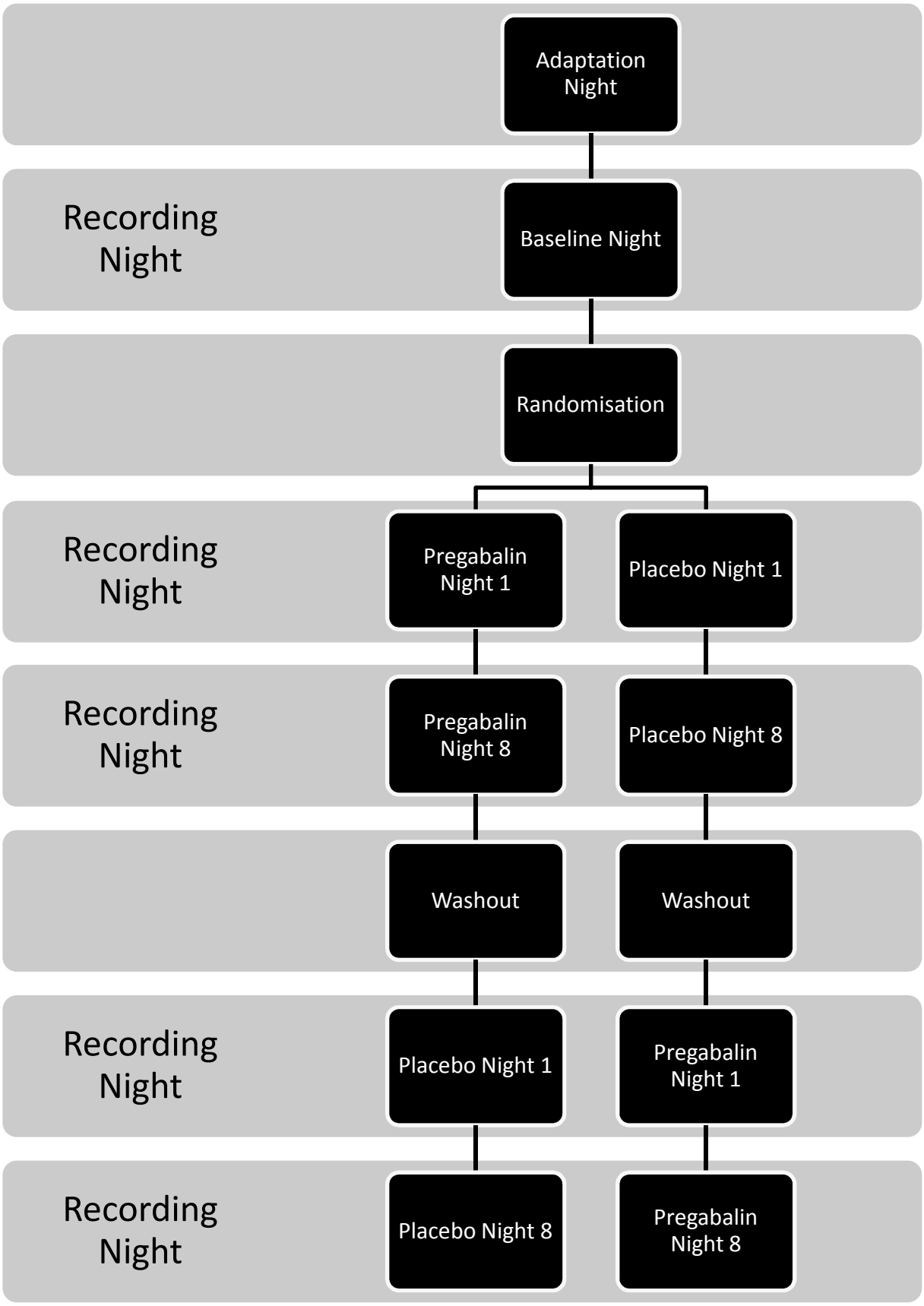

Figure 3.2.A pictorial representation of the study progression.

Ethical clearance was obtained from the University of the Witwatersrand's Human Research Ethics Committee (M070531). No funding was provided by Pfizer Pharmaceuticals or any other pharmaceutical company, nor did any pharmaceutical company have a role in the study design.

3.4 Evening Procedures

Subjects were asked to complete the following questionnaires on recording nights before bedtime:

- Fatigue Severity Scale (Appendix 1, (Krupp et al., 1989, Crofford et al., 2005))
- Becks Depression Inventory. (Appendix 2, (Beck et al., 1961))
- Pittsburgh Sleep Quality Index (Appendix 3, (Buysse et al., 1989))
- Insomnia Severity Index.(Appendix 4, (Bastien et al., 2001))

Sleep Quality: subjects were asked to rate their previous night's sleep within 10 minutes of getting out of bed after nights 8 of treatments using two 100 millimeter visual analogue scales. The first visual analogue scale was anchored at exhausted (0) and refreshed (5). The second was anchored at very restless (0) and very sound (5) (Appendix 6).

Side effects list: On a daily basis, subjects were also asked to list any side effects they experienced during the treatment phases.

3.5 Recording night procedures

Standard polysomnography was performed by a Master's of Science student in the Wits Dial a Bed Sleep Laboratory, on a computerized EEG system (Cadwell Easy EEG, version 2.0.2, Cadwell Laboratories Inc, Kennewick WA). Electrode sites were cleaned with an electrode gel (Nu Prep Gel, D.O. Weaver and Company, USA) and a skin toner (Johnson and Johnson, South Africa). Electrodes were filled with 10-20 conductive paste (D.O Weaver and Company, USA) and held in place with a hypo allergic tape (Micropore Medical Tape, 3M, South Africa). Pairs of electrodes were placed according to the 10-20 method over the submentalis muscle to record muscle activity (EMG) and next to each eye to record eye movements (EOG: infraorbital and supraorbital). Eye electrodes were referenced ROC/A1, LOC/A2. Two ground electrodes were placed on the forehead, two electrodes on the scalp (EEG C3, C4), and reference electrodes on the contra lateral mastoid (A1, A2) (Rechtschaffen and Kales, 1968). EEG electrodes were referenced as C3/A2 and C4/A1. Impedances of electrodes were checked before recording and were below 15KΩ.

On each recording night subjects arrived at the sleep laboratory at least one and half-hours before their normal bedtime. Subjects took either the 50mg pregabalin or placebo capsule every night for eight consecutive nights, one and a half hours before the subject's own selected bedtime. Subjects were prepared for polysomnography and retired to bed at their preselected bedtime (lights off) and allowed to awaken at their own selected time (lights on). The treatments were ingested an hour before subjects preselected bedtime.

3.6 Sleep scoring

The sleep lab administrator removed identifying characteristics from the sleep recordings to make them anonymous. Sleep records were divided into thirty-second epochs and scored according to standard criteria by me who was blind to the identity and treatment of the subjects (Rechtschaffen and Kales, 1968). Time spent in each sleep stage was calculated as a percentage of the total sleep time for each recording. Wake after sleep onset was calculated as the time spent awake after sleep onset latency, inclusive of movement periods greater than 15 seconds.

Time in bed was taken as the time (min) from lights out until lights on (min). Sleep onset latency was defined as the time from lights out until the first epoch of stage one sleep. Total sleep time was regarded as the time spent asleep from sleep onset latency to lights on. REM onset latency was defined as the time to REM sleep from sleep onset. Sleep efficiency was defined as the time spent in bed asleep divided by the time spent in bed expressed as percentage of the total time in bed.

