Using Antihistamines as a Sleep Aid

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November 2012

Thesis submitted in fulfilment of the requirements for the degree of Master of Pharmacy at the University of Canberra, Australian Capital Territory, Australia
Abstract

Background:

Approximately 8.9% of the Australian population aged 20 years and over experience a sleep disorder. Many treatments are used for the treatment of sleep disorders including antihistamines, available without a prescription. Few studies have investigated the usage of antihistamine sleep aids and their efficacy.

Objectives:

The aims of this study were to determine the:

- characteristics of patients requesting antihistamines as sleep aids; and
- usage and perceived efficacy of antihistamine therapy for insomnia in a sub-sample of the study population.

Design:

The study was based on a convenience sample of community pharmacy clients seeking an antihistamine product as a sleep aid in a community pharmacy. It was conducted in 7 community pharmacies around the Australian Capital Territory (ACT) metropolitan area. Participants were surveyed in two phases.

The phase I survey was completed by clients recruited by the participating pharmacies whilst in the pharmacy.

A more detailed phase II survey was administered by the researcher during a follow-up telephone call and assessed the effectiveness of the antihistamine and other factors related to causes of insomnia, such as caffeine, alcohol consumption and smoking status.

Both questionnaires based on DSM-IV and ICSD criteria as well as the Insomnia Severity Index.

Results

Seventy-three participants completed the Pharmacy questionnaire with 48 agreeing to participate in the telephone follow-up survey. The population was predominantly female (n=47, 63.5%). The likelihood of seeking treatment significantly increased with age, female
gender, and smoking. Difficulty initiating or maintaining sleep and frequent awakening also increased with increasing age. Participants with a lower education level were more likely to experience sleep problems. Herbal (52.1%) and non-prescription products (50.7%) had been used before receiving the antihistamine, indicating a lack of effect. Using antihistamine was associated with marked improvements in sleep parameters with 97.9% of participants rating an antihistamine as helpful. The main antihistamine side effects reported were drowsiness and nausea.

**Conclusion**

Poor sleep pattern symptoms were associated with many factors including increasing age. Antihistamines were an effective treatment to improve sleep patterns.
Acknowledgments

I take this opportunity to express my profound gratitude and deep regards to my guide Dr. Greg Kyle for his exemplary guidance, monitoring and constant encouragement throughout the course of this thesis. The blessing, help and guidance given by him time to time shall carry me a long way in the journey of life on which I am about to embark.

I also take this opportunity to express a deep sense of gratitude to staff members of Saudi Arabian Cultural Mission for their cordial support and guidance, which helped me in completing this task through various stages.

I am obliged to staff members of Australian Pharmacy Group and Capital Chemist Pharmacies for their cooperation during the period of my project.

Lastly, I thank almighty, my wife, my parents, and friends for their constant encouragement without which this project would not be possible.
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<td>5-HT</td>
<td>5-hydroxytryptamine</td>
</tr>
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<td>5-HTP</td>
<td>5-hydroxytryptophan</td>
</tr>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>ACT</td>
<td>Australian Capital Territory</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>AMH</td>
<td>Australian Medicines Handbook</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood Brain Barrier</td>
</tr>
<tr>
<td>BEACH</td>
<td>Bettering the Evaluation and Care of Health</td>
</tr>
<tr>
<td>BzRAs</td>
<td>Benzodiazepine Receptor Agonists</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and Alternative Medicines</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavioural Treatment</td>
</tr>
<tr>
<td>CBT-I</td>
<td>Cognitive Behavioural Therapy treatments for Insomnia</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CT-I</td>
<td>Cognitive Therapy for chronic Insomnia</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P</td>
</tr>
<tr>
<td>DRN</td>
<td>Dorsal Raphe Nuclei</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th Edition</td>
</tr>
<tr>
<td>DSST</td>
<td>Digit Symbol Substitution Test</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>EOG</td>
<td>Electro-oculography</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalized Anxiety Disorder</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma Amino Butyric Acid</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HT 7</td>
<td>Heart-7 Points</td>
</tr>
<tr>
<td>ICSD</td>
<td>International Classification of Sleep Disorders</td>
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<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
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<tr>
<td>ISI</td>
<td>Insomnia Severity Index</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<tr>
<td>NREM</td>
<td>Non Rapid Eye Movement</td>
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<tr>
<td>NRS</td>
<td>Numerical Rating Scale</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter</td>
</tr>
<tr>
<td>PCG</td>
<td>Posterior Cingulate Gyrus</td>
</tr>
<tr>
<td>PCPA</td>
<td>P-chlorophenylalanine</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnographic</td>
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<tr>
<td>PSQI</td>
<td>Pittsburg's sleep-quality index</td>
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<td>RAS</td>
<td>Reticular Activating System</td>
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<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
</tr>
<tr>
<td>SCN</td>
<td>Suprachiasmatic Nuclei</td>
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<td>SCT</td>
<td>Stimulus Control Therapy</td>
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<td>SCT</td>
<td>Symbol Copying Task</td>
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<td>SHE</td>
<td>Sleep Hygiene Education</td>
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<td>SRT</td>
<td>Sleep Restriction Therapy</td>
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<tr>
<td>SSRIs</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
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<td>SWS</td>
<td>Slow Wave Sleep</td>
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<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour Necrosis Factor α</td>
</tr>
<tr>
<td>TST</td>
<td>Total Sleep Time</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WASO</td>
<td>Wakening After Sleep Onset</td>
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</table>
Chapter 1: Introduction and Literature Review

Sleep and sleep physiology

Sleep is a reversible state of unconsciousness and unresponsiveness to the surrounding environment (Carskadon & Dement, 2005). It is typically accompanied by horizontal posture (lying down), behavioral stillness, closed eyes, and differential breathing (Carskadon & Dement, 2005). The current understanding of the physiology of sleep suggests that it is a multifaceted biobehavioral process (Hallet al., 2008; Hall, 2010). Alterations in sleep occur throughout the lifespan of an individual, from infancy through old age, and may also be affected by several factors such as gender, socioeconomic status, marital status and mental or physical health conditions (Carrier et al., 2001; Carskadon & Dement, 2005; Hall et al., 2009; Ohayon et al., 2004).

It was widely believed that sleep is a passive and inactive state, however sleep is now considered to be an active state in which several different metabolic processes, tissue restoration, memory consolidation, and homeostatic balance are sustained (Adam, 1980; Alvarez & Ayas, 2004; Ancoli-Israel, 2006; Benca & Quintas, 1997). Brain and body activity have both been demonstrated during sleep (Adam, 1980; Alvarez & Ayas, 2004; Ancoli-Israel, 2006; Benca & Quintas, 1997), hence its dismissal as an inactive process. Memory consolidation also occurs during sleep (Stickgold, 2005) and sleep quantitatively and qualitatively changes new memory representations (Diekelmann & Born, 2010). Although it is well-recognized that sleep is an important homeostatic process, several aspects remain elusive such as why sleep is required for a healthy lifestyle, the duration of sleep required and the degree of adverse effects which occur when insufficient sleep is achieved (Okun, 2011). Studies investigating sleep deprivation or restriction in healthy individuals found significant alterations in central and peripheral physiology associated with functional changes in cognition, performance and behavior (Irwin et al., 2006; Lim & Dinges, 2008; Redwine et al., 2000; Sari et al., 2008; Spiegel et al., 1999; Spiegel et al., 2002; Spiegel et al., 2004; Stricker et al., 2006; Vgontzas et al., 2004).

Sleep is identified based on behavioral and physiological changes which occur in the brain’s electrical rhythms during sleep (Chokroverty, 2009). Behavioral changes involve “a lack of mobility or slight mobility, slow eye movements, characteristic sleeping posture, reduced
response to external stimulation, increased reaction time, elevated arousal threshold, a weakened cognitive function and a reversible unconscious state” (Chokroverty, 2010). Physiological changes have been observed in studies investigating findings of electroencephalogram (EEG), electro-oculography (EOG) and electromyography (EMG) (Karlen et al., 2009; Shinar et al, 2006). These changes are listed in Table 1. Sleep onset is characterized by steady alterations in these behavioral and physiological aspects(Madsen et al., 1991a; NHLBI, 2003 ; Somers et al., 1993).

Table 1: Physiological changes during the NREM and REM sleep

<table>
<thead>
<tr>
<th>Physiological Process</th>
<th>NREM sleep*</th>
<th>REM sleep*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain activity</td>
<td>Decreases from wakefulness</td>
<td>Increases in motor and sensory areas, while other areas are similar to NREM</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Slows from wakefulness</td>
<td>Increases and varies compared to NREM</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Decreases from wakefulness</td>
<td>Increases (up to 30 percent) and varies from NREM</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>Decreases from wakefulness</td>
<td>Increases significantly from wakefulness</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Similar to wakefulness</td>
<td>Absent</td>
</tr>
<tr>
<td>Respiration</td>
<td>Decreases from wakefulness</td>
<td>Increases and varies from NREM, but may show brief stoppages; coughing suppressed</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>Increases from wakefulness</td>
<td>Increases and varies from wakefulness</td>
</tr>
<tr>
<td>Body temperature</td>
<td>Is regulated at lower set point than wakefulness; shivering initiated at lower temperature than during wakefulness</td>
<td>Is not regulated; no shivering or sweating; temperature drifts toward that of the local environment</td>
</tr>
<tr>
<td>Sexual arousal</td>
<td>Occurs infrequently</td>
<td>Greater than NREM</td>
</tr>
</tbody>
</table>

*NREM – Non-rapid eye movement REM – Rapid eye movement


Sleep stages
Based on experimental findings from physiological measurements (EEG, EOG and EMG), sleep can be divided broadly into two phases, each with independent functions and controls: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. In an adult human, the first one third of sleep is principally NREM or slow-wave sleep and the most REM sleep occurs in the last third of the sleep cycle (Carskadon & Dement 2005). NREM sleep comprises 75 to 80% of the total sleep period in adult humans and is categorized into four stages (NREM stages 1 to 4) as per the traditional Rechtschaffen and Kales scoring manual(Rechtschaffen & Kales,1968). However, the American Academy of Sleep Medicine (AASM) published a sleep scoring manual in 2007, which only divides sleep into three stages (N1, N2, N3) based on EEG findings (Iber et al.,2007).
REM sleep comprises the remaining 20 to 25% of the total sleep period (Chokroverty, 2010). A well-defined characteristic of REM sleep is rapid eye movements in all directions and abolition of skeletal muscle activities throughout the body (except the diaphragm and extraocular muscles) (Wills & Garcia, 2002). Blood pressure and heart rate fluctuate and irregular respiration and tongue movements also occur (Chokroverty, 2010). NREM sleep is characterized by a general reduction in responsiveness to external stimuli associated with slow eye movements (Czisch et al., 2004). As a result, the healthy adult experiences a sequence of stages from wakefulness to sleep onset to NREM and then to REM sleep. Each phase is associated with specific physiological characteristics involving brain activity which can be monitored by an electroencephalogram (EEG), muscle tone measured by an electromyogram (EMG), and eye movements detected by an electroculogram (EOG) (Carskadon & Dement, 2005; Fuller et al., 2006).

For more than 40 years, the only standard for describing the sleep process was the Manual of Sleep Classification devised by Rechtschaffen and Kales (Rechtschaffen & Kales, 1968). This manual divides sleep into seven distinct stages: wake, stage 1, stage 2, stage 3, stage 4, stage REM, and movement time. Although widely accepted, the rules of Rechtschaffen and Kales have been criticized for allowing subjective analysis (Danker-Hopfe et al., 2004). Consequently, there is enormous variation in the visual evaluation of sleep stages (Danker-Hopfe et al., 2004). Furthermore, the rules set down by Rechtschaffen and Kales were formulated for young healthy adults (Himanen & Hasan, 2000) and may not be relevant or directly applicable to elderly individuals.

The Manual of Sleep Classification by Rechtschaffen and Kales was revised in 2007 by the American Academy of Sleep Medicine (AASM) (Iber et al., 2007) and produced a new guideline for terminology, recording method, and scoring rules concerning sleep processes. The manual developed by the AASM (Iber et al., 2007) is an amalgamation of a review of the literature, analysis and consensus. It addresses seven topics: digital analysis and reporting parameters, visual scoring, arousal, cardiac and respiratory events, movements and pediatric scoring (Iber et al., 2007). A significant alteration is a change in terminology: in the AASM classification, sleep stages S1 to S4 (as per Rechtschaffen and Kales’ manual) are referred to as N1, N2, and N3; with N3 reflecting slow wave sleep and is a combination of Rechtschaffen and Kales stages S3 and S4 (Anderer et al., 2010). Stage REM is now called stage R, wakefulness is called W stage and the stage “movement time” has been eliminated from the AASM manual (Anderer et al., 2010). The AASM manual also states that 3 EEG derivations
must be recorded (Silber et al., 2007). The AASM manual has also other definitions such as the sleep-wake transition, slow wave sleep, REM sleep, arousals and major body movements (Moser et al., 2009). The ASSM manual also simplifies several context rules and the recommendation of sampling rates and filter settings for polysomnographic (PSG) reporting and user interfaces to aid computer-assisted sleep analysis (Iber et al., 2007).

**Physiological changes during sleep**
Changes occur is several body systems during sleep (Choudhary & Choudhary, 2009). These alterations do not cause major discomfort in healthy individuals, but may have a detrimental impact on fragile individuals, for example patients suffering from cardiovascular diseases (Parker and Dunbar, 2005). The physiological changes that occur during sleep are:

- **Cardiovascular:** Alterations in blood pressure and heart rate occur. For example, transient rises in blood pressure and heart rate occur with K-complexes¹, arousals, and large body movements (Blasi et al., 2003; Catcheside et al., 2002; Tank et al., 2003). These are predominantly regulated by the autonomic nervous system (Trinder et al., 2001). In addition, the risk of myocardial infarction in the morning is increased due to a sharp increase in heart rate and blood pressure that accompany awakening (Mulcahy et al., 1993);

- **Sympathetic-nerve activity:** A reduction in sympathetic vascular tone occurs during NREM sleep; but, due to the momentary increase in blood pressure and heart rate that follows K-complexes, a burst of sympathetic-nerve activity arises during NREM sleep (Wolk et al., 2005). There is an increase in sympathetic activity during REM sleep when compared to wakefulness (Somers et al., 1993). This may provide protection to the brain against potentially damaging intravascular pressure changes or hyperperfusion during REM sleep (Cassaglia et al., 2009).