3.7 Statistical analysis

Data were analysed using a commercial statistical package (GraphPad Instat Software Inc., version 3, 1997, USA). A two-tailed probability of $P<0.05$ was considered to be statistically significant.

The effect of placebo and pregabalin on the data obtained from polysomnography and questionnaires were compared. Variances within completed data sets were analysed with a repeated measures analysis of variance (RM ANOVA) with a Bonferroni *post hoc* test to analyse parametric data. Where data was missing, the analysis was modified accordingly.

For variables where there was no statistical significance between pregabalin and placebo, data from the pregabalin and placebo nights were combined and compared to baseline using a paired t test.

A two way ANOVA was used to evaluate the effects of time, treatment and the interaction of time and treatment on sleep onset latency, slow wave sleep, total sleep time, total time awake, wake after sleep onset or sleep changes per hour for the pergabalin nights verse placebo.

Correlations between the objective and subjective data were analysed using a Spearmans rank test.

Data from the pregabalin night eight was compared to baseline using a paired t test. The data from the t test was used in the equation $n_2= (t_2/t_1)^2x(n_1)$, where n_2 is the new sample size needed to show significance, t_1 is the current t value and t_2 is the t value from the t table (Freedman et al., 1998). This formula provides the sample size necessary to detect whether there is really significance.

4. RESULTS

The subjects experienced insomnia for a minimum of six months (range: 6 months-26 years) with the severity of the insomnia being stable in the month before starting the study. None of the subjects kept the same sleep-wake cycle over weekdays and weekends. Sleep over the weekend was more erratic and weekend sleep did not result in improved subjective sleep. While all subjects reported having difficulty with sleeping after awakening, only two subjects left their bed if they could not sleep.

Subjects had a median age of 36 years as well as a median BMI of 25 (Table 4.1). While subjects did consume caffeinated beverages, the use of these beverages was not excessive. Only one subject smoked and two subjects exercised regularly. All subjects had no other conditions besides the insomnia, and subjects were not using any medication (Table 4.2). Subjects did not report any head injuries or complications with surgery or any nasal congestion. Two subjects were previously prescribed medication to assist with sleep (Table 4.3). While subjects only reported insomnia as a problem, only two subjects reported their health as being in excellent condition (Table 4.4).

Most subjects indicated that insomnia had some impact on their quality of life. Insomnia was reported to interfere with relationships (3 subjects), household chores (2 subjects) and work performance (5 subjects) (Table 4.5). None of the subjects reported having suicidal thoughts, or being treated with server stress, depression or anxiety. All subjects reported that they did not nap during the day (Table 4.5). Daytime sleepiness was reported as occurring often (n=2) and

occasionally (n=4) and most subjects (n=5) reported feeling energetic and alert only occasionally. Daytime fatigue was a common symptom reported by all subjects (Table 4.6).

Subjects also reported that their sleep was of either moderately poor quality (n=6) or extremely poor quality (n=2) (Table 4.7). Six subjects reported being low on energy, seven subjects reported feeling drowsy, and two subjects felt confused on awakening (Table 4.7). Subjects did not display any symptoms of restless legs, night terrors or narcolepsy. Subjects also reported that the severity of the sleep problem was stable (Table 4.8). No subjects were experiencing any form of pain, narcolepsy symptoms, or symptoms of restless legs. One subject experienced gasping and shortness of breath occasionally and one subject snored (Table 4.9). Five of the subjects consistently experienced tossing and turning at night (Table 4.9). The Becks Depression Inventory showed that subjects were not suffering from depression as the data was within the normal range (Table 4.10, Table 4.11). The median score of the Fatigue Severity Scale showed that subjects were suffering from mild fatigue (Table 4.10, Table 4.11), while the Insomnia Severity Scale showed that the subjects were suffering from insomnia of moderate severity (Table 4.11). The Pittsburg Sleep Quality Index confirmed that the subjects were suffering from poor sleep (Table 4.10). The subjects also experienced poor sleep as indicated by the scores on the Pittsburg Sleep Quality Index (Table 4.10). The median perceived time to fall asleep was 27 minutes, with subjects getting up an average of six times a night (Table 4.10).

Table 4.1 The demographics of the subjects.

Variable	Median
Age (years)	36 (CI 23-47)
Height (m)	1.62 (CI 1.45-1.69)
Weight (kg)	71.2 (CI=48,96)
BMI ($kg.m^{-2}$)	25 (CI=19,30)

Table 4.2 Current lifestyle of the subjects

Variable	Amount	No	Yes
Do you drink tea, coffee or soda?		1	7
How much do you drink per day?	2 cups per day		
Do you smoke?		7	1
How much do you smoke per day?	less than half a pack		
Do you exercise regularly?		5	2
Are you taking any herbal products		7	1

Table 4.3 Current health of subjects

Variable	No	Yes
Are you on any medication?	8	0
Current illness	8	0
Problems with nasal congestion or discharge	8	0
Do you use decongestants	8	0
Have you ever had a head injury	8	0
Complications with surgery or anaesthesia	8	0
Previously prescribed medication to assist sleep	6	2

Table 4.4 Perceived state of health of the subjects

Perceived health	Number of Subjects
Excellent	2
Good	3
Moderately good	2
Fair	1

Table 4.5 Daytime functioning of subjects

Variable	Yes	No
Does you sleep problem interfere with your relationships	3	5
Does you sleep problem interfere with your household chores	2	5
Does you sleep problem interfere with your job performance	5	3
Have you ever had a car accident or near miss because of falling asleep while driving?	0	8
Do you take naps during the day?	0	8
Has your memory been getting worse lately?	0	7
Have you had difficulty concentrating?	0	7
Have you been feeling more irritable?	1	7
Have you been treated for depression, anxiety, or severe stress?	0	8
Have you thought of suicide lately?	0	8

Table 4.6 Perceived energy and fatigue of subjects

Variable	Never	Infrequently	Occasionally	Often	Always
Do you feel fatigue in the daytime even when not sleepy?			5	2	1
Do you feel sleepy in the daytime?	1		4	2	
How often do you feel alert and energetic for an entire day?	2		5		

Table 4.7 Perceived sleep of the subjects

Variable	Yes
Do you consider yourself to be a very poor sleeper	6
Do you consider yourself to be a moderately poor sleeper	2
Are your sleep habits very regular	5
Are your sleep habits usually quiet regular	3
Do you feel low on energy when you wake up to start your day?	6
Do you feel drowsy sleepy when you wake up to start your day?	7
Do you feel confused when you wake up to start your day?	2

Table 4.8 Sleep behaviour of the subjects

Variable	Yes	No
Do you sleep alone?	6	2
Do you have any pets in bed with you?	0	8
Do you get up at night to provide care for someone?	0	8
Is your sleep disturbed due to pain or discomfort?	0	8
In response to intense emotion do you feel muscle weakness?	0	8
Before you fall asleep do you experience vivid, frightening dreams?	0	8
Have you ever awakened from sleep and found your body paralysed?	0	8
Do you have difficulty sleeping because your legs are restless	0	8
Is your sleep problem remaining the same	8	0
Anyone told you that you stop breathing at night	0	8
Are you experiencing any new stressors?	0	8
Are you dieting?	1	7
Sleep talking during childhood	5	3
Teeth grinding during childhood	2	6

Table 4.9 Sleep habits of subjects

Variable	None of the time	Occasionally	Some of the time	Most of the time	Always
Previous polysomnography	8				
Snoring	7	1			
Gasping	7	1			
Shortness of breath	7	1			
Chest pains	5	2			
Heart palpations	7	1			
Night sweats	4	3			
Tossing and turning	1			4	1
Leg or body jerks	6	2			
Teeth grinding	7		1		
Nightmares	6	2			
Falling out of bed	5	3			
Heartburn or gas pains	7	1			

Table 4.10 The sleep profiles of subjects.

Variable	Median	Confidence interval of median
Becks Depression Inventory	9.8	5,14
Fatigue Severity Scale	36	26,74
Pittsburg Sleep Quality Index	12	10,15
Insomnia Severity Index	17	12,22
Perceived total sleep time (min)	302	247,357
Sleep onset latency (min)	27	15,38
Epworth Sleepiness Scale	5	1, 18
Perceived sleep onset latency (min)	37	33, 47
How many times do you wake up at night?	6	2, 8
Time to bed	22:30h	21:10, 23:15
Time to sleep	23:10h	22:47, 23:30
Normal wake time	04:12h	03:50, 05:30

Table 4.11 Subjective sleep variables at baseline and explanation of scores.

Subjective scale	Explanation of results	Baseline score
Becks Depression Inventory	1-10 Normal 11-16 Mild mood disturbance 17-20 Borderline clinical depression 21-30 Moderate depression 31-40 Severe depression over 40 Extreme depression	10 (5, 14)
Insomnia Severity Index	8–14 = sub threshold insomnia; 15–21 = clinical insomnia of moderate severity 21–28 = severe clinical insomnia	17 (12, 22)
Pittsburgh Sleep Quality Index	≤ 5 associated with good sleep quality > 5 associated with poor sleep quality	12 (10, 15)
Fatigue Severity Scale	> 36 suffering from fatigue	36 (26, 74)

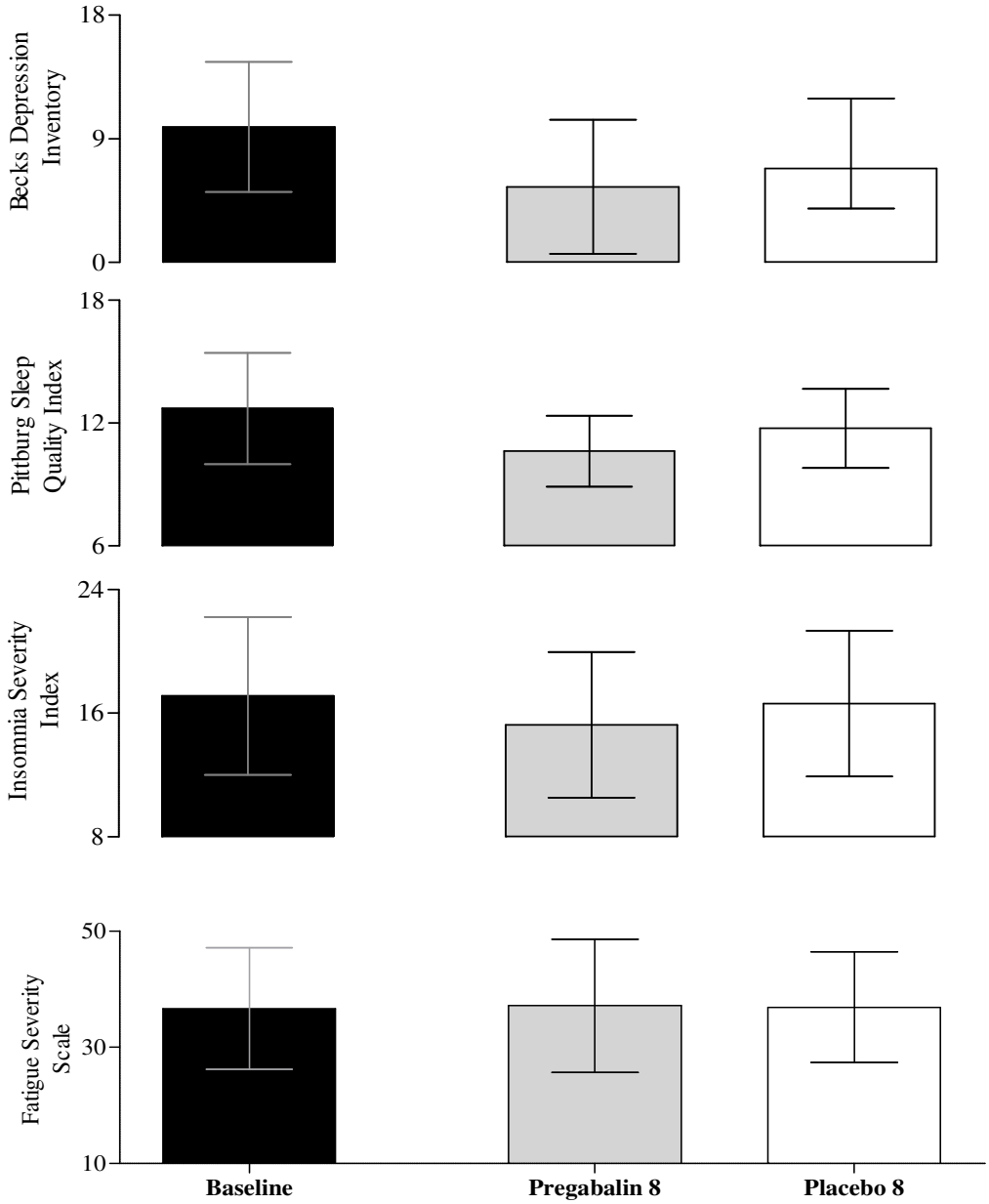

Figure 4.1 Mean and CI of the scores for the Becks Depression Inventory (P= 0.1503, Kruskal-Wallis statistic 3.791), Pittsburg Sleep Quality Index (P= 0.2252 Kruskal-Wallis statistic 2.982), Insomnia Severity Index (P =0.7517 Kruskal-Wallis statistic 0.5710) and Fatigue Severity Scale (P=0.9826 Kruskal-Wallis statistic 0.03509) for eight female chronic primary insomniacs at baseline and after using pregabalin and placebo for eight nights. There were no statistical differences in any of the subjective scales when compared to baseline or placebo.

4.1 Side effects of pregabalin and placebo

Pregabalin at 50mg was tolerated well when compared to placebo. One subject experienced depression, confusion, headaches, dizziness, lethargy on pregabalin and a headache, a dizzy spell, depression, moodiness, a digestive problem, and aggression during the week while using placebo. Other side effects that occurred once during the placebo week was a dizzy spell (one subject), stomach cramps (one subject) and constipation (one subject).

4.3 Subjective data

Pregabalin did not alter any subjective sleep scores associated with insomnia when compared to baseline or placebo that were measured in my study, nor did pregabalin alter subjects' perception of restlessness or restfulness of sleep at administration on night one or eight (Table 4.12, Figure 4.1). After one week of pregabalin use as a sleep aid, there was no statistical significance difference in Becks Depression Scores, Pittsburgh Sleep Quality Index, Fatigue Severity Scale or Insomnia Severity Scale score when compared to baseline and placebo (Figure 4.1). The mean scores for these variables at baseline were higher than scores in normal sleepers and the mean scores remained above normal levels for the duration of the study (Figure 4.1, Table 4.11).

4.4 Polysomnographic data

Variables of sleep including sleep onset latency, total sleep time, wake after sleep onset and sleep efficiency were not significantly affected by eight nights of pregabalin administration when compared to placebo (Table 4.12). There were no significant differences in the amount of time spent in sleep stages 1, 2, slow wave sleep or REM sleep nor in the number of sleep stage changes per hour over the night (Table 4.12). There was also no significant difference in any of the objective sleep variables when the pregabalin and placebo values were averaged and compared to baseline (Table 4.13).