- **Respiratory:** During REM sleep, ventilation and respiratory flow become accelerated and irregular (Krieger, 2000; Simon et al., 2002). Additionally, rib cage movement is decreased and upper airway resistance is increased due to the absence of tone in the intercostal muscles and upper airway muscles during REM sleep (Parker and Dunbar, 2005). Several factors are involved in hypoventilation during NREM sleep including

---

¹ Negative sharp wave which is immediately followed by a positive component from background activity on the EEG (Colrain et al., 2010).
diminished pharyngeal muscle tone (Krieger, 2000; Simon et al., 2002). Ventilation and respiratory flow usually show ineffective adaptive responses during sleep. Furthermore, the cough reflex is suppressed during both REM and NREM sleep (Lee & Birring, 2010). More generally, there is also a reduction in ventilatory responses to hypoxia and hypercapnoea during NREM sleep compared to wakefulness and further decreases occur during REM sleep (Choudhary & Choudhary, 2009). Similarly, the arousal response to respiratory resistance (resistance to breathing in or out) is lowest in stage 3 and stage 4 sleep (Douglas, 2005).

- **Cerebral blood flow:** During NREM sleep, cerebral blood flow and metabolism are drastically reduced (Zoccoliet al., 2002). However, total blood flow and metabolism in REM sleep are similar to wakefulness (Madsen et al., 1991a), but increase in the limbic system (involved with emotions), and visual association areas (Madsen et al., 1991b). Limbic lobe regions such as the anterior cingulate cortex (ACC) and posterior cingulate gyrus (PCG) are less activated during NREM sleep compared to wakefulness (Kaufmann et al., 2006).

- **Renal:** During sleep (REM and NREM) urine flow and excretion of sodium and potassium are reduced (Agarwal, 2007). These alterations in renal function during sleep are multifaceted and include changes in renal blood flow, glomerular filtration, hormone secretion, and sympathetic neural stimulation (Van Cauter, 2000; Buxton et al., 2002).

- **Endocrine:** Sleep regulates the secretion of growth hormones, thyroid hormone, and melatonin (Brandenberger et al., 2000; Shibui et al., 2003). Growth hormone secretion reaches a maximum during early sleep and usually occurs throughout slow wave sleep (Born & Wagner, 2009). Melatonin induces sleepiness by decreasing the alerting effect from the suprachiasmatic nucleus, and is influenced by the light-dark cycle, with its secretion being suppressed by light (Parker and Dunbar, 2005).

**Function of sleep**

Sleep has a restorative function and its requirement is a fundamental physiological need having similar homeostatic properties to hunger or thirst (Rohers et al., 2005). Mounting evidence emphasizes the importance of sufficient sleep showing it is highly correlated to the health of an individual. Several studies have demonstrated that disturbed sleep adversely
affects health contributing to ailments ranging from the common cold (Cohen et al., 2009), depression (Cole & Dendukuri, 2003) postpartum depression (Okun et al., 2009) and cardiovascular disease (Gangwisch et al., 2006; Meisinger et al., 2007). Therefore, disturbed sleep or sleep deprivation can affect the entire body, as a consequence of the multifaceted regulation of sleep by multiple brain regions, immune and endocrine factors, and various neurotransmitters (Benca & Quintas, 1997). In addition to health, several studies have shown that sleep is important for facilitating consolidation of memory and improved ability for learning (Lauderdale et al., 2006).

What controls sleep?
Sleep is controlled by a complex mechanism. Sleep and wakefulness are predominantly regulated by the reticular formation in the brainstem and the reticular activating system (RAS) in association with the thalamus (Cook,2008). These reticular systems network with NREM sleep mechanisms in the basal forebrain, generating slow wave electrical activity in the cerebral cortex (Cook, 2008). The REM sleep generator, located in the pons, periodically disrupts this process to reactivate the brain (Cook,2008). Wakefulness is caused by activating the brainstem and basal forebrain structures by a direct excitatory effect of orexins on cholinergic neurons in the basal forebrain and monoaminergic and cholinergic neurons in brainstem (Eggerman et al., 2001; Sakurai, 2007). This activation disrupts sleep cycles and causes stimulation and arousal of the nervous system (Amzica, 2002; Zisapel, 2007).

Sleep is also regulated by three important hormones synthesized in the pons: noradrenaline, acetylcholine and serotonin (also known as 5-hydroxytryptamine or 5-HT)(Cook,2008). Other regulatory hormones include orexin and hypocretin which are deficient in narcolepsy (Nishino et al., 2010). Regulation of circadian rhythms is achieved by the hypothalamus, specifically, the suprachiasmatic nucleus which is reset daily by light, and by melatonin released from the pineal gland during darkness (Datta and MacLean, 2007).

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2 Orexin and hypocretin are neuropeptide, produced in hypothalamic neurons, are fundamental regulators of sleep and wakefulness. These peptides activate wake-active monoaminergic and cholinergic neurons in the brain and hypothalamus stem to maintain a long, consolidated awake period. (Sakurai, 2007).
Role of Serotonin (5-HT) in the Sleep – wake cycle
There is much controversy surrounding the debate as to the role 5-HT plays in sleep regulation (Jouvet, 1999; Ursin, 2002). The literature of the 1960s and early 1970s indicated that NREM sleep requires the 5-HT system. If this system is not functional, possibly as a result of damage to the raphe nuclei (housing neuronal cell bodies producing 5-HT) or the exhaustion of 5-HT by p-chlorophenylalanine (PCPA- a 5-HT synthesis inhibitor), insomnia occurs which can be reversed by administering 5-hydroxytryptophan (5-HTP) (a precursor of 5-HT) (Jouvet, 1999; Ursin, 2002). However, from the late 1970s, the literature showed that 5-HT was responsible for the initiation and maintenance of slow wave sleep (SWS) (Monti, 2011). For example, by inducing a rise in the release and synaptic availability of 5-HT (by electrically stimulating the dorsal raphe nuclei (DRN)), wakefulness was stimulated (Cespuglio et al., 1979). Conversely, inactivation of DRN stimulates sleep (Cespuglio et al., 1979). The claim that 5-HT promoted wakefulness was supported by the rates of serotonergic raphe neuronal firing (Cespuglio et al., 1981; Lydic et al., 1987; McGinty & Harper, 1976; Trulson & Jacobs, 1979) and release of 5-HT (Cespuglio et al., 1990; Gemma et al., 1979; Portas et al., 1994; Portas et al., 1998). Furthermore, DRN activity is state-dependent; peaking throughout wakefulness, decreasing during NREM sleep, and ceasing to fire during REM sleep (Ursin, 2002). Indeed NREM sleep can be increased when 5-HT2 receptors are blocked (Dugovic, 1992). Serotonergic neurons in the DRN reduce the activity of neurons located in the preoptic area, the anterior hypothalamus and the adjacent basal forebrain which enhance sleep(Saper et al., 2001; Ursin, 2002). In addition, noradrenergic (brainstem) and hypocretinergic/orexinergic (hypothalamus) neurons promote wakefulness and also stimulate the activity of each other (Jones, 2005).

An endeavour to incorporate and unite these seemingly conflicting data led to the hypothesis that 5-HT directly stimulates wakefulness and also promotes the synthesis and/or release of factors which induce sleep (Jouvet, 1999). Serotonin subtype receptors (5-HT1A and 5-HT2) are involved in sleeping and waking (Bjorvatn & Ursin, 1998; Ursin, 2002) Sleep occurs as a result of the 5-HT inducing the release of sleep-promoting factors which inhibit neurons involved in stimulating wakefulness (Jouvet, 1999). Studies conducted on rats and mice indicate that regulation of arousal states by 5-HT relies on the degree and timing of activation of the 5-HT system and the time that has elapsed following activation (Imeri et al., 2005; Imeri et al., 2000; Morrow et al., 2008). Enhancement of 5-HT release, by administration of 5-hydroxytryptophan, results in the initial response being an increase in wakefulness and a
decrease in NREM sleep (Imeri et al., 2005; Imeri et al., 2000; Morrow et al., 2008). This rapid increase strongly indicates a direct effect of 5-HT. However, if the dose of 5-hydroxytryptophan is too low, activation of the 5-HT system may be insufficient to stimulate sleep-inducing factors, as the 5-HT activation needs to be maintained for sufficient time. A higher physiological dose of 5-hydroxytryptophan results in an increase in NREM sleep, following a short delay, (Imeri et al., 2005; Imeri et al., 2000; Morrow et al., 2008). This delayed increase in NREM sleep constantly happens in the dark stage of the light-dark cycle, independent of when 5-hydroxytryptophan was administered (Imeri et al., 2005; Imeri et al., 2000; Morrow et al., 2008). These findings indicate that the exact consequence of serotonergic activation on sleep-wake behaviour rely on both the degree and timing of activation.

The data generated from the studies discussed above concur with observations that administration of selective serotonin re-uptake inhibitors over a short period of time increases wakefulness first and then increases NREM sleep (Ursin, 2002). The earliest studies exploring the relationship between 5-HT and sleep only reported behavioural observations and did not contain polygraphically defined determinations of vigilance states (Ursin, 2002). Even so, these studies showed biphasic responses to administration of 5-HT in which behavioural ‘activation’ was followed by ‘depression’ (Ursin, 2002).

Serotonin suppresses REM sleep

Serotonergic neurons in the raphe nuclei and noradrenergic neurons in the locus coeruleus, are regarded as part of the mechanisms that regulate REM sleep by inhibiting the neurons that promote REM sleep (Lu et al., 2006; McCarley, 2007). Reduced serotonergic activity allows generation of REM-sleep, consistent with findings that inhibition of the 5-HT system by pharmacological agents stimulates REM sleep whereas stimulation of 5-HT synaptic availability hinders REM sleep (Ursin, 2002). Thus, experimental findings show that administration of 5-hydroxytryptophan activates the 5-HT system which inhibits REM sleep, irrespective of the dose and timing of administration (Imeri et al., 2000; Imeri et al., 2005; Morrow et al., 2008). The finding that mice deficient in 5-HT1A or 5-HT1B receptor subtypes experience longer REM sleep than control mice indicates that 5-HT1A or 5-HT1B receptor subtypes mediate REM sleep inhibition by 5-HT (Adrien et al., 2004). A similar response is found by blocking the same receptor subtypes with pharmacological agents (Adrien et al., 2004). Naturally, this does not preclude 5-HT inhibiting REM sleep by interacting with
other 5-HT receptor subtypes. In conflict with the ‘REM-off’ role of 5-HT, findings which show that a 5-HT₁ receptor antagonist inhibits REM sleep (Hagan et al., 2000) and people deficient in 5-HT₁ receptors spend a shorter time in this phase of sleep (Hedlund et al., 2005) suggest that 5-HT may play a facilitator (or permissive) role in regulation of REM-sleep via this specific receptor subtype.

**Insomnia**

**Definition of insomnia**
Insomnia is defined according to the International Classification of Sleep Disorders (ICSD) as an almost nightly complaint of insufficient sleep or the feeling of being unrested after the habitual sleep period (International Classification of Sleep Disorders: Diagnostic and Coding Manual, 1990). Insomnia criteria have also been specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (Diagnostic and Statistical Manual of Mental Disorders, 1994) as difficulty initiating sleep (sleep onset), maintaining sleep (sleep maintenance), and/or poor quality of sleep (non-restorative sleep) for at least one month. Thus, the presence of long sleep latency (onset), frequent nocturnal awakenings, or prolonged periods of wakefulness during the sleep period or even frequent transient arousals are evidence of insomnia. As a result, insomnia can be thought of both as a symptom and as a sign.

**Why is insomnia a problem?**
Hajak (2000) estimated that one third of the adult population in the industrialized world experience sleep disorders. It impacts on all aspects of life – work productivity, family life and mental health (Léger & Bayon, 2010).

Insomnia is a common sleep disorder that is a significant health problem in Australia (Dollman et al., 2003). According to ‘Wake up Australia: The Value of Healthy Sleep’ (Access Economics, 2004), over 1.2 million (6%) Australians suffer from sleep disorders and insomnias are high prevalent. Insomnia is a very common complaint for presentation to medical practitioners (Attarian, 2000). Consequently, management of insomnia has become a major health challenge in Australia. The Bettering the Evaluation and Care of Health (BEACH) program (April 2006 and March 2008) found sleep disorders were managed
across Australia 2,987 times at a rate of 1.6 contacts per 100 general practitioners (GP) encounters which extrapolates to approximately 1.7 million GP visits annually across Australia (Charles et al., 2009). The research found that insomnia was more likely to be treated in female patients than males (Charles et al., 2009).

Age is a significant factor with sleep problems and, according to Ancoli-Israel (2005), occurs in over 50% of adults aged 65 and older (Ancoli-Israel, 2005). Age alters normal sleep patterns but it is not necessarily a factor for sleep disorders as total sleep time linearly decreases with age at a rate of approximately 10 minutes per decade (Ohayon et al., 2004). Foley et al (1995) found greater than 50% of people aged over 65 reported difficulty in initiating sleep and, after falling asleep, problems in maintaining their sleep. This issue can lead to daytime sleepiness, feelings of being un-rested, chronic fatigue and an increased risk of falls and accidents (Foley et al., 1995). Insomnia can also result in memory impairment and decreased productivity which has an impact on quality of life (Roth and Ancoli-Israel, 1999; Simon and VonKorff, 1997). Moreover, insomnia is a significant issue for older adults who suffer from ill health and depend on medications (Cook, J. & Ancoli-Israel, S. (2006) because many commonly prescribed medications have insomnia as a side effect (Kim et al., 2009). These medications are central nervous system stimulants (e.g. modafinil, methylphenidate), antihypertensives (e.g. β-blockers, α-blockers), respiratory medications (e.g. theophylline, salbutamol), chemotherapy, decongestants (e.g. pseudoephedrine), hormones (e.g. corticosteroids, thyroid hormones), psychotropics (e.g. SSRIs, atypical antidepressants, MAO inhibitors) and diuretics (Kamel & Gammack, 2006; Neikrug & Ancoli-Israel, 2010). Therefore, stimulating medications and diuretics should, wherever possible, be administered in the morning and sedating medications should be taken before bedtime. Insomnia has a higher prevalence in older women who are either separated, divorced or widowed (Leger et al., 2000), however, Doghramji (2006) found that the prevalence of insomnia also increased also in men over the age of 85.

Classification of insomnia:
The ICSD and DSM-IV list different classes of insomnia based on the cause (DSM-IV, 1994; ICSD, 1990). The DSM-IV differentiates between primary sleep disorders, sleep disorders related to other mental disorders, sleep disorders due to general medical conditions, and
substance stimulated sleep disorders (DSM-IV,1994). Likewise, the ICSD classifies insomnia as follows (ICSD, 1990):

- Intrinsic insomnia: e.g. psychophysiological insomnia, sleep state misperception;
- Extrinsic insomnia: e.g. inadequate sleep hygiene, environmental sleep disorder, hypnotic dependent sleep disorder;
- Insomnia associated with a mental disorder: psychoses, mood disorders, alcoholism;
- Insomnia associated with neurological disorders: dementia, parkinsonism, fatal familial insomnia; and
- Insomnia associated with other medical disorders: cardiac ischemia, nocturnal asthma, fibromyalgia, gastroesophageal reflux.

It is important to distinguish between primary and secondary insomnia to identify any associated conditions and ensure these conditions are treated appropriately rather than focusing solely on the insomnia alone.

The ICSD-2 codes insomnia under the broad heading of dyssomnias, either intrinsic or extrinsic sleep disorders (ICSD-2 2nd, 2005). Based on the severity, it classifies insomnia into three types as follows (ICSD-2 2nd, 2005):

1. Mild insomnia: almost nightly feeling of an insufficient amount of sleep or not feeling adequately rested. There is little or no evidence of impairment of social or occupational functioning, but there may be restlessness, irritability, mild anxiety, daytime fatigue, and tiredness.

2. Moderate insomnia: nightly feeling of an insufficient amount of sleep or not feeling adequately rested after the habitual sleep episode. There is mild or moderate impairment of social or occupational functioning and restlessness, irritability, anxiety, daytime fatigue, and tiredness are always present.

3. Severe insomnia: nightly feeling of an insufficient amount of sleep or not feeling adequately rested. There is severe impairment of social or occupational functioning with restlessness, irritability, anxiety, daytime fatigue, and tiredness.

It is important to differentiate between the different types of insomnia and investigate factors that could affect the onset, duration, remissions and relapses of insomnia. An accurate diagnosis is particularly important to determine appropriate therapies and indicate therapeutic success in relieving symptoms or preventing relapses.
Assessment of insomnia

The diagnosis of insomnia takes into consideration three main aspects:

- History of the sleep patterns of the patient;
- Medical history; and
- Psychiatric history (Sateia and Pigeon, 2004).

The sleep history requires a chronological review of sleep patterns from childhood (Pigeon, 2010). Assessing the sleep history can allow for the identification of the time of onset of insomnia and any factors which may have contributed to its initiation (Buysse et al., 2005). A sleep history should also include details of situations which have occurred during the patient’s life, a 24 hour sleep behavior diary, how an unsatisfactory night varies from a night in which the individual has experienced satisfactory sleep, identifying any sleep patterns that exist, any treatment the individual may have received and the extent of their success (Pigeon, 2010).

A component of the sleep history includes any investigations to identify any secondary causes of insomnia (Ward & Ward, 2006). Differential diagnosis involves differentiation of primary insomnias from a co-morbid insomnia (Pigeon, 2010). There are many reasons to delay commencing insomnia treatment including untreated or unstable medical or psychiatric conditions, substance abuse, stable medical conditions (e.g. gastroesophageal reflux disease, cardiopulmonary disorders, seizure disorders, some neuroendocrine disorders, sleep apnea, bipolar disorder), severe mental illness or active substance dependence, arthritis and urinary retention (Kim et al., 2009; Pigeon, 2010). Other authors recommend treating co-morbid conditions and insomnia concurrently as individual conditions could result in greater improvements in each than treating either separately (Roth, 2009).

Several self-report instruments are widely used for the assessment of sleep quality and daytime sleepiness (Buysse et al., 2008). Among the most popular are the “Pittsburgh Sleep Quality Index” (Buysse et al., 1989), which gives a global assessment of sleep and the Insomnia Severity Index (Bastien et al., 2001) designed for insomnia. The most constructive and helpful self-report measure is to keep a daily sleep diary for 1-2 weeks (Winkelman, 2009). A sleep diary records the time the patient goes to bed, an estimate of the time it takes for the patient to fall asleep, number of awakenings and the length of time a patient spends awake during the night, final awakening and time the patient gets out of bed (Pigeon, 2010). These data, averaged over the 1-2 week period, allows a patient’s sleep continuity, including latency to sleep, wake time, average time spent in bed, total sleep time and sleep efficiency.
(sleep time divided by time spent in bed) to be determined (Pigeon, 2010). A wrist-worn actigraph can determine objective measures of sleep (Sadeh, 2011). This device measures physical activity during sleep with an inbuilt 3-dimensional accelerometer and a light sensor (Paquet et al., 2007). The periods of time which are spent asleep and awake are determined by analyzing the movement data (Saddichha, 2010).

Although not as useful as a full-night polysomnographic recording, actigraphy is more reliable than sleep logs which depend on the patients’ recall of how many times they woke up or how long they slept during the night (Ancoli-Israel et al., 2003). Unless paradoxical insomnia or another sleep disorder (forexample, sleep apnoea) is suspected, polysomnography is not used in the routine diagnosis of insomnia (Kushida et al., 2005) because it can be invasive, high cost, and disruptive to sleep (Blackwell et al., 2008). Polysomnography is considered the gold standard as it combines measurements taken by an electroencephalogram (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), pulse oximetry, and air flow rate (Blackwell, 2008). Together, these measurements can reveal several findings such as periodic limb movement disorder, sleep apnoea, and narcolepsy (Krystal et al., 2002).

The Epworth Sleepiness Scale (ESS) rates the likelihood of becoming drowsy and dozing off during situations when one is normally awake such as: sitting and reading; watching television; sitting inactively in a public place; being a passenger in a car for an hour; lying down to rest in the afternoon; sitting and talking to someone; sitting quietly after lunch without alcohol or waiting at a traffic signal in a car (Johns, 1991). The ESS is rated on the following 4-point scale:

- 0 – no chance of dozing;
- 1 – slight chance of dozing;
- 2 – moderate chance of dozing; and
- 3 – high chance of dozing.

A total score higher than 16 across the eight questions (maximum possible score: 24) is suggestive of daytime drowsiness, while a score of 11 is indicative of a possible disorder characterized by excessive sleepiness.

A vital consideration for family members or primary care practitioners is that any assessment of sleep is not the norm in standard practice. Therefore, simple questions such as "how are you sleeping?" can reveal the presence of a chronic insomnia and could be used as a
screening tool in the community pharmacies. As the prevalence of insomnia is relatively high in the population, valuable information can be obtained from asking these simple questions, leading to a more comprehensive assessment of sleep or possibly a referral for dealing with insomnia.

**Role of the pharmacist**

Patients suffering from insomnia are likely to attempt self-treatment (Wickwire & Collop, 2010). Of these, approximately one-third decide to self-medicate (Daley *et al.*, 2009 & Bartlett *et al.*, 2008). A sleep health survey conducted in 2008 demonstrated that in Australia, 89% of patients with insomnia stated that they did not seek professional medical advice regarding their insomnia (Bartlett *et al.*, 2008). Studies revealed that alcohol and over-the-counter (OTC) sleep aids were typically used by insomniacs to self medicate (Sivertsen *et al.*, 2009; Drake *et al.*, 2003). Sedating antihistamines and herbal sleep promoting products are the only products available without prescription that are approved for insomnia treatment (Kippist *et al.*, 2011). In Australia, sedating antihistamines (in single ingredient products) are classified as Pharmacist Only Medicines, that is, a patient must discuss the appropriateness of the medicine with a pharmacist before purchase (Therapeutic Goods Administration, 2011). The prospect for pharmacists to act as a primary intervention delivery point is apparent.

In a study concerning pharmacies in the Greater Sydney Area (New South Wales, Australia), pharmacists providing medicines to treat obstructive sleep apnea, stated that they believed they should have an increased role in the treatment of sleep disturbances such as insomnia (Black *et al.*, 2007).

Kippist *et al* (2011) found that pharmacists should educate patients complaining of acute insomnia with regard to positive sleep health. However, pharmacists may require training about approaches for the management/treatment of insomnia. Acute insomnia should be managed before it progresses to chronic insomnia (Pigeon, 2010). Therefore, pharmacists have an important role to provide advice about positive sleep health practices to those presenting to a community pharmacy with acute insomnia (Kippist *et al.*, 2011). Pharmacists have an important role in screening sleep disorders such as insomnia and providing sleep health education. Implementing individual counseling and treatment recommendations for insomnia, will help to reduce the burden of disease and the risks of potential consequences.
Many medications can affect sleep and sleep patterns. These include:

- Stimulants (e.g. modafinil, methylphenidate);
- Antihypertensives (e.g. β-blockers, α-blockers);
- Respiratory medications (e.g. theophylline, salbutamol);
- Chemotherapy;
- Decongestants (e.g. pseudoephedrine);
- Hormones (e.g. corticosteroids, thyroid hormones);
- Psychotropics (e.g. SSRIs, atypical antidepressants, MAO inhibitors); and
- Diuretics (Kamel & Gammack, 2006; Neikrug & Ancoli-Israel, 2010).

Therefore, pharmacists have an important role to investigate other potential causes of insomnia when an antihistamine is requested as a sleep aid to improve quality use of medicines.

In an Australian study assessed practice, when over the counter pharmacist-only sleep medication (Restavit) was requested in the Australian community pharmacy setting, and found that only 30% of requests were handled entirely by the pharmacist (Kashyap et al., 2012). A history of symptoms and underlying causes of insomnia was only taken in 28% of the interactions (Kashyap et al., 2012). As the pharmacist is the primary point of contact for people who request assistance with insomnia, this suggests a gap in patient care in community pharmacy. Other authors have found that if a pharmacist investigates the underlying causes of insomnia, they can provide information on lifestyle changes that can reduce the risk of primary insomnia (Roth et al., 2007; Wolkove et al., 2007).

Epidemiology of Insomnia
Insomnia is frequently associated with being female and in the elderly (Ohayon, 2002). Other sociological and economical factors have been also correlated with insomnia (Ohayon, 2002). This section provides a commentary about several of these factors.

Gender
Several studies have provided strong evidence that insomnia is more prevalent in women, showing a higher rate of reported insomnia symptoms (Léger et al., 2000; Ohayon et al., 1997), daytime consequences (Hoffmann, 1999; Léger et al., 2000) and dissatisfaction with sleep (Yeo et al., 1996). A meta-analysis study reported that insomnia is approximately 1.4
times more prevalent among women than men (95% confidence interval: 1.28–1.55) (Zhang & Wing, 2006). This ratio has been shown to increase slightly after 45 years of age (Voderholzer et al., 2003). It has also been reported that women are twice as likely to be diagnosed with insomnia (Ohayon, 2002). Together, these findings suggest that an intrinsic factor in women may be a causative factor of insomnia. Owens et al (1998) and Punyahotra et al (1997) suggested menopause could be this intrinsic factor. A random sample study of 3243 subjects (aged ≥18 years) using phone interviews found that menopausal women exhibited higher rates of sleep disturbances than women who were pre-menopausal (Ohayon, 2006). Other studies disagree; most notably Young et al. (2003) assessed objective and subjective sleep quality of 589 premenopausal, perimenopausal, and postmenopausal women using objective measures (full in-laboratory polysomnography) and self-reported sleep problems. They found that menopause was not associated with decreased sleep quality (Young et al., 2003).

**Age**

Individuals of all ages complain of unsatisfactory sleep and the prevalence of insomnia increases with age (Ancoli-Israel and Ayalon, 2006; Wolkove et al., 2007), approaching 50% in those aged over 65 years (Ancoli-Israel, 2005; Hetta et al., 1999). In 2000, the National Institute of Aging in United States conducted a survey of 9000 metropolitan adults, and found that 28% of participants experienced disturbed sleep, reporting difficulty in initiating and maintaining sleep (Ancoli-Israel, 2000). In the USA, the rate of insomnia in the elderly is approximately 5% (Kamel and Gammack, 2006). Several studies indicate that elderly patients experience less slow wave sleep (SWS) and REM sleep (Ancoli-Israel, 2000; Ancoli-Israel and Ayalon, 2006). Consequently, the elderly spend most of the night in stage 1 and 2 light sleep. Australian estimates also show an increasing incidence of insomnia symptoms with age (Deloitte Access Economics, 2011).

Certain physiological changes occur with aging and have been correlated to detrimentally affecting sleep. One such physiological change that is known to occur with age is the circadian rhythm (Münch et al., 2005) where the timing and functioning is altered. As age increases, an individual feels sleepy earlier and consequently wakes up earlier (Carrier et al., 2002). In addition, decreased melatonin levels have been demonstrated in the elderly, reducing their ability to sleep (Dijk et al., 2000). As a consequence of a disrupted sleep patterns, there is a reduction in sleep quality and total sleep time, producing discontinuous sleep and multiple early morning stirrings.
Socioeconomic status
Several studies have demonstrated a relationship between socioeconomic status and frequency of sleep complaints (Grandner et al., 2010). These studies illustrate that individuals with a relatively low socioeconomic status exhibit a higher frequency of sleep complaints (Adams, 2006; Friedman et al., 2007; Hale, 2005; Lauderdale et al., 2006; Patel, 2007). Arber et al (2009) also reported that employment status is associated with sleep problems. Unemployed women have reported an increased frequency of sleep problems (Arber et al., 2009; Grandner et al., 2010) implying that these factors could be additive. Sleep complaints were attributed to other issues such as race/ethnicity, marital status, income, and educational level(Grandner et al., 2010). Men who are homemakers had a considerably higher incidence of sleep complaints that their female homemaker (Grandner et al., 2010). These findings indicate that various mechanisms may contribute to the susceptibility of men and women to sleep complaints. Grandner et al. (2010) suggested that sleep complaints reported by men may be influenced by the effects of both socioeconomic factors such as education, employment, and income in association with socio-demographic factors such as race, marital status and age.Gellis et al.(2005) found that the frequency of insomnia in individuals of lower education status was high, even after accounting for ethnicity, gender and age.

Marital Status
There is a lack of research efforts exploring the correlation between sleep complaint frequency and marital status. Hale (2005) found that single people were either short or long sleepers in comparison to married couples. Divorced individuals experience more sleep complaints than those who are married or single (Ohayon,2002).

Education and Income
It has been reported that individuals with a lower education status and lower income are more prone to insomnia (Hartz et al., 2007; Rocha et al., 2002). Such studies propose that there is an inverse relationship between degree of sleep complaints and the level of education achieved by both men and women; men of lower educational levels are more likely to exhibit sleep problems than women (Grandner et al., 2010). Studies involving multivariate analyses show that education and income status are independent of the prevalence of insomnia (Arber et al.,2009). A better indication to assess sleep problems including insomnia would be to analyze a combination of several factors such as age, gender, education and income status.
Causes of Insomnia

The most widely accepted model describing the characteristics of chronic insomnia, the 3-P model, was initially proposed by Spielman (Spielman, 1986 & Spielman and Glovinsky, 1991) and later refined by Morin (1993). The model addresses three main points: Predisposing conditions, Precipitating circumstances, and Perpetuating factors (Spielman, 1986 & Spielman and Glovinsky, 1991; Morin 1993).