A two way ANOVA revealed no significant time of treatment or interaction effects, for sleep onset latency, slow wave sleep, total sleep time, total time awake, wake after sleep onset or sleep changes per hour (Table 4.12). Values of the pregabalin and placebo periods for sleep onset latency, slow wave sleep, total sleep time, total time awake, wake after sleep onset and sleep changes per hour were combined and compared to baseline with a paired t test. There were no significant differences for sleep onset latency, slow wave sleep, total sleep time, wake after sleep onset or sleep changes per hour showing that there was no placebo effect (Table 4.13).

Using the equation $n_2= (t_2/t_1)^2 x(n_1)$, the sample size needed to detect significance was calculated and the results for each variable are displayed in Table 4.14. A minimum of 16 insomniacs would be needed to detect a significant difference, if the significant difference existed in sleep onset latency.

The correlation between polysomnographic data and objective data were compared using a Speramans correlation (Table 4.15). There were no correlations between any of the objective data and subjective data.

Table 4.12. The effects of treatment, time and their interaction and the effects of pregabalin and placebo on sleep parameters in eight primary insomniacs.

	Pregabalin		Placebo		Interaction		Column Factor		Time	
Variable	Mean	CI	Mean	CI	P Value	F	P Value	F	P Value	F
Percent of time in stage 1	7.7	4.2; 11.2	7.1	4.2; 10.0	0.44	0.61	0.71	0.14	0.57	0.35
Percent of time in stage 2	30.7	22.7; 38.7	32.8	25.5; 40.0	0.89	0.02	0.68	0.17	0.89	0.02
Percent of time in slow wave sleep	23.7	18.3; 29.1	22.5	17.3; 27.7	0.24	1.43	0.91	0.01	0.41	0.67
Percentage time in REM	25.3	20.5; 30.2	23.8	17.4; 30.4	0.60	0.28	0.65	0.2	0.77	0.09
Number of sleep changes per hour	10.2	7.5; 12.9	10.3	8.8; 11.7	0.82	0.05	0.86	0.03	0.89	0.01
Total sleep time (min)	321.4	263.9; 378.9	341.4	297.0; 385.7	0.78	0.07	0.57	0.32	0.7	0.15
Wake after sleep onset (%)	10.1	5.3; 14.9	10.0	5.9; 14.1	0.99	0.23	0.25	1.37	0.07	3.70
Sleep efficiency (%)	89.6	85; 94	89.5	86; 93	0.42	0.65	0.57	0.33	0.57	0.90
REM latency (min)	92.3	63.4; 121.3	80.5	52.7; 108.3	0.60	0.28	0.66	0.20	0.77	0.09
Sleep onset latency	17	7.6; 26.5	18	11.5; 23.4	0.11	2.68	0.96	0.01	0.16	2.07
Restfulness	2.1	1.4; 2.7	2.3	1.6; 2.3	0.75	0.10	0.15	2.22	0.37	0.82
Restlessness	2.8	1.8; 3.7	2.7	1.9; 3.4	0.18	1.86	0.91	0.91	0.1	3.70

Table 4.13 The results after averaging the polysomnography data for the pregabalin and placebo nights. No significant differences were observed for any variable when baseline was compared to the combined means of the pregabalin and placebo nights.

Variable	Baseline	CI	Mean of pregabalin and placebo nights	CI	P Value	T value
Sleep onset latency	27	16; 38	17	11,24	0.10	1.9
Wake after sleep onset	25	13; 38	21	9; 34	0.53	0.7
REM onset latency	90	71; 108	86	63; 110	0.80	0.3
Movement time (min)	3	2; 5	4	2; 4	0.41	0.9
% of time awake	15	6; 14	10	8; 23	0.06	2.3
Total sleep time	303	248; 358	333	290; 376	0.19	1.5
Sleep changes per hour	12	9; 12	10	10; 14	0.32	1.1
Sleep efficiency	85	77; 92	90	86; 93	0.07	2.1
REM (%)	27	19; 30	25	16; 38	0.62	0.5
Slow wave sleep (%)	22	18; 26	23	19; 27	0.65	0.5
Stage 2 (%)	32	25; 39	27	21; 33	0.09	2.0
Stage 1 (%)	6	5; 10	8	2; 10	0.44	0.82

Table 4.14. The number of people that are needed to establish the significance if a statistical difference existed between pregabalin and placebo. Values are expressed as median (CI).

Polysomnography variable	Pregabalin Night 8	Baseline	Sample size needed to detect significance
Sleep onset latency (min)	17 (5, 28)	28 (19, 35)	16
Total sleep time (min)	32 (262, 384)	348 (248, 358)	68
Wake after sleep onset (min)	23 (8, 52)	25 (13, 37)	64
Sleep efficiency (%)	85 (75, 95)	84 (77, 92)	433
Slow wave sleep (min)	20 (13, 27)	22 (17, 28)	2120

Table 4.15. The **Spearman's** rank correlation coefficient between the objective and subjective sleep variables.

Variable	Fatigue Severity Scale		Insomnia Severity Index		Pittsburgh Sleep Quality Index		Becks Depression Inventory		Exhausted		Sound	
	Spearman's r	P	Spearman's r	P	Spearman's r	P	Spearman's r	P	Spearman's r	P	Spearman's r	P
Percentage of time awake	-0.11	0.78	0.08	0.84	0.22	0.60	0.38	0.34	0.44	0.27	0.19	0.19
Wake after sleep onset	0.04	0.92	0.19	0.66	0.06	0.88	-0.52	0.18	0.24	0.57	-0.41	0.31
Total sleep time	-0.32	0.44	-0.48	0.23	0.10	0.81	-0.61	0.11	-0.32	0.44	-0.02	0.97
Sleep Efficiency	-0.22	0.59	-0.28	0.50	0.48	0.21	-0.09	0.84	-0.4	0.33	0.39	0.35
Sleep onset latency	-0.19	0.65	-0.14	0.75	-0.35	0.40	-0.44	0.28	0.43	0.29	-0.52	0.08
Sleep changes per hour	-0.55	0.16	-0.35	0.39	0.36	0.38	0.08	0.84	0.45	0.27	0.335	0.47
REM Latency	0.49	0.22	0.51	0.20	0.05	0.89	0.07	0.06	0.1	0.10	0.54	0.13
REM	0.09	0.83	0.26	0.53	0.44	0.28	0.44	0.28	0.01	0.10	-0.16	0.70

5. DISCUSSION

This study is the first to have tested the effects of an α2δ calcium channel blocker on objective and subjective sleep parameters in pain free female patients with chronic primary insomnia. This study also was designed as a pragmatic study that allowed subjects to choose their own sleep and wake time. The results of my study showed that a once-daily dose of 50mg pregabalin at night 90 minutes before bed time did not alter any of the subjective or gross polysomnographic measurements that were measured related to sleep. In particular, administering pregabalin at that dose did not relieve the primary insomnia in any way.

The insomnia experienced by the subjects was not due to depression, other sleep disorders, or pain as confirmed during interviews and the medical sleep history questionnaire. Perceived sleep quality was rated as poor as confirmed by the Pittsburgh Sleep Quality Index and the sleep history questionnaire (Table 4.13 and Table 4.5). Subjects perceived duration of sleep and objective sleep duration was confirmed to be of poor sleep quality, similar to that of other insomniacs (Table 4.12). Objective data from polysomnography at baseline also shows that the subjects were insomniac, as they had decreased amount of sleep efficiency, a low amount to total sleep time and high sleep onset latency when compared to normal controls (Table 5.1). The results of these variables are similar to that of insomniacs in other studies (Martoni et al., 2012, Edinger et al., 2003). Objective and subjective data combined show that subjects were suffering from a moderate form of insomnia.