Predisposing conditions include hyperarousal, familial history, and anxiety predisposition and may increase an individual’s susceptibility to develop insomnia (Morin, 1993). The recent advances achieved in the genetics of sleep disorders (Taheri and Mignot, 2002) will expand our understanding of these predispositions and also the invulnerabilities for developing insomnia by augmenting the current knowledge of circadian rhythm disorders, narcolepsy, and sleep apnea.

The most commonly studied predisposition is hyperarousal, more specifically cognitive hyperarousal (Bonnet and Arand 1995; Morin 1993, Perlis et al. 1997). Robertson et al (2007) demonstrated that patients suffering from insomnia are cognitively aroused and are less sleepy in the bedroom before sleep than individuals who do not suffer from insomnia. Functional neuroimaging has revealed that individuals with insomnia exhibit elevated activation during sleep from subcortical areas but reduced prefrontal cortical activation while the individual is awake (Nofzinger et al. 2004). This shows the brain activity of patients with insomnia is elevated during sleep and reduced during the wake state. These findings positively correlate with the symptoms of insomnia during the night and fatigue during the day. Nofzinger (2005) suggests that daytime fatigue may stem from the sleep deficit and unsatisfactory restoration of the prefrontal cortex during the previous night. The reduced prefrontal cortical activation during the day in insomniacs can be treated using multicomponent, nonpharmacological treatments, acting to enhance prefrontal activation during the day using cognitive behavioral therapy, body temperature and bright light interventions, sleep hygiene, and physical activity counseling (Altena et al. 2008).

A study conducted by Espie (2002), suggests that hyperarousal does not comprehensively elucidate the development of insomnia. Espie suggests that falling asleep is automatic, and can be disturbed and hampered by several factors (Espie, 2002). Therefore, hyperarousal and other variables which precipitate and maintain insomnia are mechanisms that hinder the
normal automatic process governing satisfactory and restorative sleep. Espie suggests that an
effective treatment such as Sleep stimulus control therapy can restore normal sleep and wake
mechanisms (Espie, 2002).

Precipitating factors such as illness, family, work and other aspects of life that induce stress
may detrimentally affect the sleep patterns of an individual (Bastien et al. 2004). The
preliminary reaction to sleep difficulty is usually worry and reflection about insomnia, and
this can predict whether acute symptoms will convert into a chronic condition (Bélanger et
al. 2006). As insomnia progresses, patients exhibit behavioral and cognitive responses that
gradually become maladaptive and feed into a cycle of insomnia. This may lead to the
development of increased arousal.

Maladaptive sleep habits (such as extended time in bed, irregular sleep-wake schedules,
irregular napping or sleep-incompatible activities in bed), dysfunctional cognitions (including
worry and unrealistic expectations) and arousal (physiologic, emotional, and cognitive) are
the perpetuating or maintaining factors that are targeted by insomnia treatments (Bootzin et al.
1996).

Circadian rhythm disorders are also a causative factor for insomnia (Bjorvatn & Pallesen,
2009). In combination, interaction of circadian and sleep homeostatic processes cause sleep
and wake timing (Achermann, 2004; Borbely & Achermann, 1999). The homeostatic
mechanisms involved in balancing sleep and wake states and are dependent on wakefulness
(Vitiello, 2009). With increasing wakefulness, the drive to sleep is increased (Vitiello, 2009).
Conversely, when sleep occurs, the drive is decreased. Therefore, wakefulness can lead to the
onset and maintenance of sleep throughout the night. Although daytime wakefulness in
individuals suffering from insomnia seems normal, sleep is difficult, and can become
disturbed. Thus, sleep homeostasis can become deregulated (Pigeon & Perlis, 2006). The
circadian clock regulates sleep and wakefulness (Zee & Manthena, 2007). Cues such as light,
meal times, and social activity aid the control of circadian rhythms (Harvey et al., 2011).
Maladaptive sleep behaviors, developed as a result of insomnia, can disturb the cues the
circadian clock needs to regulate the sleep - wake cycle (Pigeon & Perlis 2006).
Consequences of insomnia

Economic consequences
The annual cost of workplace accidents due to insomnia in Australia was estimated to be approximately A$1.9 billion (Hillman et al., 2006). A recent report shows that indirect costs related to sleep disorders and conditions attributable to them were estimated to be A$4.3 billion in 2010 (Deloitte Access Economics, 2011). These studies show that insomnia has financial consequences and the economic impact is increasing. More detailed analyses are available in the USA where insomnia is projected to have direct and indirect costs in excess of US$100 billion annually (Fullerton, 2006). The direct costs consist of physician visits, prescriptions and procedures have been estimated to cost US$13 billion per annum (Walsh & Engelhardt, 1999). In fact, Ozminkowski and colleagues suggest that insomnia costs a young adult patient approximately US$1,253 more in direct health care expenses than individuals who do not suffer from insomnia (Ozminkowski et al., 2007). The indirect costs linked with insomnia include motor vehicle and workplace accidents, reduced productivity, and absenteeism account for the majority of the economic consequences of insomnia. Patients with insomnia are two and a half times more likely to be involved in a motor vehicle accident as a consequence of unsatisfactory sleep and rest as opposed to individuals who do not suffer from insomnia (Hillman et al., 2006; Roth & Ancoli-Israel, 1999).

Cognitive, social and vocational consequences
A number of studies demonstrate that individuals with chronic insomnia experience more difficulty with intellectual, social and/or vocational functioning, as opposed to individuals who do not suffer from insomnia or have occasional bouts of insomnia (Drake et al, 2003; Léger et al, 2006; Szelenberger et al, 2000). There appears to be debate concerning the association of insomnia and cognitive activity. Many subjective studies report that there is a positive correlation between chronic insomnia and compromised cognitive performance (Carey et al., 2005; Roth & Roehrs, 2003; Shochat et al., 1999). In contrast, objective investigations have not discovered any reliable evidence of cognitive deficits in patients with chronic insomnia (Orff et al., 2007). According to Espie et al (2006) and Harvey (2002), this inconsistency may be related to an attentional bias for negative performance. However Orff and colleagues suggest that this discrepancy may be due to the patient’s appreciation of the fact that additional effort is needed to uphold normal performance (Orff et al., 2007).
Chronic insomnia is also linked to impaired social functioning, specifically, a reduced capability to deal with trivial annoyances and a decreased ability to appreciate time with family and social life. This is accompanied by impaired interpersonal relationships with spouses (Shochat et al., 1999). In regards to vocational aspects of life, patients with insomnia report a decrease in job satisfaction and productivity, and increased absence (Léger et al., 2006).

**Health consequences**

1. **Mood disorders**

   There is mounting evidence that insomnia plays a role in new onset and recurrent major depressive disorder (MDD) (Pigeon & Perlis, 2007). Several cross-sectional studies have been conducted to determine the incidence of both insomnia and depression (Livingston et al., 1993; Stewart et al., 2006; Taylor et al., 2005). These studies demonstrated that the prevalence of both disorders is relatively high and often are experienced by individuals of all ages, but particularly, in older patients and women (Livingston et al., 1993; Taylor et al., 2005. Overall, the prevalence of insomnia was 15% and that of depression is 8-9% (Benca, 2005; Tsuno et al., 2005). Baseline estimates of prevalence rates for insomnia and depression in a study based on the National Institute of Mental Health Epidemiologic Catchment Area data were 10% and 5% respectively (Ford & Kamerow, 1989). Among the patients suffering from insomnia, 23% were depressed while among patients with depression, 42% reported insomnia (Ford & Kamerow, 1989). A more stringent diagnostic approach was taken by Stewart et al. (2006) and the prevalence rates obtained from this study were 5% for insomnia and 3% depression. Of those with insomnia, 21% were depressed, whereas of those with depression, 40% had insomnia (Stewart et al., 2006).

   Generally, these studies show that the probability of experiencing depression as a consequence of insomnia background is approximately twice that of having insomnia in the context of depression. However the overall incidence of experiencing both conditions concurrently is the same regardless of the primary complaint.

   One recent study investigating and scrutinising clinical trial data obtained from a primary care-based depression intervention indicates that comorbid insomnia is a risk factor highly correlated with unremitting depression (Pigeon et al., 2008). Patients with insomnia that
persevered across a baseline and three month assessment had a reduced depression treatment response at 6 and 12 months compared to patients with insomnia at one or neither of the baseline and two month time points.

There is also a relationship between insomnia and suicide among adolescents. A study found suicide completers showed high rates of sleep difficulties including insomnia when compared with community controls both within the week preceding suicide and within their most recent depressive episode (Goldstein et al., 2008).

Insomnia is a risk factor for developing depression, although it is not the only contributing risk factor. Together these data demonstrate that incident and persistent insomnia can be predictive for new onset depression and recurrent depression.

2. Anxiety disorders & substance abuse disorders
Experimental data concerning the relationship between sleep disorders such as insomnia and generalized anxiety disorder (GAD) is more scarce. Mahendran et al (2007) conducted a retrospective chart audit involving patients presenting with insomnia, where GAD was the most common associated psychiatric disorder. However, causality was not assessed – merely association. Mahendran et al (2007) stated that sleep disturbance is a common symptom of several mood disorders including depression and GAD. A cross-sectional study showed that among individuals with insomnia, 36% presented with at least one anxiety disorder compared to only 19% of individuals who did not suffer from insomnia (Breslau et al., 1996). In insomniac patients, 8% also had GAD, 6% a panic disorder, 5% obsessive-compulsive disorder and 25% had various other phobias (Breslau et al., 1996).

Similar evidence shows that there is a strong correlation between substance abuse and sleep disturbances such as insomnia (Ford & Kamerow, 1989, Weissman et al., 1997, Breslau et al., 1996). Substance abuse was twice as prevalent in patients suffering from insomnia than those who do not experience insomnia (Ford & Kamerow, 1989, Weissman et al., 1997, Breslau et al., 1996). Patients with insomnia undergoing alcohol withdrawal treatment are also twice as likely to report using alcohol as a sleep aid than individuals without insomnia (Brower et al., 2001).

3. Medical disorders and conditions
A strong correlation exists between sleep and immunity (Krueger et al., 2001). Insomnia has been shown to be linked to alterations in innate immunity including reduced activity of
natural killer cells (Cover & Irwin, 1994; Irwin et al., 1996). Higher levels of interleukin-6 (IL-6) during the evening and a change in the circadian distribution of IL-6 and tumour necrosis factor α (TNF-α) from night to day have been reported by Vgontzas et al (2002). In addition, Burgos et al (2006) suggest that IL-6 secretion is negatively correlated with reported sleep quality duration of slow wave sleep. Although suggestive, these data do not provide solid evidence of a direct correlation between insomnia and an increased likelihood of developing an immune-mediated disease. Similarly, although evocative, the scarce data collected from studies concerning the consequences of insomnia on the adaptive immune system, do not definitively correlate insomnia to the development of infectious diseases.

Sleep disturbance (not necessarily insomnia) has been associated with Type II diabetes mellitus and glucose homeostasis dysregulation, gastrointestinal distress, and several chronic pain conditions (Gottlieb et al, 2005; Jarrett et al, 2000; Wilson et al, 2002). Insomnia has also been demonstrated to be highly prevalent in HIV-infected patients (Rubinstein et al., 1998). Longitudinal epidemiologic studies show that insomnia significantly increases the possibility of developing hypertension and cardiovascular disease (Phillips and Mannino, 2007; Suka et al, 2003). Suka et al (2003) assessed the effect of insomnia on the development of hypertension in Japanese telecommunication workers (n= 4,797 male) using the annual health check database were followed up for four years or until they developed hypertension. The result showed increased risk of hypertension was associated with insomnia [OR 1.96:(1.42-2.70)] (Suka et al., 2003). Phillips and Mannino (2007) followed 11,863 participants without cardiovascular disease and 8,757 participants without hypertension over 6 years, the result showed that insomnia was correlated to only a slight increase in the risk of developing hypertension [OR 1.2:(1.03-1.30)] and a larger risk of cardiovascular disease [OR 1.5:(1.1-2.0)].

While definitive evidence is yet to be obtained linking insomnia to psychiatric disorders, the available data make this a reasonable proposition. As consequences on society and individuals are substantial, research efforts and development of treatment strategies should be directed towards this disorder, although the current treatments are effective.
Treatment of Insomnia

1-Non-pharmacological treatment of Insomnia
A wide range of insomnia interventions involve psychological and behavioural treatments. During the 1970s and 1980s, the common treatments for insomnia were relaxation, paradoxical intention, and stimulus control therapy (Bootzin & Epstein, 2011). The 1999 review by the American Academy of Sleep Medicine (AASM) (Morin et al., 1999a), found the evidence supporting sleep restriction therapy and multicomponent treatment was limited, and these treatments were therefore rendered somewhat effective. Presently, multicomponent treatment packages are perceived to be effective and have increased in popularity (Nau et al., 2005). These usually include a combination of stimulus control therapy, sleep restriction therapy, and sleep hygiene and education and relaxation training (McCurry et al., 2007). Several cognitive behavioural therapy treatments for insomnia (CBT-I) studies dedicate particular sessions to cognitive restructuring (Morin et al., 1999b; Jacobs et al., 2004), during which incorrect understanding and outlooks taken by the patient are recognised, confronted, and transformed. Other CBT-I studies employ cognitive components during education that consider fallacies about sleep, sleep requirements, the relationship between sleep and aging, sleep loss, sleep drive, and circadian rhythms (Edinger et al., 2001; Epstein & Dirksen, 2007). Cognitive therapy has not been subjected to controlled testing as a single-component intervention for insomnia (Bélanger et al., 2006), but it has been subjected to trials in an open clinical series (Harvey et al., 2007). Therefore CBT is regularly recommended as an initial therapy, however the evidence supporting it as part of a multi-faceted treatment approach is strong.

Polysomnography has demonstrated the efficacy of multi-component programs (Edinger et al., 2001; Morin et al., 1999b), and the CBT component has shown better results than pharmacological treatment (Morin et al., 1999b). These studies were conducted on elderly patients suffering from primary insomnia and may not be generalizable. The findings of Lichstein et al (2000) indicated that CBT was also effective for secondary insomnia cases by demonstrating that insomniacs who also suffered from medical and psychiatric disorders were successfully treated using CBT. Using the multi-component program, Espie et al (2001) reported that two thirds of the participants exhibited sleep within the normal range following treatment. Therefore, in 2006 the AASM recommended the use of multi-component therapy and concludes that they are effective in the treatment of chronic insomnia (Morgenthaler et al., 2006).
Stimulus Control Therapy
The first non-pharmacological treatment exclusively designed for insomnia was stimulus control therapy (SCT), proposed by Bootzin (1972, 1977). Since its introduction, SCT has become the gold standard against which novel non-pharmacological interventions are tested (Bootzin & Epstein, 2011). The theory behind SCT is that the bed and bedroom no longer act as discriminative stimuli for sleep (Ebben & Spielman, 2009; Harsora & Kessmann, 2009). Insomniacs tend to associate the bed and bedroom with behaviours that are not conducive for sleep (Passarella & Duong, 2008) such as watching television, eating, reviewing the day’s events, planning, worrying, lying awake and becoming anxious and frustrated from trying to fall asleep. There is also a Pavlovian conditioning component where the bed and bedroom become conditioned stimuli for stress and frustration which accompany the experience of being unable to fall asleep (Bootzin & Epstein, 2011). SCT endeavours to reinforce the bed and bedroom as positive cues for inducing sleep, to weaken them as cues for behaviours that are not conducive with sleep, and to initiate a regular sleep-wake pattern (Pigeon, 2010).

The stimulus control instructions are as follows (Bootzin 1972, 1977):

1. Only lie down to go to sleep when sleepy;
2. The bed should only be used for sleep and not for other activities including reading, watching television, eating, or worrying in bed. The only exception to this rule is sexual activity;
3. If you cannot fall asleep quickly (within 10 minutes) leave the bedroom and move to another room until you feel sleepy;
4. If you still cannot fall asleep, repeat step 3. Do this as often as is necessary throughout the night;
5. Wake up and get out of bed at the same time every morning, regardless of how much sleep you achieved during the night to help achieve a consistent sleep rhythm; and
6. Do not nap during the day.

Establishing new sleep habits is important to overcome symptoms of insomnia and therefore, the bed and bedroom must be reserved for sleep and sexual activities only (Lande & Gragnani, 2010). By leaving the bed and bedroom when an individual cannot sleep reduces sleep anticipatory anxiety, dysfunctional sleep-related cognitions, and arousal (Morin &
Epsie, 2003). In addition, this will also probably increase the individual’s sleep debt and homeostatic sleep drive. Undergoing SCT increases the likelihood that the patient will quickly fall asleep and stay asleep throughout the night, thus reinforcing the bed and bedroom sleep (Morin, 2004). Furthermore, abiding by a set time for waking each day will affect the circadian clock and allow the development of a regular sleep-wake schedule (Morin, 2004). The procedures and instructions of SCT are thoroughly rationalised and explained to patients before they undergo treatment (Bootzin & Epstein, 2000). Meta-analyses and systematic reviews (Morin et al., 1999a; Morin et al., 2006) indicate that SCT is extremely effective, and is probably the most successful, single-component non-pharmacological intervention for insomnia. Despite its lack of testing as a single intervention during the past decade (Pallesen et al., 2003, Reidel et al., 1998), SCT is frequently included in multicomponent interventions (Lichstein et al., 2000; Morin et al., 1999b; Morin et al., 2004; Rybarczyk et al., 2002).

**Sleep Restriction Therapy**

Spielman et al (1987) devised a behavioural treatment for insomnia known as sleep restriction therapy (SRT). SRT is based on the fact that patients suffering from insomnia waste too much time in bed trying to sleep, leading to greater wakefulness, disrupted sleep, and variability in the timing of sleep and wake. SRT focuses on consolidating sleep and initiating and maintaining a steady sleep-wake schedule by reducing the time the patient spends in bed, this will maximise the homeostatic drive for sleep (Vitiello, 2009) reversing unregulated sleep homeostasis which is the consequence of a long period to get to sleep commonly seen in insomniacs. The update issued by AASM in 2006 suggests that SRT is effective and, as per their guidelines, is recommended in the treatment of chronic insomnia (Morgenthaler et al., 2006).

A personalized sleep-wake schedule involves reducing the time spent in bed to the estimated average time the individual spends asleep (Harvey & Tang, 2003). This is usually determined during two weeks at least of the patient maintaining sleep diaries (Petit et al, 2003). The therapist and the patient then decide allowable time in bed for the following week (Taylor & Roane, 2010). A bedtime is then determined that allows the patient an amount of time in bed equivalent to the baseline average total sleep time (Taylor & Roane, 2010). For example, if the mean total sleep time is 5.5 hours, and the wake time is 5:30 am, then a bedtime is set at midnight for the first week of treatment. During treatment, the bedtime is extended 15 -30 minutes each week, depending on the sleep experienced the preceding week (Spielman et al., 1987).
Wohlgemuth & Edinger (2000) suggest that the time spent in bed is possibly less than what is required as the total sleep time. The concept of ‘total sleep time’ is frequently underestimated by insomniacs (Smith et al, 2002). Consequently, partial sleep deprivation results, an increase in the homeostatic sleep drive occurs and sleep consolidation occurs (Morin, 2004). Thus, patients develop a regular sleep-wake cycle (Spielman et al, 1987). These individuals are not prescribed less than 5.5 hours in bed (Taylor & Roane, 2010). The treatment plan usually takes six weeks to notice an improvement (Rubenstein et al. 1990), although Spielman & Glovinsky (1991) advise a treatment period of eight weeks. As six weeks is required to notice an improvement in patients, the study could be enhanced by extending the period of the experiment to at least 10-12 weeks.

SRT has commonly been used as a single treatment (Friedman et al. 2000) and has become included in multicomponent treatments (Edinger et al., 2001; Espie et al., 2001). Studies which conducted a follow up of patients undergoing SRT, demonstrated that these patients continue to experience restricted sleep following 6–12 months post-treatment, increasing total sleep time and sleep efficiency (Spielman et al., 1987; Friedman et al., 2000). An adjustment of SRT is sleep compression. This involves steadily decreasing the time spent in bed over the course of the treatment rather than the abrupt decline used in SRT (Spielman et al., 1987). Studies show that older adults with insomnia experience more success with sleep compression (Lichstein et al., 2001; Reidel et al., 1995).

**Sleep Hygiene and Education**

Sleep hygiene and education (SHE) involves educating the clients on sleep and providing advice on lifestyle choices concerning sleep hygiene (Harvey & Tang, 2003). Sleep education informs individuals about several aspects of sleep including sleep processes and function, developmental changes which occur during sleep, sleep homeostasis, circadian rhythms, and individual sleep requirements (Bootzin et al., 1996; Lacks, 1987). Sleep hygiene is a set of rules designed to improve sleep experienced by individuals. Such rules are, for example, to place the bedroom clock out of sight and to avoid consumption of caffeine (4 hours before bedtime), nicotine (2 hours before bedtime) and alcohol (2 hours before bedtime) (Hauri, 1991; Pallesen et al., 2001; Yang et al., 2010). Experts in the field have not yet agreed upon a standard definition for sleep hygiene (Stepanski & Wyatt, 2003), and consequently, the phrase is often erroneously used by healthcare providers to refer to stimulus control therapy (SCT) (Edinger & Wohlgemuth, 1999). There are no studies documented in the literature that employ the same set of sleep hygiene instructions. Although there is a principal set of sleep
hygiene instructions, specific recommendations are varied (Stepanski & Wyatt, 2003). A critical strategy used in insomnia intervention is education, (Morin et al., 1999a), which helps patients suffering from insomnia to understand theory-based interventions such as SCT and sleep restriction therapy (SRT). Therefore, SHE is usually provided during the early stages of the cognitive-behavioural treatment (CBT) intervention period (Morin et al., 1999a). Although the effectiveness of SHE is limited (Morin et al., 1999a), it is still a vital part of multicomponent intervention studies (Edinger & Sampson 2003; Espie et al., 2007; Morin et al., 2004; Reidel, 2000).

**Cognitive Therapy**

Cognitive therapy is a component of CBT and is a successful means of treating insomnia (Morin, 2004). There are two types cognitive therapy used to treat insomnia. The first is a cognitive therapy devised by Morin (1993) which is based on Beck’s therapy for depression (Beck et al., 1979). This therapy uses a cognitive restructuring approach that targets the erroneous beliefs and attitudes about sleep harboured by insomniacs. The second cognitive therapy is Harvey’s (2005) approach which focuses on cognitive processes which sustain insomnia. These include observing sleep related threat, misperceptions of sleep and daytime deficit, and behaviours that support obstructive beliefs (Harvey, 2005).

Although the two therapies target beliefs and attitudes about sleep, they employ different approaches to achieve the therapeutic goal of treating insomnia.

**Cognitive Restructuring**

Cognition plays a significant role in the manifestation of insomnia (Morin, 1993). The primary targets of cognitive restructuring are the dysfunctional cognitions and sleep disturbing thoughts concerning insomnia harboured by individuals suffering from insomnia (Milner & Belicki, 2010). These included impractical sleep expectations, misperceptions about the causes of insomnia and misguided perceptions of the consequences of insomnia (Bélanger et al. 2006). Cognitive restructuring treatment is personalized and begins with the identification of the problems specific to the patient. This is achieved by examining specific examples of disrupted sleep and asking the patient to complete a questionnaire entitled ‘Dysfunctional Beliefs and Attitudes about Sleep’ (Morin et al., 1993). The dysfunctional cognitions which are held by the patient are challenged and reformed using various psychological techniques. Multicomponent treatment studies in regards to insomnia have included cognitive restructuring as a component of the treatment (Morin et al., 1999b, Morin et al., 2004).
Cognitive Therapy for Insomnia

Based on previous theoretical work concerning cognitive processes which occur during insomnia and success of cognitive therapy in other psychological disorders, Harvey developed a cognitive model (Harvey, 2002) and therapy (Harvey, 2005) for insomnia. This model suggests that cognitive processes which maintain insomnia include daytime variables (Harvey, 2002). The five actions that maintain insomnia are worry, selective attention to and monitoring for sleep-related threats, misperception of sleep and daytime deficits, unhelpful beliefs about sleep, and counterproductive safety behaviours (Harvey, 2005). The cognitive therapy for chronic insomnia (CT-I) developed by Harvey occurs in three stages (Harvey, 2005). The first stage (conceptualisation) involves the therapist and patient developing a personalised cognitive model of daytime and night-time issues that explain the errant cycles experienced by the patient (Harvey, 2005). The intervention phase (second stage) uses the day time and night time models for experiments designed and employed by the patient to test and revert processes which are involved in maintaining insomnia (Harvey, 2005). The final stage of CT-I deals with findings recorded during the behavioural experiments, identification of treatment gains, relapse prevention, and setting goals to maintain the benefits achieved throughout the treatment (Harvey, 2005).

A trial of Harvey’s approach (Harvey et al., 2007) involving 19 patients receiving individual treatment from 6 to 22 sessions (average 14) demonstrated a major enhancement in sleep and reduction in daytime impairment that was sustained through a one year follow-up period. Although these findings are promising, there was no control group in the study, and several sessions were provided which reduced cost-efficiency compared to other treatment options.

2-Complementary and Alternative Medicines (CAM)

Acupuncture

Acupuncture is a widely accepted alternative medicine that involves inserting thin needles into meridian points around the body (Sok et al., 2003). A few studies have assessed the efficacy of acupuncture in the treatment of insomnia by utilising polysomnography, particularly those conducted by Montakab (1999) and Spence et al (2004). While both of these studies provided evidence supporting improved sleep with acupuncture, the study conducted by Spence et al (2004) was not placebo-controlled. The placebo acupuncture simulates the acupuncture procedure without penetrating the skin (Streitberger & Kleinhenz, 1998). This study also showed an increase in secretion of nocturnal endogenous
Spence et al. (2004) also found decreased stress/anxiety experienced by patients compared to pre-treatment levels. This was measured using State-Trait Anxiety Inventory form which is a questionnaire involving two, 20-item scales designed to gauge state and trait anxiety (Spielberger, 1972). The majority of studies conducted on acupuncture mainly report subjective measures to evaluate patient satisfaction, subjective relief of symptoms, and duration of sleep (Spence et al., 2004). Although the results of this study are subjective, from a patient’s perspective, acupuncture appears to be extremely successful (Sok et al., 2003).

Yeung et al. (2009) conducted a randomised, single-blind, placebo-controlled, parallel-group to evaluate the short-term efficacy of electroacupuncture for the treatment of primary insomnia. The study involved 60 Chinese adults who report having insomnia 3 or more nights per week (Yeung et al., 2009). Participants were either subjected to electroacupuncture 3 times per week for 3 weeks or placebo acupuncture “non-invasive acupuncture” connected to the same electric stimulator but with zero frequency and amplitude (Yeung et al., 2009). Yeung et al. (2009) did not demonstrate any significant difference between the placebo acupuncture and the electroacupuncture. Although, a placebo-needle does not penetrate the skin, the patient feels that penetration (Streitberger & Kleinhenz, 1998). The placebo needle has been shown to be sufficiently reliable (Streitberger & Kleinhenz, 1998; White et al., 2003) to be used in research of the effects of acupuncture (Streitberger & Kleinhenz, 1998).

Huang et al. (2009) conducted a study to evaluate the therapeutic effects of needle-rolling acupuncture therapy for chronic insomnia. A total of 180 chronic insomniacs were randomly divided into two groups, a treatment group (90 cases) treated by the needle-rolling therapy and a positive control group (90 cases) treated with clonazepam (Huang et al., 2009). The treatment course for both the two groups was 5 treatments per week for 4 weeks (Huang et al., 2009). The therapeutic effects were evaluated based on improvement of symptoms as assessed in traditional Chinese medicine and the Pittsburg's sleep-quality index (PSQI) (Huang et al., 2009). The needle rolling group showed significant improvement in the effective rate, the total score of PSQI, and in the scores of sleep-quality, sleep-efficiency, hypnotic and daytime function (Huang et al., 2009). However, after a 3-month follow-up period, no significant difference between the two groups was observed for the effective rate, but there were still significant improvements in the needle rolling group in sleep-efficiency, hypnotic, and daytime function of the PSQI (Huang et al., 2009).
Wang et al (2008) carried out a randomised single-blind trial to determine the efficacy of short-term abdominal acupuncture as a treatment for insomnia in Chinese women over two weeks. Forty-four patients between the ages of 22 and 56 were divided into two groups: acupuncture (n = 23) or medication (n = 21) group (Wang et al., 2008). The acupuncture group received abdominal acupuncture once a day for the first three days and once every three days for the remaining duration of the study (Wang et al., 2008). In addition, they also received a placebo tablet once a day (Wang et al., 2008). Subjects in the medication group were treated with sham acupuncture and received an effective dose of 1mg of the benzodiazepine derivative estazolam (positive control) once a day (Wang et al., 2008). The effect of abdominal acupuncture in relieving insomnia was more effective than the estazolam and sham acupuncture treatment in adult women (Wang et al., 2008). Although, this study confirms abdominal acupuncture to be an effective treatment for insomnia, it had two main drawbacks: the small sample size and the short time span of the study. Furthermore, due to the short testing period, this study did not conduct any follow-up and thus could not comment on the potential effectiveness and side effects of prolonged acupuncture use.