Table 5.1 Sleep parameters from polysomnogaphy of my insomniacs when compared to normal sleepers and insomniacs. Also shown are the ratings on the subjective scales and my subjects scores (Martoni et al., 2012). Data are shown as mean (±SD)

Variable	Insomniacs	My insomniacs	Normal sleepers
Total sleep time (min)	364 (12.1)	302.8 (66)	370.5 (10.1)
Sleep onset latency(min)	17.9 (2.9)	28 (10.5)	14.0 (2.8)
Wake after sleep onset (min)	75.1 (7.7)	45 (53.8)	34.2.(6.4)
Sleep efficiency (%)	79.4 (1.6)	83.7 (9.1)	88.8 (1.3)

The effects of pregabalin was assessed at nights one and eight as pregabalin other studies showed that pregabalin had an effect on sleep from the first night of administration (Hindmarch et al., 2005). In addition, other studies confirmed that the effects that pregabalin had on sleep after one week was sustained for the duration of the study (Sabatowski et al., 2004). In my study, there was no statistically significant reduction in sleep onset latency when pregabalin and placebo were compared to baseline, showing that the time taken to fall asleep remained unchanged with pregabalin and placebo use. The time spent in slow wave sleep, REM sleep, stages one and two of sleep remained unchanged. Also unaffected after eight nights of using pregabalin and placebo was wake after sleep onset and total sleep time. Taken together these results indicate that 50mg of pregabalin at night before bedtime neither affected the objective measures of sleep as measured with polysomnography. Besides pregabalin not altering objective sleep, the placebo also failed to alter subjective sleep parameters in the insomniacs. This is unusual as insomnia studies usually show a placebo effect. It is likely that the lack of a placebo effect in this study is due to the pragmatic study design. Other possibilities are that subjects had a low level of expectantly of treatment which lead to no placebo effect, or that the fact that insomnia experienced by the insomniacs in this study was of moderate severity, while the placebo effect is more pronounced in studies that utilize insomniacs that suffer from severe insomnia (Perlis et al., 2005).

Nightly use of pregabalin for one week at 50mg also failed to change subjective variables that were measured with the Becks Depression Inventory, Fatigue Severity Scale, Insomnia Severity Scale and the Pittsburg Sleep Quality Index. Subjects' perception of depression, fatigue, insomnia and sleep quality remained unchanged after one week of using pregabalin and placebo when compared

to baseline, in spite of the subjects displaying fatigue, insomnia symptoms and poor sleep quality on subjective questionnaires (Table 4.12). Pregabalin and placebo also had no effect on how exhausted or rested and restless subjects perceived the previous night's sleep to be when compared to baseline, implying that the subjects perceived sleep quality was unaffected.

Subject recruitment for this study proved challenging. Potential subjects who met the criteria were found; however, they were not willing to sleep at the sleep laboratory as they viewed the nights at the sleep laboratory as an inconvenience. If polysomnography was conducted at home, it is likely that more subjects would have been recruited. While it may be argued that the sample size used in this study was too small to detect significance, small sample sizes are not uncommon in polysomnographic studies and it is possible to detect statistical significant differences among polysomnographic and subjective variables if they do exist (Le Bon et al., 2003, de Haas et al., 2007, Parker et al., 2005). If the sample size was 68 people, changes may have been observed in sleep onset latency, wake after sleep onset and slow wave sleep (Table 4.14). Whether these changes would have been in favor of the pregabalin or placebo group is unknown, but the trend in my data show that wake after sleep onset was higher in the pregabalin group, suggesting that sleep is more interrupted with pregabalin use than with placebo even though the pregabalin group had a reduced sleep onset latency.

There were no statistically significant differences in the subjective sleep variables between the nights on which pregabalin or placebo were administered. The observable changes after one week on pregabalin are too small to be detected by subjective tests, and perhaps a longer duration on

both treatments could have yielded some significance. While a single dose of 50mg pregabalin failed to show changes in perceived sleep quality, a higher and more frequent dose may have resulted in changes to perceived sleep quality and other insomnia symptoms.

Insomnia drug trials usually require subjects to adhere to strict sleep-wake times on subjects: for example, subjects are required to spend a fixed eight hour period in bed, regardless of whether they are asleep or awake (Erman et al., 2006). Rigidly designed clinical insomnia studies also intentionally select insomniacs with severe forms of insomnia that include with long durations of sleep onset latency and short total sleep times (Krystal et al., 2003). I intentionally designed the trial to have a minimum impact on a subject' day-to-day activities, and I did not screen subjects by total sleep times and sleep onset latency. Instead any healthy female between the ages of 18-55 with chronic primary insomnia could participate in this study. By allowing my subjects to choose their sleep-wake times my study reflected how subjects might use a hypnotic in their own home environment. By not screening and selecting subjects with severe insomnia symptoms, my study better reflects the effect of pregabalin on general primary insomniacs within the population. Subjects were also allowed to perform any activities that they would normally do if they were in the home environment. The study design can be improved further if sleep were monitored within the home environment using ambulatory polysomnographic equipment.

Data from polosomnography did not have a strong correlation with any of the subjective variables that were measured. The lack of any correlations between objective and subjective sleep is not unusual among both insomniac and normal sleepers (Baker et al., 1999, Bastien et al., 2003, Xu et

al., 2011). Both insomniacs and normal subjects overestimate the time asleep and the time to sleep onset, while underestimating the total sleep time (Baker et al., 1999, Bastien et al., 2003, Xu et al., 2011). The inaccuracy in measuring subjective sleep among insomniacs is greater than normal sleepers (Bastien et al., 2003, Xu et al., 2011). My study did not request subjects to estimate any of the variables that were directly measured by polysomnography; rather the questionnaires were used to assess the impact of pregabalin on insomnia severity and daytime functioning.

Pregabalin is normally prescribed at 50mg twice daily and is usually titrated upwards up to a final dose. As we were investigating the use of pregabalin as a hypnotic, a twice-daily dose of pregabalin was not used in this study, as insomniacs would have been unwilling to endure the potential hypnotic effects of pregabalin during the day. The pilot study showed that when pregabalin was used once daily it was not well tolerated at doses above 50mg, with subjects reporting dizziness, sleepiness and irritability. A once daily dose of 100mg pregabalin caused a significantly higher level of light-headedness, visual disturbance and difficulty with walking in the group of patients using pregabalin post-surgery (Paech et al., 2007). Similarly, even a once daily dose of 75mg of pregabalin resulted in dizziness, headache and blurred vision (Jokela et al., 2008). From clinical studies it could be inferred that high doses of pregabalin are better tolerated when prescribed multiple times throughout the day however, further studies should be done to confirm this hypotheses. It is likely that the onetime dosage of pregabalin was responsible for the large amounts of side effects seen in the pilot study when pregabalin was used at relatively small doses. This study intentionally picked the highest therapeutic dose of pregabalin whose side effects would not have been debilitating to the subjects.