Da Silva et al (2005) studied the effects of acupuncture on pregnant women who suffered from insomnia compared to patients undergoing conventional treatment alone (sleep hygiene). The study examined 30 conventionally treated pregnant women who were divided into two groups: study group (hygiene and acupuncture) and control group (sleep hygiene only (Da Silva et al., 2005). The study group consisted of 17 patients with the remaining 13 patients in the control group (Da Silva et al., 2005). The patients were all treated for 8 weeks (Da Silva et al., 2005). This study demonstrated that acupuncture alleviated insomnia during pregnancy with the study group showing a statistically significant decrease in insomnia than the control group (Da Silva et al., 2005). Although this study showed that acupuncture was effective for the treatment of insomnia, objective measures such as polysomnography and actigraphy were not used for the evaluation of insomnia. Patients were asked to give a single rating on a Numerical Rating Scale (NRS) of zero to 10, where zero represented good sleep and 10 the worst insomnia possible. Using a scale such as the NRS used in this study cannot be taken as an objective measure. Nonetheless, subjective self-reported measures indicate the impact on the individual, however, more reliable data may be generated by using objective measures such as polysomnography and actigraphy.

Nordio and Romanelli (2008), evaluated the efficacy of an acupressure device, heart 7-insomnia control consisting of “a soft rubber pin, kept in place by an adhesive plaque”
This device was positioned on heart 7 points (HT7 points) located on the wrists in 20 insomniacs, every night for 3 weeks compared to a placebo treatment in which the device was placed on non-HT7 points in 20 insomniacs (Nordio and Romanelli, 2008). The results of this study indicated that the device H7-insomnia control is more effective in enhancing the quality of sleep in insomniacs, than the placebo treatment.

Chen et al (1999) tested the efficacy of acupressure in improving the sleep quality of insomniacs. This study included 84 patients divided into 3 groups, each consisting 28 patients. The groups were the acupressure group, a placebo acupressure group, and a control group (Chen et al., 1999). The same massage routine was used in the acupressure group and the placebo acupressure group, with different acupoints and conversation whereas only conversation was used in the control group (Chen et al., 1999). This study found that acupressure was significantly more effective than both the placebo acupressure and control treatments in the PSQI total score, sleep latency, sleep duration and sleep quality (Chen et al., 1999).

In summary, acupuncture is effective at improving sleep quality and duration. However, these apparently positive results must be integrated with clinical trials. Thus, the beneficial effect of acupuncture may be as a result of the small sample sizes or short follow-up periods used and need to be confirmed in large and rigorously designed randomised controlled trials.

**Valerian**

Valerian is a flowering plant which approximately 200 species (Komori et al., 2006). The species *Valeriana officinalis* is commonly employed in the treatment of insomnia and anxiety (Benke et al., 2009; Bent et al., 2006). Valerian is extracted using a variety of extraction methods either aqueous or ethanol extracts (Wheatley, 2005), with differing yields. The aqueous extraction method yields approximately 270–900 mg of valerian extract while the ethanolic valerian extraction produces 300–600 mg of valerian extract (Taibi et al., 2007). Valerian results in sedation most likely by the inhibiting the breakdown of γ-aminobutyric acid (GABA) or GABA-like metabolites (Ringdahl et al., 2004). Moreover, Muller et al (2002) published *in vitro* research which revealed another mechanism of action, finding valerian binding at A1 adenosine receptors; however, the *in vivo* implications of this research remain unclear.

One study (n = 128) of valerian examined the effects of an aqueous valerian extract administered in doses of 400 mg to participants who were “good sleepers” (comprising 52%
of participants) and “poor sleepers” (comprising 48% of participants) in a randomized, double-blinded, placebo-controlled crossover study (Leathwood et al., 1982). Subjective sleep latency and sleep quality were significantly improved (Leathwood et al., 1982). Elderly “poor sleepers” reported the most considerable improvement in sleep quality (63%) (Leathwood et al., 1982). However, almost half of this group (43%) was treated with placebo, and the difference was not statistically significant (Leathwood et al., 1982). In younger individuals who considered themselves as poor sleepers, valerian significantly improved sleep quality (Leathwood et al., 1982). No difference between placebo and valerian concerning subjective daytime sleepiness was reported (Leathwood et al., 1982). The major limitation of this study was the lack of data for objective sleep measures.

In an uncontrolled study conducted by Dominguez et al (2000), patients suffering from insomnia who were receiving mental health services were given valerian for two weeks to complement their psychotropic program. The initial dose of valerian was 470 mg and was administered on nights 1–3 (Dominguez et al., 2000). The dose was increased to the maximum dose of 1,410 mg after the first week if patients found lower doses to be ineffective (Dominguez et al., 2000). After one week of treatment, 11 of the 20 participants reported a “moderate” improvement in their sleep quality at a mean valerian dose of 940 mg (Dominguez et al., 2000). By the second week, all participants had raised their dose to 1,410 mg (Dominguez et al., 2000). Nine rated their insomnia “moderately to extremely” improved, while six patients rated their insomnia “extremely” improved (Dominguez et al., 2000). However, Dominguez et al (2000) neglected to mention which features of their sleep disturbances were improved.

Coxeter et al (2003) conducted a study where 450 mg of valerian was administered to chronic insomniacs for a period of one week during which the participants kept a sleep diary. Coxeter et al (2003) could not demonstrate that valerian was more effective than a placebo in a series of randomized n-of-1 trials (Coxeter et al., 2003). Similarly, Jacobs et al (2005) conducted a randomized, double-blind, placebo-controlled trial using a novel Internet-based design showed that a dose of 6.4 mg of valerenic acids which is an active ingredient of valerian (Dietz et al., 2005) given for 28 days did not significantly reduce insomnia or anxiety in comparison to a placebo in an Internet-based study (Jacobs et al., 2005). However, there are doubts about the results generated by Jacobs et al (2005) as the dose administered appears to be very low, but it is difficult to extrapolate an equivalent dose of valerian due to no information being provided about the valeric acid concentration in the product(s) used. The
use of the Internet in the literature is limited and internet recruitment of participants may lead to samples containing dubious representativeness. In particular, obtaining external validity may pose a problem (Braithwaite et al., 2003). It remains unclear as to whether randomised controlled trials can be conducted solely using the Internet. Thus, the results obtained by Jacobs et al (2005) may not be valid.

In a randomised, crossover, double-blind, placebo-controlled trial carried out by Balderer & Borbély (1985), an aqueous solution of valerian extract was administered to 18 participants who did not experience sleep problems. Of these participants, 8 attended polysomnographic studies and were given either placebo or valerian (900 mg) for 5 nights in a laboratory setting (Balderer & Borbély, 1985). The remaining 10 participants were monitored for wrist-activity and were given either placebo, valerian (450 mg) or valerian (900 mg) over a period of 3 nights at home (Balderer & Borbély, 1985). In the laboratory study, the latency to stage 2 sleep was reduced from an average of 25.4 minutes to 19.2 minutes and wakefulness after sleep onset decreased from an average of 29.6 minutes to 19.0 minutes (Balderer & Borbély, 1985). However, these results were not statistically significant, probably due to the small sample size. Conversely, in the home study, valerian significantly enhanced sleep latency and wake time after sleep onset in a dose-dependent manner when comparing 450 mg and 900 mg doses. However, there was no reported change in sleep quality and data concerning wrist activity was inconclusive (Balderer & Borbély, 1985). The participants exhibited a considerable increase in activity during the middle third of the night when administered valerian (900 mg), in comparison to placebo, but this nighttime activity was reduced in the last third of the night (Balderer & Borbély, 1985). Also, there were mixed results regarding objective assessments of sleep latency. Although this study provides insights into the effect of valerian on sleep, its major limitation is the fact that valerian was only administered for 1 or 2 nights in to participants who did not complain of sleep disturbances.

Leathwood & Chauffard (1985) evaluated the effect of an aqueous valerian extract (450 mg and 900 mg doses) and placebo in 8 patients suffering from insomnia by recording objective measures (wrist actigraphy). The results revealed a reduction in sleep latencies following a 450 mg dose of valerian for four non-consecutive nights (from 15.8 ± 5.8 minutes to 9.0 ± 3.9 minutes, $P < .01$) (Leathwood & Chauffard, 1985). Conversely, a dose of 900 mg did not produce additional improvements in sleep latency and the higher dose yielded a considerably higher rate of morning sleepiness (Leathwood & Chauffard, 1985). However, in contrast to
the previous study, increasing the dose of valerian to 900 mg did not show any additional benefit. In fact, the 900-mg dose led to a significant increase in morning sleepiness.

Schulz et al (1994) conducted a placebo-controlled study, using polysomnography, to elucidate the effect of valerian in elderly patients experiencing disturbed sleep. Eight elderly insomniacs were given valerian and 6 were administered a placebo (Schultz et al., 1994). The participants took valerian (450 mg) or placebo 1 hour before retiring on day 1 of the study, and on days 2-8, they took valerian or placebo 3 times a day with food but not at bedtime (Schultz et al., 1994). Participants given valerian exhibited no change in sleep efficiency, however, Valerian was shown to reduce the proportion of stage 1 sleep with no change was seen in the placebo group (Schulz et al, 1994). Slow wave sleep (SWS; sleep stages 3 and 4) showed a significant gradual increase to night 8 but REM sleep was unchanged by valerian (Schulz et al., 1994). However, when compared to placebo, no differences in polysomnographic parameters were observed in the valerian group, neither was there a change in sleep quality and day or evening alertness (Schulz et al., 1994). The limitations of this study include its small sample size and the fact that many vital sleep parameters, including sleep latency, were different between the participants who were given placebo or valerian.

Using polysomnographic measurements, Donath et al (2000) compared the effects of using valerian for 1 night against a 14-day period in a randomized, double-blind, placebo-controlled trial of 16 insomnia patients administered 600 mg of valerian-root extract. Donath et al (2000) reported that one 600mg dose of valerian did not considerably alter subjective or objective sleep measures. However, following a 14-day period, significant changes were observed including reduced subjective sleep latency and a reduced objective latency to slow-wave sleep when compared to placebo (Donath et al 2000). However, no alterations in subjective sleep quality or other objective measures including sleep efficiency were noted. Although slow-wave sleep time was shown to be increased when given valerian, slow-wave sleep time was also increased with placebo, with no statistically significant difference between the two (Giedke & Breyer-Pfaff, 2000).

Stevinson & Ernst (2000) reviewed nine randomised, double-blind, placebo-controlled clinical trials which were designed to establish the effectiveness of valerian for the treatment of insomnia. However, some of these studies had methodological flaws in areas such as randomisation, blinding, compliance, withdrawal, confounding variables, diagnostic criteria,
and statistical analysis. Thus, Stevinson & Ernst (2000) found the evidence supporting the use of valerian to treat insomnia was inconclusive.

Valerian products are also marketed which contain additional herbal extracts such as hops, lemon balm and passion flower, each ingredient with its own sedative effects (Taibi et al., 2007). Such products which contain a combination of ingredients may exhibit an additive or synergistic effect, increasing the effectiveness of the product, thus these products are thought to be more effective than a single ingredient. The efficacy and safety of a valerian-hops combination was evaluated by Morin et al (2005) against diphenhydramine in the treatment of mild insomnia in a multicenter, randomised, placebo-controlled, parallel-group study. A total of 184 adults (110 women, 74 men; mean age of 44.3 years) with mild insomnia were given two tablets of standardised extracts of a valerian and hops combination each night for 28 days (n = 59), placebo for 28 days (n = 65), or 2 tablets of diphenhydramine (25 mg) for 14 days followed by placebo for 14 days (n = 60) (Morin et al 2005). Slight improvements of subjective sleep parameters were observed in participants taking the valerian-hops combination or diphenhydramine (Morin et al 2005). Although insignificant, valerian-hops caused a larger decrease in sleep latency compared to placebo and diphenhydramine (Morin et al 2005). Diphenhydramine yielded significantly larger increases in sleep efficiency and total sleep time as compared to placebo throughout the initial 14 days of treatment (Morin et al 2005). No significant differences among the groups were reported for any of the sleep continuity variables measured by polysomnography (Morin et al 2005). Furthermore, no changes in sleep stages 3-4 and rapid eye movement sleep were observed with any of the treatments tested (Morin et al 2005). Participants in the valerian and diphenhydramine groups expressed that the severity of their insomnia was lower relative to placebo following the 14-day treatment period (Morin et al 2005). The quality of life of the participants who were administered a combination of valerian-hops had significantly improved as compared to the placebo group following 28 days of treatment (Morin et al 2005). No significant residual effects or serious adverse events were reported with the use of either valerian or diphenhydramine (Morin et al 2005). Similarly, after discontinuation of valerian or diphenhydramine, no rebound insomnia was observed (Morin et al 2005). Thus, Morin et al (2005) concluded that both a valerian-hops combination and diphenhydramine alone caused a slight hypnotic effect as compared to placebo. Furthermore, improved sleep was achieved with a valerian-hops combination and led to an enhanced quality of life (Morin et al 2005). Both treatments seemed to be safe as they did not cause severe side effects nor did
they cause rebound insomnia following discontinuation. Thus, a valerian-hops combination and diphenhydramine may be a helpful part of a treatment strategy for mild insomnia.

Lindahl and Lindwall (1989) showed that a valerian preparation containing valerian 400 mg, hops 375 mg, and lemon balm 160 mg was more effective than a control after one night of administration, without causing any adverse side effects. This study is limited, however, as the duration of the treatment was short (only 1 night), the small sample size, and the deficit of objective sleep measures. In contrast, Leathwood et al (1982) demonstrated that a valerian product with valerian 120 mg and hops 60 mg yielded no changes in sleep latency or sleep quality in healthy individuals following administration for three non-consecutive nights, however, the doses were lower than those used by Lindahl and Lindwall (1989) (without the lemon balm). This particular preparation caused several more reports of individuals feeling “more sleepy than usual” when compared to the placebo group (Leathwood et al., 1982).

Similar results were achieved in patients suffering from mild insomnia who were given a preparation of valerian 374 mg and hops 83.8 mg for 28 days (Morin et al., 2005). No significant effect in sleep parameters using sleep diaries and PSG were observed (Morin et al., 2005).