Studies that have examined the effectiveness of pregabalin in treating chronic pain, epilepsy, anxiety disorders and depression all have used pregabalin twice or more daily. Studies examining the effects of pregabalin on sleep in the presence of another primary condition showed that pregabalin caused an improvement to the primary cause of the sleep complaint and also a change in sleep measures (Table 5.2). It has been shown that epilepsy seizure frequency is linked to the occurrence and severity of insomnia (Piperidou et al., 2008). The presence of chronic neuropathic pain is also has a negative effect on sleep, and the successful treatment of chronic neuropathic pain results in an improvement of sleep (Singh et al., 1998, Affleck et al., 1996).

Both chronic primary insomnia and pain related insomnia share common characteristics such as the pattern, duration and severity of the sleep disorder as well as the levels of sleep related anxiety and pre-sleep arousal (Tang et al., 2012). My study failed to show any objective or subjective sleep enhancing effect that could be gain by using pregabalin at doses of 50mg once daily in patients suffering from chronic primary insomnia. It is possible and indeed likely, that the changes in objective and subjective measures of sleep seen in other studies are a result of alleviating the condition that causes the insomnia and not a result of a direct sleep-enhancing effect of pregabalin.

The drug doses used in these trials were between 150-600mg administered two times a day, much higher than the dose that I used. Three hundred mg's of pregabalin twice daily caused a reduction in the number of awakenings as well as a reduction in wake after sleep onset, but sleep onset latency and the percentage of time in each sleep stage remained unchanged in patients with well-

controlled epilepsy (de Haas et al., 2007). While subjective sleep variables within the Medical Outcomes Sleep Scale also showed changes, there was not always a correlation with objective polysomnographic data (de Haas et al., 2007). For example, the Medical Outcomes Sleep Scale showed an improvement in sleep quantity, which was not reflected by an increase in sleep efficiency in patients' objective data. Another study examining pregabalin in a patient group given a dosage between 150mg-375mg (average dose 210mg) pregabalin twice daily (as an add-on therapy in treating epilepsy) showed an increase in the percentage time spent in REM sleep with no changes in wake after sleep onset or sleep onset latency (Romigi et al., 2009). Similarly, in addition to alleviating pain, pregabalin improved subjective sleep as well as perceived quality of life and fatigue in patients with neuropathic pain.

To date there has only been one study that has examined the effects of pregabalin on sleep in symptom-free subjects, which concluded that pregabalin increases slow wave sleep and decreases sleep onset latency in healthy subjects (Hindmarch et al., 2005). In this study, subjects were given three doses of 150mg pregabalin daily for three days – a much higher dosage than the manufacturer's recommended starting dose of 75mg twice daily for pain relief and maintenance dose of 75mg-150mg twice daily, which is well below the dose used in this trial. In light of the side effects experienced during my pilot study, it was surprising that no mention was made as to the side effects and their frequency when normal subjects were on pregabalin and placebo at doses of 150mg (Hindmarch et al., 2005).

Table 5.2 Key papers on the effects of pregabalin on sleep and mood in patients with secondary insomnia.

	Gender	Sample size	Duration	Dose	Design	Primary complaint	Outcome of primary complaint	Outcome of sleep variables	Outcome of mood variables
Epilepsy sleep and pregabalin (de Haas et al., 2007)	Male and female	17	4 weeks	300mg/day	Placebo controlled trial	Epilepsy	No change to epileptic variables	Reduction in awakenings Improvement on the Medical Outcomes Study Sleep Scale	None
Epilepsy and sleep and pregabalin (Romigi et al., 2009)	Male and female	12	3 months	150-375mg/day	Case series	Epilepsy	Reduction in seizure frequency	Increase in rapid eye movement sleep and Epworth Sleepiness Score	None
Neuropathic pain sleep and pregabalin (Roth et al., 2012)	Male and female	119		300-450mg/day	Double blind randomized cross over placebo controlled trial	Pain	Reduction in pain scores	Improvement in objective sleep	None
Fibromyalgia and pregabalin (Crofford et al., 2005)	Male and female	529	8 weeks	150-450mg/day	Placebo controlled trial	Pain	Reduction of pain	Improvement on the Medical Outcomes Study Sleep Scale	Improvement in Multidimensional Assessment of Fatigue and Short Form 36 Health Survey
Peripheral Neuropathic Pain (Moon et al., 2010)	Male and female	240	10 week	150-600mg/day	Placebo controlled	Pain	Reduction of pain	Reduction in Daily Sleep Interference Scale	None
Neuropathic pain sleep and pregabalin (Freynhagen et al., 2005)	Male and female	338	12 week	150-600mg/day	Placebo controlled	Pain	Reduction of pain	Reduction in Daily Sleep Interference Scale	None

Gabapentin, pregabalin's predecessor, also altered sleep in a manner similar to that of pregabalin. Gabapentin increased slow wave sleep in healthy subjects at doses of 1800mg per day (Foldvary-Schaefer et al., 2002). Similar to pregabalin, gabapentin improved sleep in 18 patients with insomnia related with alcohol withdrawal when prescribed at doses between 200mg-900mg (Conroy et al., 2006). Significant differences when compared to baseline were observed after using gabapentin for sleep efficiency, wake after sleep onset and decreased nocturnal arousals (Conroy et al., 2006). A case report also revealed that 500mg gabapentin once daily, effectively controlled insomnia in two chronic primary insomniacs (Rosenberg, 2003). Even though these studies seem to imply that gabapentin may be a useful hypnotic alternative, unlike pregabalin, gabapentin does not have linear pharmokinetics and takes 3-4 hours to reach its peak plasma concentration. The problems that are likely to be encountered with gabapentin as a sleep aid are similar to the problems that I encountered using pregabalin; the correct dose to enhance sleep would most likely cause too many daytime side effects that insomnia patients would be unlikely to tolerate.

The next step would be to examine the effects of 100mg and 75mg pregabalin once nightly on objective and subjective variables in chronic primary insomniacs while paying particular attention to the side effects that are experienced by patients. Alternatively, the next insomnia study investigating the effects of pregabalin on sleep could increase the dose of pregabalin every evening by 25mg-50mg to at least 150mg once daily. It may also be useful for future studies to try to split the insomniac recruitment into two groups comprising of those insomniacs who suffer from sleep onset problems as well as those insomniacs that suffer from difficulty with sleep maintenance. As insomnia can be a result of chronic pain and a reduction in pain scores can

result in improved sleep, it is difficult to distinguish the direct effect pregabalin has on sleep in patients with pain. Similarly, it is difficult to draw conclusions about the effect pregabalin has on sleep and generalized anxiety disorder or epilepsy. However, all future clinical studies examining the effects of pregabalin should evaluate the effects that pregabalin has on sleep in these studies. Ideally having a polysomnography performed at baseline and at the study endpoint would be optimal, but subjective variables measured before and after treatment could also prove useful. Sleep data from these studies could help determine at what doses of pregabalin sleep changes occur, as well as what variables will most likely be impacted by pregabalin administration. It is also important to investigate why the healthy subjects in my pilot study had such an adverse reaction to a once day dose of pregabalin, and whether or not the starting 150mg dose of pregbalin that was used in other studies had any side effects, as well as the severity of the side effects. Future studies should evaluate whether home based polysomnography results in an increased recruitment rate in an insomniac population. The effectiveness of 50mg of pregabalin should also be tested as an anxiolytic or analgesic in order to evaluate if pregabalin has any effect at this dose, or if this dose is below the threshold of treatment.

In conclusion, even though pregabalin does have sleep enhancing effects in some studies and is therefore being used as an off label treatment for insomnia, I have failed to find any sleep enhancing effects that may be gained from using pregabalin once a day with a dose of 50mg before bedtime in patients with chronic primary insomnia. I have also demonstrated that a once daily dose above 50mg of pregabalin was not well tolerated in normal subjects. Until an optimal once daily dose of pregabalin for the treatment of primary insomnia can be described which

balances the side effects with the sleep enhancing effects, it is premature to prescribe pregabalin as a sleep aid in chronic primary insomniacs.

Appendix 1: Fatigue Severity Scale

(Krupp et al., 1989)

The Fatigue Severity Scale is a method of evaluating the impact of fatigue on you. The Fatigue Severity Scale is a short questionnaire that requires you to rate your level of fatigue.. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

- A low value (e.g., 1); indicates strong disagreement with the statement, whereas a high value (e.g., 7); indicates strong agreement.
- It is important that you circle a number (1 to 7); for every question.

During the past week, I have found that:	**Disagree <----> Agree**						
My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
Exercise brings on my fatigue.	1	2	3	4	5	6	7
I am easily fatigued.	1	2	3	4	5	6	7
Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Appendix 2: Becks Depression Inventory

(Beck et al., 1961)

Instructions: Please circle the number by the response for each question that best describes how you have felt during the past seven (7) days. Please do not omit any questions. Make sure you check one answer for each question. If more than one answer applies to how you have been feeling, check the higher number. If in doubt, make your best guess.

1 0- I do not feel sad.
1 - I feel sad.
2 - I am sad all the time and I can't snap out of it.
3 - I am so sad or unhappy that I can't stand it.

2. 0 - I am not particularly discouraged about the future.
1 - I feel discouraged about the future.
2 - I feel I have nothing to look forward to.
3 - I feel that the future is hopeless and that things cannot improve.

3. 0 - I do not feel like a failure.
1 - I feel I have failed more than the average person.
2 - As I look back on my life, all I can see is a lot of failures.
3 - I feel I am a complete failure as a person.

4. 0 - I get as much satisfaction out of things as I used to.
1 - I don't enjoy things the way I used to.
2 - I don't get real satisfaction out of anything anymore.
3 - I am dissatisfied or bored with everything.

5. 0 - I don't feel particularly guilty.
1 - I feel guilty a good part of the time.
2 - I feel quite guilty most of the time.
3 - I feel guilty all of the time.

6. 0 - I don't feel I am being punished.
1 - I feel I may be punished.
2 - I expect to be punished.
3 - I hate myself.

7. 0 - I don't feel disappointed in myself.
1 - I am disappointed in myself.
2 - I am disgusted with myself.
3 - I hate myself.

8. 0 - I don't feel I am any worse than anybody else.
1 - I am critical of myself for my weaknesses or mistakes.
2 - I blame myself all the time for my faults.
3 - I blame myself for everything bad that happens.

9. 0 - I don't have any thoughts of killing myself.
1 - I have thoughts of killing myself, but I would not carry them out.
2 - I would like to kill myself.
3 - I would kill myself if I had the chance.

10. 0 - I don't cry any more than usual.
1 - I cry more now than I used to.
2 - I cry all the time now.
3 - I used to be able to cry, but now I can't cry even though I want to.

11. 0 - I am no more irritated by things than I ever am.
1 - I am slightly more irritated now than usual.
2 - I am quite annoyed or irritated a good deal of the time.
3 - I feel irritated all the time now.

12. 0 - I have not lost interest in other people.
1 - I am less interested in other people than I used to be.
2 - I have lost most of my interest in other people.
3 - I have lost all of my interest in other people.

13. 0 - I make decisions about as well as I ever could.
1 - I put off making decisions more than I used to.
2 - I have greater difficulty in making decisions than before.
3 - I can't make decisions at all anymore.

14. 0 - I don't feel that I look any worse than I used to.
1 - I am worried that I am looking old or unattractive.
2 - I feel that there are permanent changes in my appearance that make me look unattractive.
3 - I believe that I look ugly.

15. 0 - I can work about as well as before.
1 - It takes an extra effort to get started at doing something.
2 - I have to push myself very hard to do anything.
3 - I can't do any work at all.

16. 0 - I can sleep as well as usual.
1 - I don't sleep as well as I used to.
2 - I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 - I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 - I don't get more tired than usual.
1 - I get tired more easily than I used to.
2 - I get tired from doing almost anything.
3 - I am too tired to do anything.

18. 0 - My appetite is no worse than usual.
1 - My appetite is not as good as it used to be.
2 - My appetite is much worse now.
3 - I have no appetite at all anymore.

19. 0 - I haven't lost or gained much weight, if any, lately.
1 - I have lost or gained more than five pounds.
2 - I have lost or gained more than ten pounds.
3 - I have lost or gained more that fifteen pounds.

20. 0 - I am no more worried about my health than usual.
1 - I am worried about physical problems such as aches and pains, or upset stomach, or constipation.
2 - I am very worried about physical problems and it's hard to think of much else.
3 - I am so worried about my physical problems that I cannot think of anything else.

21. 0 - I have not noticed any recent change in my interest in sex.
1 - I am less interested in sex than I used to be.
2 - I am much less interested in sex now.
3 - I have lost interest in sex completely.

Appendix 3: Pittsburgh Sleep Quality Index

(Buysse et al., 1989)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep did you get that night? (This may be different than the number of hours you spend in bed_____

	Not during the past month (0)	**Less than once a week (1)**	**Once or twice a week (2)**	**Three or more times a week (3)**
5. During the past month, how often have you had trouble sleeping because you…				
a. Cannot get to sleep within 30 minutes				
b.Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem as it been for you to keep up enthusiasm to get things done?				
	Very good (0)	**Fairly good (1)**	**Fairly bad (2)**	**Very bad (3)**
9. During the past month, how would you rate your sleep quality overall?				

Appendix 4: Insomnia Severity Index

(Bastien et al., 2001)

For each question below, please circle the number corresponding to your response.

1. Please rate the current (i.e., last month) SEVERITY of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
a) Difficulty falling asleep:	0	1	2	3	4
b) Difficulty staying asleep:	0	1	2	3	4
c) Problem waking up too early:	0	1	2	3	4

2. How SATISFIED/dissatisfied are you with your current sleep pattern?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all	A little	Somewhat	Much	Very Much
0	1	2	3	4

4. How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all noticeable	A little noticeable	Somewhat noticeable	Much noticeable	Very much noticeable
0	1	2	3	4

5. How WORRIED/distressed are you about your current sleep problem?

Not at all	A little	Somewhat	Much	Very much
0	1	2	3	4

Appendix 5: Sleep History Questionnaire

(Stood, 2001)

Please provide us with the following information:

Date: _____

Name: _____

Birth date: _____ Age: _____ Race: _____

Marital status: _____

Occupation: _____ Weight:_____ Height: _____

Collar size: _____

What is your main sleep problem?

_____

When did this problem begin?

_____

(Circle one) Is your problem: Increasing Decreasing Remaining the same

Do you snore when you sleep? YES _____ NO _____

If you do snore, please circle in which position:

ALL BACK SIDES STOMACH

Has anyone ever told you that you stop breathing at night? YES _____ NO ____

CURRENT MEDICAL INFORMATION

Are you currently receiving any medical treatment? YES _____ NO _____

If yes, please provide the following information:

Current illness (i.e. high blood pressure, diabetes, heart problems, thyroid, depression, etc.)

1. _____

2._____

Current medications (please list dose also)

1. _____

2._____

3. _____

How would you describe your current state of health?

Excellent ___ Good ___ Moderately good ___Fair ___ Poor ___ Very Poor ___

Do you have problems with nasal congestion, obstruction, or discharge?

YES _____ NO _____

Do you use nasal decongestants (tablets, sprays, etc.) to help you get to sleep?