The effectiveness of valerian for other sleep-related problems, apart from insomnia, has also been studied. Poyares et al (2002) investigated valerian as a possible method to assist in benzodiazepine withdrawal in a doubleblind study consisting of 19 participants. Participants decreased their benzodiazepine use and randomly received either a placebo or 100mg of a valerian extract 3 times a day (Poyares et al 2002). The sleep patterns of all participants were compared to those of healthy individuals (Poyares et al 2002). Using a visual analogue scale, subjective reports of sleep quality were $7.4 \pm 0.9$ on valerian compared to $5.4 \pm 0.8$ on placebo (Poyares et al 2002). The result of this study revealed that the placebo significantly reduced objective sleep latency, while valerian slightly increased sleep latency following treatment (Poyares et al 2002). However, wakefulness after sleep onset, was found to be decreased when administered valerian and increased when given the placebo (Poyares et al 2002). Therefore, the overall sleep efficiency was similar in both groups following treatment with either valerian or placebo (Poyares et al 2002). Poyares et al (2002) suggest that the reduced wakefulness after sleep onset may justify the subjective observation of improved sleep in patients given valerian, although the sleep latency was increased.
The main conclusion that these studies suggest is that although valerian produces minimal adverse effects, it does not drastically improve the symptoms of disturbed sleep associated with insomnia (Taibi et al., 2007).

Conflicting results have been obtained by the research conducted to determine the effectiveness of valerian as a sleep aid. The contradictory results are likely to be the consequence of differences in the individuals taking part in the study, the design and methodology of the study, the preparation and extraction methods used, dose and sleep assessment measures.

**St. John’s wort**

St. John’s wort (*Hypericum perforatum*) is a herb used for several medicinal purposes such as in the treatment of depression, anxiety, and fatigue. The active ingredients in St. John’s wort are believed to be hyperforin and hypericin (Meolie et al., 2005). Unfortunately, most clinical studies do not address the effect of St. John’s wort on insomnia (instead, the main focus of the research is on depression). No double-blind placebo controlled studies examining the effects of St. John’s wort on insomnia were found in the literature. However, limited data on the effects of St. John’s wort on sleep were located.

A placebo-controlled, PSG study of healthy individuals who did not suffer from mood or sleep disturbances evaluated the effect of St. John’s wort on sleep (Sharpley et al., 1998). A dose of 0.9 mg St. John’s wort considerably increased REM sleep latency versus a placebo (84 vs 69 minutes, respectively, *P* = .03) (Sharpley et al., 1998). A second group of healthy individuals were given a higher dose of St. John’s wort (1.8 mg) (Sharpley et al., 1998). The average REM latency was not significantly increased when given this higher dose of St. John’s wort versus a placebo (104 vs 64 minutes, respectively, *P* = .15) (Sharpley et al., 1998).

Another placebo-controlled, double-blind, randomized crossover study conducted on 11 older female volunteers (mean age 59.8 ± 4.8 years) study examined the effects of St. John’s wort on sleep (Schulz, 2001). The findings revealed a pronounced increase in slow-wave activity when given St. John’s wort and in comparison to individuals taking the placebo (Schulz, 2001). Slow-wave sleep increased during active treatment with St. John’s wort, and decreased when being treated with the placebo (Schulz, 2001). It was unclear as to whether or not the alterations in sleep architecture reported were correlated with an improvement in insomnia. Furthermore, these studies were conducted on healthy individuals, and therefore, the results obtained from these studies may not apply to patients suffering from symptoms characteristic
of insomnia. In addition, these studies made extracts of St. John’s wort, and therefore it the effectiveness of commercially available St. John’s wort is unknown. Furthermore, the components and extraction methods used by these studies were different and thus prevent the simplification of the generated results.

Several studies have documented the adverse effects associated with St. John’s wort. These are gastrointestinal complaints, dizziness, fatigue, anxiety and headaches (Barnes et al., 2001; Greeson et al., 2001; Harrer et al., 1999; Müller et al., 1997; Schulz, 2001; Woelk, 2000). In a study involving commercially available St. John’s wort preparations the side effects which were the most common were gastrointestinal symptoms, allergic reactions, tiredness, anxiety and confusion (Woelk et al., 1994). A few studies also report photosensitivity and phototoxicity as side effects of use of St. John’s wort (Bove, 1998; Brockmöller et al., 1997; Lane-Brown, 2000).

Drug interactions involving St. John’s wort have also been well documented. Several studies conducted in vivo demonstrate the ability of St. John’s wort to stimulate the cytochrome P450 (CYP) system, particularly isoenzyme 3A4 (Breidenbach et al., 2000a; Breidenbach et al., 2000b; Dürr et al., 2000; Markowitz et al., 2000; Roby et al., 2000; Ruschitzka et al., 2000). Many prescribed drugs are metabolised by the CYP450 isozyme 3A4 (CYP3A4), and therefore there is a significant risk of a pharmacokinetic drug interaction (Izzo & Ernst, 2009). Hyperforin can induce CYP3A4 and is likely to be the most common component for St John’s wort interactions (Moore et al., 2000). The difficulty in predicting interactions lies in the fact that many of the St. John’s wort products available on the market are standardised for hypericin content only (Henderson et al., 2002). Intestinal P-glycoprotein is also induced by St. John’s wort (Dürr et al., 2000; Hennessy et al., 2002). The most significant interactions are usually seen in patients suffering from cardiovascular disease, HIV, cancer and depression (Mannel, 2004). Serum digoxin levels are significantly decreased (Dürr et al., 2000; Gurley et al., 2008). Furthermore, a decrease in the bioavailability of indinavir, a nonnucleoside reverse-transcriptase inhibitor has been reported (Piscitelli et al., 2000). Decreased serum cyclosporin levels, and acute organ rejection following kidney, heart and liver transplants have been documented (Barone et al., 2000; Di et al., 2008; Karlrova et al., 2000; Ruschitzka, 2000). St. John’s wort also reduces the concentration of amitriptyline and its metabolite nortriptyline (Johne et al., 2002). Menstrual bleeding has occurred in a few women who are taking oral contraceptives, which may a consequence of an increase in CYP3A4 induction and subsequent decrease in hormone concentrations (Yue et al., 2000).
Pharmacodynamic interactions can also occur with St Johns Wort. When sertraline, nefazodone or paroxetine are taken in conjunction with St. John’s wort, serotonin syndrome has been reported (Lantz et al., 1999). This may be associated with the serotonin-inducing effects of St. John’s wort, and consequently, St. John’s wort should not be used concurrently with selective serotonin reuptake inhibitors.

**Kava**

Kava is derived from the roots of *Piper methysticum*, a plant indigenous to the South Pacific (Humberston et al, 2003). Kava has sedative and anesthetic properties and as such, supplements containing kava are used to ease menopausal symptoms, anxiety and insomnia (Bilia et al, 2002). These products are usually made from raw plant material or concentrated extracts. However, an unforeseen side effect of kava kava has been reported since 1999, that is, severe hepatotoxicity (including cases of liver failure which necessitated a liver transplantation) (From the Centers for Disease Control and Prevention [CDC], 2003). In 2002, the FDA issued a statement concerning the potential for developing hepatotoxicity when using products containing kava kava (FDA, 2002). In Australia, Therapeutic Goods Administration (TGA) initiated a voluntary recall of kava-containing medicines following hepatotoxicity and deaths from liver failure associated with medicine containing kava (TGA, 2005). Also, the TGA issued safety alerts to Australian consumers and health professionals about concerns, “the most serious of which involved death or liver transplantation.” (TGA, 2005). The CDC published the results of its investigation in the United States with regards to the cases of liver failure caused by kava kava and reviewed the cases in Europe (Morbidity And Mortality Weekly Report, 2002). Since then, many European countries have limited the sale of products containing kava kava (Centers for Disease Control and Prevention, 2003). Hepatotoxicity induced by kava arises from administration of anxyolytic ethanolic, acetonic kava extracts and aqueous kava extracts (Teschke, 2010). Thus, due to the possibility of developing severe liver toxicity, particularly in patients with a pre-existing liver disease or liver injury, kava kava (either ethanolic or aqueous) should not be advocated in the treatment of insomnia.

A meta-analysis conducted by Pittler & Ernst (2000) showed that in the treatment of anxiety, kava caused stomach complaints, restlessness, tremor, headache and tiredness. Wheatley (2001) showed that stress-induced insomnia was alleviated after treatment of kava for a period of six weeks at a dose of 120 mg of kava. The insomnia was further reduced by six
weeks treatment with 600 mg valerian (Wheatley, 2001). The side effects of kava reported in this study were gastric disturbances, and dry mouth (Wheatley, 2001).

A frequent symptom which occurs in association with an anxiety disorder is sleep disturbances (Ohayon et al., 2000). Jacobs et al (2005) reported that a dose of 300 mg kava for 28 days did not produce a significant decrease in anxiety or insomnia using the Insomnia Severity Index and State-Trait Anxiety Inventory, respectively. Conversely, administration of kava (200 mg) for four weeks (compared to placebo) produced major improvements in sleep quality, restorative effects of sleep and reduced anxiety in individuals experiencing anxiety derived sleep disturbances from a non-psychotic origin (Lehrl, 2004). Several sleep questionnaire scores showed significant improvement in sleep and anxiety including the Hamilton Rating Scale for Anxiety, self-rating scales of well being, and the Clinical Global Impressions scale (Lehrl, 2004).

As is the case in many of these products, there are some non-controlled data suggesting the effectiveness of kava to alleviate insomnia. However, there is a limited number of objective and/or placebo controlled trials to show the efficiency of kava in treatment of insomnia. Furthermore, the benefits of using kava must be weighed against the risks of consuming this product; in particular the potential of developing liver toxicity.

**Melatonin**

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesised in the pineal gland located in the posterodorsal aspect of the diencephalon, just above the cerebellum (Grozinsky-Glasberg et al., 2010). Its biosynthesis and secretion occurs nocturnally and its release is inhibited in the presence of light (Reiter et al., 2010) on the retinal ganglion cells (Brainard et al., 2008; Jasser et al., 2006).

Melatonin secretion is synchronised by the environmental light/dark cycle via the suprachiasmatic nucleus (Sarrazin et al., 2011). Melatonin levels begin to rise in the evening and peak between 2:00 and 4:00am (Arendt et al., 2008). The high density of melatonin receptors in the hypothalamic suprachiasmatic nuclei (SCN) (Dubocovich et al., 2010), suggests that melatonin promotes sleep and regulates the sleep-wakefulness cycle by acting on specific receptors. The mechanism by which melatonin acts during sleep, (excluding its modulation and regulation of the circadian rhythm, known as phase shifting), remains elusive, but it is thought that melatonin acts by stimulating specific melatonin receptors (Roth, 2001).
Melatonin has a half-life ranging from 0.5-2 hours, with doses up to 5 mg producing less residual daytime drowsiness (Randall et al., 2008). The most common adverse effects reported in published studies are headache, dizziness, and drowsiness (Buscemi et al., 2005; Pandi-Perumal et al., 2007). Melatonin supplements have been demonstrated to be relatively safe when taken for a short period of time (days to weeks) (Randall et al., 2008). Treatment with prolonged release of melatonin showed efficacy for primary insomnia without withdrawal symptoms, or suppression of endogenous melatonin production, with up to 12 months continuous therapy (Lemoine et al., 2011).

Riemann et al (2002) observed a delay in the secretion of melatonin and considerable reductions in melatonin concentrations during the night in insomniacs. Melatonin in doses ranging from 0.3–5 mg produced no major differences in sleep measures compared to placebo therapy (Montes et al., 2003; James et al., 1990). These sleep measures included sleep efficiency; total sleep time; latency to sleep; number of nocturnal awakenings; average length of the non-REM/REM cycle; proportion of stage 1, 2, delta sleep, and REM sleep; total minutes of each sleep stage; and in the latency to REM sleep (Montes et al., 2003; James et al., 1990). Furthermore, a double blind randomised placebo controlled crossover study found healthy older volunteers (aged over 65 years) had no improvement in the quality of their sleep when administered 5 mg immediate release melatonin at bedtime (Baskett et al., 2003).

Touitou (2001) suggests that the endogenous melatonin secretion significantly decreases as the age of an individual increases. Consequently, sleep efficiency decreases and circadian rhythm disturbances increase. Conversely, a major improvement in subjective evaluations of sleep and daytime alertness in patients suffering from insomnia was shown when they were administered a much higher melatonin dose of 75mg, in a placebo-controlled study (MacFarlane et al., 1991). An oral dose of 0.1-0.3 mg melatonin is sufficient to achieve physiologic circulating levels of melatonin (Zhdanov, 2005). As the dose of melatonin used by Macfarlane et al (1991) was significantly higher than the physiologic dosage range (0.5–1 mg), the safety issues regarding this dose require further intensive study.

Supplemental melatonin seems to improve sleep efficiency in people with a secondary sleep disorders (Buscemi et al., 2004) and age-related insomnia (Luthringer et al., 2009; Riemersma-van der Lek et al., 2009). Buscemi et al. (2004) produced an evidence based report in which they highlighted the increased sleep efficiency following treatment with melatonin. Improved sleep efficiency was observed in elderly patients at doses ranging from 0.1–3.0 mg (Garfinkel et al., 1995; Zhdanova et al., 2001). These doses increased nocturnal
plasma concentrations to within the normal physiological range (Garfinkel et al., 1995; Zhdanova et al., 2001).

Overall, the data available regarding melatonin as a treatment for the management of primary insomnia shows mixed results. However, melatonin has the ability to alter phase shifting and therefore it is effective in elderly patients suffering from primary insomnia with reductions in endogenous melatonin and insomnia associated with sleep circadian rhythm disorder. Melatonin improves the quality of sleep (Lemoine et al., 2007) and alleviates symptoms of jet lag (Herxheimer and Petrie, 2002).

**Tryptophan**

L-tryptophan is an essential amino acid that cannot be synthesised by the body and must be obtained from the diet (Paredes et al., 2009). Once absorbed, L-tryptophan can be endogenously converted to both serotonin and then melatonin (Martins and Gloria, 2010; Russo et al., 2009). It is well documented that low serotonin levels are correlated with depression, anxiety, and insomnia (Reimold et al., 2008; Vashadze, 2007) – see above (Role of serotonin). Despite this, there is a lack of evidence supporting the use L-tryptophan supplements to treat these disorders (Fetveit 2009; Randall et al., 2008). Nonetheless, L-tryptophan supplements have been used in the treatment of some forms of depression, anxiety, and insomnia (Silber and Schmitt, 2010).