YES _____ NO _____

PAST MEDICAL HISTORY

Have you ever had a sleep study before? YES _____ NO _____

Are you currently using Oxygen or CPAP? YES _____ NO _____

Please list all past major medical problems below:

Illness/Surgery/Accident Date

1. _____

2. _____

3. _____

4. _____

Have you ever had a head injury? YES _____ NO _____

Any complications with surgery and/or anesthesia? If so please explain:

_____

_____

List any medications you might be allergic to and the side affect:

_____

Has anyone ever prescribed you medications to help with your sleep problem?

YES _____ NO _____

What was the medication(s), and did you feel it helped?

CURRENT BEHAVIOUR

Do you drink alcohol? YES _____ NO _____

If so, how much and how frequently? _____

Do you drink coffee, tea or soda? YES _____ NO _____

If so, how much per day? _____

Do you smoke? YES _____ NO _____. If so, number of packs per day?

_____

Do you exercise regularly? YES _____ NO _____

How often do you eat (including snacks) within two hours of trying to go to sleep?

_____

Are you on a diet right now? YES _____ NO _____

How long since you started?

_____

Are you currently taking anything (herbal, homeopathic, prescription, pharmacy over-the-counter) for your general health or to help with your sleep?

YES _____ NO _____.

Product: _____

Daytime functioning

Do you feel **FATIGUE** (tiredness, exhaustion, lethargy) in the daytime even when not sleepy?

No ____ Infrequently____ Occasionally ____ Often ____ Always _____

Do you feel **SLEEPY** (or struggle to stay awake) in the daytime?

No ____ Infrequently____ Occasionally ____ Often ____ Always _____

If so, under what circumstances do you fall asleep easily?

_____ Driving _____ After Meals _____Meetings, class, church

_____ Other _____ On the Telephone _____ Watching TV/Reading

Have you had a car accident or near miss because of falling asleep driving?

YES _____ NO _____

Were you sleeping well before the incident, or had you been keeping late hours, etc?

_____

Do you fall asleep during the day enough to interfere with your (check all that apply):

Household chores?_____ Marriage/ Relationships? _____

Job performance?_____

How often do you feel alert and energetic for an entire day?

Never _____ Upon occasion _____ Most of the time _____ All of the time _____

Do you take naps (intentional and/or unintentional) during the Day?

YES _____ NO _____.

If yes, please list the time and frequency below:

_____

_____

Do you feel refreshed after your naps? YES _____ NO _____

Mood

Has your memory been getting worse lately?

_____

Have you had difficulty concentrating lately?

_____

Have you been feeling more irritable lately?

_____

Have you ever been treated for depression, anxiety, or severe stress?

YES _____ NO _____

If yes, what were the circumstances and how were you treated?

_____

How much stress would you say you were under right now?

_____

If you are under stress, is it related to: Work ____ Personal life ____ Other ____

Have you been feeling more depressed lately?

_____

Have you been feeling: Hopeless _____ Helpless _____

Worthless _____ Useless _____?

Have you seriously thought about suicide recently?

_____

How is your appetite?

_____

How much weight have you: Lost _____ or Gained _____ in the past year?

Current sleep behavior

Do you sleep alone? YES _____ NO _____

If NO, who sleeps in bed with you?

Spouse___ Significant other___ Child/Parent ___

Do you have any pets that sleep in bed with you? YES _____ NO _____

Do you consider yourself to be a:

Very good sleeper _____ Moderately poor sleeper_____

Moderately good sleeper_____ Very poor sleeper _____

Do you consider your bed partner to be a:

Very good sleeper _____ Moderately poor sleeper_____

Moderately good sleeper_____ Very poor sleeper _____

How regular are your sleep habits?

Very Regular _____ Usually quite irregular _____

Usually quite regular _____ Very irregular _____

Weekdays, what time do you usually go to bed? _____

Does this vary by: Minutes _____Hours_____?

Weekdays, what time do you get up in the morning? _____

Does this vary also? _____

Approximately how long does it take you to fall asleep after turning out the lights? _____

When you wake up during the night, how difficult is it for you to go back to sleep? _____

If you cannot sleep, do you get out of bed? YES _____ NO _____

Do you watch television to help you sleep? YES _____ NO _____

How many times do you wake up at night on average?

_____

How many hours do you feel you actually sleep on weeknights? _____ Hours

Do you keep the same sleep schedule on weekends (or days off from work)?

YES _____ NO _____

If no, what is your bedtime: _____ waking time: _____ and do you feel better on weekends? Yes____ No____

How often do you get up at night to provide care for someone (child, invalid, spouse)? _____

How often is your sleep disturbed because of pain or discomfort?
_____

Describe your normal work hours: (i.e. do you work mon-fri 9to 5 , list all jobs and time of work)
_____
_____

If you do shift work, how often does your shift change?_____

In general, what effect does shift work have on your sleep complaint?
___Marked worsening
___Some worsening
___ No effect
___Some improvement
___Marked improvement
___Precipitates problem

How do you feel when you wake up to start your day?
___ Alert, awake
___Energetic
___ Refreshed
___Anxious

___ Drowsy, sleepy

___ Low energy

___ Confused

___ Depressed

In response to intense emotion (laughter, anger, surprise) have you felt sudden muscle weakness in your legs, neck, or other extremities? (This does not refer to known muscle or joint problems, or to lightheadedness.)

YES _____ NO _____.

Please describe the emotions involved and what muscles went limp:

_____

Before you are fully asleep do you have very vivid, sometimes frightening, hallucination like dreams ?

YES _____ NO _____.

Have you ever awakened from sleep and found that your body was "paralyzed" and you couldn't move at all, even though you could breathe and see?

YES _____ NO _____.

Do you have difficulty falling asleep because your legs are restless or have crawling sensation ?

YES _____ NO _____.

Family sleep history

Has any member of your family been diagnosed with a sleep problem?

YES _____ NO _____.

If yes, what was the diagnosis, and what is their relation to you?

Has any member of your family died in their sleep? YES _____ NO _____.

During your sleep, do you currently (in the last six months) have problems with the following:

BEHAVIOR	ALWAYS	MOST OF THE TIME	OCCASIONALLY	NEVER
Choking/Gasping				
Shortness of breath				
Chest pains				
Heart palpitations				
Night sweats				
Tossing and turning				
Leg or body jerks				
Grinding teeth				
Sleep walking				
Shouting/ nightmares				
Falling out of bed				
Back pains while asleep				
Heartburn/ gas pains				
Anxiety/ panic attacks				
Morning headaches				
Dry mouth in morning				
Any other unusual behavior (describe Below)				

Childhood sleep history

Please check any of the following sleep behaviors that occurred when you were a child or an adolescent:

___ Sleep walking
___ Sleep talking
___ Bed wetting
___ Twitching or jerking
___ Head banging
___ Night terrors/screaming & shouting
___ Snoring/Asthma
___ Grinding teeth
___ Excessive sleepiness in school
___ Seizures in sleep
___ Insomnia
___ Inability to sleep until very late at night

Who should we contact in case of an emergency? Name:
_____

Relationship: _____

Telephone # _____

Is there anything else that you feel is important about your sleep/medical/psychological history that we may not have covered?

YES _____ NO _____.

Please feel free to write below and use another sheet of paper if needed.

Appendix 6: Questions evaluating previous night's subjective sleep

Please fill out the following questions within 10min of getting out of bed:

When I got up this morning I felt

Exhausted_____Refreshed

Overall, my sleep last night was

Very restless_____Very sound

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