In chronic insomniacs, supplemental L-tryptophan appears to be a successful hypnotic agent with sleep maintenance disturbances that were distinguished by 3-6 awakenings during the night (Lindsley et al., 1983). Lindsley et al (1983) observed that patients suffering from chronic insomnia self-reported a 100% improvement after taking L-tryptophan 1 g nightly for 1 week. L-tryptophan lacked any significant effects on sleep parameters measured using PSG at doses of less than 1g (Randall et al., 2008; Hajak et al., 1994). Decreases in sleep latency were reported at doses of 1-3g, but findings regarding to total sleep time, SWS and REM sleep were inconsistent.

Schneider-Helmert and Spinweber (1986) conducted a review of several studies investigating the effectiveness of tryptophan in the treatment of insomnia. Patients with chronic insomnia (characterised by problems in both sleep onset and sleep maintenance) were demonstrated to have improved sleep quality following continued administration of low L-tryptophan doses (1-5g) (Schneider-Helmert and Spinweber 1986). However, the minimum effective dose (1g from these studies) varies between individuals, and may also change depending on the degree of the sleep disturbance. Accordingly, the administered dose of L-tryptophan should be
between 1-5 g and based on the severity of the insomnia (Schneider-Helmert and Spinweber, 1986). The hypnotic effects occurred late during the treatment after 3 nights of administration (Spinweber, 1986), and sometimes after discontinuation (Hartmann et al., 1983). Treatment with L-tryptophan can also decrease sleep onset time on the first night of taking the supplement (Schneider-Helmert and Spinweber, 1986). The studies reviewed by Schneider-Helmert and Spinweber (1986) administered doses ranging from 1–15 g in young patients with insomnia. There was no dose-dependent response relationship (Schneider-Helmert and Spinweber, 1986).

Insomnia may be aggravated when the selective serotonin reuptake inhibitor, fluoxetine, is used to treat depression (Jindal, 2009). Levitan et al (2000) conducted a randomised, double-blind, placebo-controlled study where L-tryptophan (2–4 g) and fluoxetine (20 mg) were co-administered to 30 patients with depression for 8 weeks and found a considerable reduction in depression and an SWS protective effect. A reduction in slow wave sleep was observed in the group given fluoxetine plus placebo tryptophan but was not apparent in the fluoxetine plus active tryptophan group (Levitan et al., 2000).

L-tryptophan is not associated with impaired visuomotor, cognitive, or memory performance (Schneider-Helmert and Spinweber, 1986). However, L-tryptophan was withdrawn from the market in the United States due to an association between tryptophan use and eosinophilic myalgia syndrome (Michelson et al., 1994). This was caused by contamination during the manufacturing process linked to genetically engineered bacteria used (Belongia et al., 1990). Consequently, the FDA has made tryptophan available by prescription in the USA since 1991 and it is also available in Australia by prescription with the exception of medicines which contain a dose of less than 100 mg to be taken daily (Meolie et al., 2005). However, in Australia in 2001, the Complementary Medicines Evaluation committee recommended the TGA that tryptophan is unsuitable for use as an active ingredient in therapeutic goods as the evidence supporting its safety is lacking (TGA, 2001).

3-Social Treatment

Alcohol
Several studies show that alcohol ingested at bedtime shortens sleep latency, increases slow wave sleep (SWS), and suppresses rapid eye movement (REM) during the first half of sleep (Feige et al., 2006). In the second half of sleep, when the level of alcohol in the blood is low,
REM sleep increases and sleep is shallower as arousal reactions increase (Brower, 2001; Feige et al., 2006). Many insomniacs use alcohol as a sleep aid due to its sedative effect, however, evidence suggests that alcohol consumed within an hour of bedtime disturbs the second half of the sleep period (Roehrs and Roth, 2001; Roehrs et al., 1999). Alcohol alters the proportions of the various sleep stages with a reduction of REM sleep dependent on the dose of alcohol (Sagawa et al., 2011). An increase in the number of nocturnal awakenings and/or disruption of lighter stage of sleep (stage 1) during the second half of the night occur when a relatively high dose of alcohol is consumed (Sagawa et al., 2011). This disruption of sleep during the second-half of the night is known as the rebound effect (Roehrs and Roth, 2001). The rebound effect occurs as alcohol is metabolized (Roehrs and Roth, 2001). Table 2 summarises the effects of alcohol use and cessation on Sleep Architecture.

**Table 2: General Effects of Alcohol Use and Cessation on Sleep Architecture.**

<table>
<thead>
<tr>
<th>Drinking Behaviour</th>
<th>REM Sleep</th>
<th>Slow Wave Sleep</th>
<th>Sleep Continuity</th>
<th>Sleep Latency</th>
<th>Total Sleep Time</th>
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<tr>
<td>Acute Use</td>
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<tr>
<td>High dose</td>
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<td>Low dose</td>
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<tr>
<td>Chronic Use</td>
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<tr>
<td>Cessation After Chronic Use</td>
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</table>

Taken from Stein and Friedmann, 2005

↓ / ↑ - decrease / increase  ↓↓ / ↑↑ - marked decrease / increase  ↓↑ - decrease OR increase

Danel and Touitou (2004) reviewed research on alcohol and circadian rhythms and concluded that alcohol acts on the circadian timing system’s biological clock, causing it to become “desynchronized.” This conclusion was based on studies of daytime and night time melatonin levels in current or abstinent alcoholics (Danel and Touitou, 2004). Findings from such studies generally show suppressed melatonin levels compared to age-matched non-alcoholic controls (Kuhlwein et al., 2003).

Using alcohol as a sleep aid could risk development of alcohol dependence and usage may increase due to insomnia symptoms, which the subject may not link to the alcohol consumed. A ‘pre- and post-’ survey was conducted by Weissman et al. (1997) assessing alcohol use in three groups:
- Sleep disorder with no psychiatric disturbance (uncomplicated insomnia);
- Sleep disorder with a psychiatric disturbance (complicated insomnia); and
- No sleep disorder (no insomnia).

The two surveys were conducted one year apart found the uncomplicated insomnia group had a higher risk for developing alcohol dependence and abuse than individuals who did not have insomnia or the complicated insomnia groups (Weissman et al., 1997). Janson et al. (2001) conducted a longitudinal population study using mailed survey responses in 1984 (n=3201) and 1994 (n=2975) and found the prevalence of insomnia increased from 10.3% to 12.8%. Individuals with insomnia in 1994 exhibited significantly more signs of alcohol dependence than those who did not suffer from insomnia (Janson et al., 2001).

Moreover, in a study of the effects of alcohol consumption on sleep-induced breathing abnormality, Issa and Sullivan (1982) found that alcohol exacerbated breathing disturbances during sleep in a dose-dependent manner. Other clinical studies reported that alcohol consumption before bedtime was associated with an increase in the number and duration of hypopnea and apnoea (Scanlan et al., 2000; Tsutsumi et al., 2000). Roth et al. (1985) suggested that alcohol may negatively affect disordered breathing during sleep by one or more of:

- reduced hypoglossal nerve activity;
- altered carotid-body receptor function;
- depressed arousal response; and/or
- sleep fragmentation.

A study found about 30% of people suffering from chronic insomnia indicated that they use alcohol to initiate sleep and 67% of these patients reported that alcohol was effective (Ancoli-Israel and Roth, 1999). However, in PSG studies conducted by Brower et al. (2001), alcohol adversely altered measures of sleep continuity and severe alcohol dependence and depression occurred in insomniacs. Johnson et al. (1998) reported that males and people which have never been married or those separated or divorced/widowed were 1.5 times more likely to use alcohol to help induce sleep than females or married people.

Therefore, the consumption of alcohol, and its discontinuation have been correlated with disturbances of the sleep cycle. Consequently, alcohol consumption is discouraged in patients
with a sleep disorder, and pharmacists should counsel patients against the use of alcohol as a sleep aid.

### 4-Pharmacologic treatment of primary insomnia
The majority of studies conducted focus on the treatment of primary insomnia with benzodiazepine receptor agonists (BzRAs). Consequently, the literature contains significantly more evidence for the safety and effectiveness of particular drugs for the treatment of primary insomnia than for comorbid insomnia. Several classes of drugs are currently approved for the treatment of insomnia (Schutte-Rodin et al., 2008). These drugs include Therapeutic Goods Administration (TGA) approved drugs (nine BzRAs, and the histamine-1 antagonist; Table 3). The melatonin-receptor agonist ramelteon is not available in Australia. This section aims to illustrate the mechanism of action, effectiveness and safety of these classes of drugs, with a particular focus on BzRAs.

#### Table 3: Medications with TGA indication for insomnia

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dose (mg)</th>
<th>Elimination half-life (hours)</th>
<th>T_max (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunitrazepam</td>
<td>0.5-2</td>
<td>20-30</td>
<td>1-2</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>2.5-10</td>
<td>27 (16-48)</td>
<td>2 (05-5)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>5-20</td>
<td>10 (5-15)</td>
<td>05-1</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125, 0.25</td>
<td>1.5-5.5</td>
<td>2</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>7.5-30</td>
<td>4-15</td>
<td>2-3</td>
</tr>
<tr>
<td>Clobazam</td>
<td>10-30</td>
<td>17-49</td>
<td>1-4</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1-2</td>
<td>12-16</td>
<td>2</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5-12.5</td>
<td>2.4 (+/- 0.2)</td>
<td>0.5-3</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>3.75, 7.5</td>
<td>5.26 +/- 0.76</td>
<td>1.75</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>50</td>
<td>2.4 - 9.3</td>
<td>1-4</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>25-50</td>
<td>10.1</td>
<td>2-4</td>
</tr>
</tbody>
</table>

Source: (MIMS, 2012)
Benzodiazepine receptor agonists Hypnotics

Benzodiazepine receptor agonists (BzRA) hypnotics are commonly used in the treatment of insomnia and are usually prescribed as first-line therapy (Wilson and Nutt, 2011). All members of this class have been demonstrated to have some degree of effectiveness for insomnia (Schutte-Rodin et al., 2008). The major differences between these drugs are their pharmacokinetic profiles (Roehrs and Roth, 2003). The margin of safety or therapeutic index (the effective dose relative to lethal dose) is broad for BzRA hypnotics and toxicity is rare (O'Malley, 2007). Furthermore, abuse or dependence on BzRAs in the therapeutic context is uncommon (Neubauer, 2003); however, Kan et al (2004) identified a series of factors which increase the risk of developing dependence on benzodiazepines: administration of higher doses; taking the drug for an extended period of time; younger age; and a history of drug or alcohol abuse (Kan et al., 2004). Consequently, the prescriber and pharmacist should make opportunities to counsel patients with these characteristics about dependence in community and hospital practice.

The mechanism of action employed by BzRAs is common among hypnotics as they act as allosteric modulators of gamma-aminobutyric acid (GABA) activity (Lankford et al., 2008). The drug binds to benzodiazepine sites on the GABA-A receptor complex which activates chloride ion channels, and causes the inhibitory effects of GABA activity (Nutt, 2006). Some BzRAs such as clobazam, flunitrazepam, lorazepam, nitrazepam, oxazepam, temazepam and triazolam have a benzodiazepine chemical structure, while other BzRAs lack this structure, including zopiclone, zaleplon and zolpidem (Terzano et al., 2003). Those which exhibit the chemical structure of benzodiazepines seem to be non-selective, having almost equal affinity for GABA-A receptor complexes containing any of the four alpha subunits (alpha-1, alpha-2, alpha-3 and alpha-5) (Stahl, 2008). In contrast, BzRAs which do not exhibit the characteristic benzodiazepine structure usually exhibit more selectivity (Ebert and Waﬀord, 2006). For example, zolpidem and zaleplon are highly selective for the GABA-A receptor complex containing the alpha-1 subunit which may be associated with sedation effects (Nutt and Stahl, 2010). Eszopiclone appears more selective than other non-benzodiazepines, exhibiting comparable affinity for alpha-1, alpha-2, alpha-3 and alpha-5 subunits (Nutt & Stahl, 2010). However, Doble et al (1995) provide evidence in support of the theory that eszopiclone binds in a different manner than benzodiazepines. Although the functional significance of the range of binding affinities among BzRAs and their effect on sleep remains unclear, it is thought that the non-selective binding of benzodiazepines results in increased side effects (Stahl, 2008).
There are several differences among BzRAs which are clinically relevant. These are mainly related to the pharmacokinetic properties of these drugs, specifically, the duration of drug activity. The most important factors used in determining the duration of action of a drug are elimination half-life, drug dose and formulation (for example, extended release, sublingual absorption) (Ebert et al., 2006; Neubauer, 2009; Zammit, 2009a). Variation in the ability to metabolise and eliminate BzRAs in individuals leads to differences in the effectiveness and safety of these drugs among different patients. It should be noted that it is common for benzodiazepines without an indication for insomnia (not approved by FDA), such as lorazepam, clonazepam and alprazolam, to be used as hypnotics (NIH, 2005). Also, these drugs are not approved by the TGA in Australia for insomnia (AMH, 2012). The pharmacologic properties of these drugs are comparable to that of benzodiazepine hypnotics (AMH, 2012); therefore, although the efficacy of these drugs in insomnia has not been as thoroughly investigated, their effects on sleep are similar. However, they exhibit longer half-lives from 11-40 hours (Stahl, 2008).

**Efficacy and effectiveness in primary insomnia**

The majority of clinical trials on insomnia report hypnotic efficacy as measured by patient reports or polysomnography (PSG), or both (NIH, 2005). A meta-analysis of clinical trials with benzodiazepines and zolpidem conducted by Nowell et al (1997) demonstrated that, collectively, these drugs result in significant improvements in the quality and quantity of sleep in patients with chronic insomnia. However, it is noteworthy that the median duration of the studies evaluated in this meta-analysis was merely one week (Nowell et al., 1997). Nonetheless, other meta-analyses largely support the findings by Nowell et al (1997) concerning the short-term efficacy of BzRAs (Dündar et al., 2004; Holbrook et al., 2000; Smith et al., 2002). However, there may be significant limitations because meta-analyses often combine data from several drugs which may differ greatly in their pharmacokinetic properties or multiple doses of the same drug, affecting the outcome variables studied in the meta-analysis. Therefore, meta-analyses can only allow broad conclusions regarding a specifics group of drugs. More specific conclusions can be found in the individual studies which should be considered when determining which drug has the highest chance of success for treatment of a particular patient. A significant limitation of Holbrook et al (2000) is that they used benzodiazepines as a single medicine. This assumption cannot be made as benzodiazepines are in fact a class of several drugs with different pharmacokinetics properties and side effects. In addition, Holbrook et al (2000) indicate that a potential limitation to their
study is that they only assessed studies spanning over a short period (14 days or less) and therefore, no comments concerning the efficacy and safety of long-term trials can be made. Dundar et al (2004) reported that limitations of the data analysed hampered their ability to draw conclusions from their review. They found only small differences between the drugs analysed in their study, but these differences were difficult to quantify (Dundar et al, 2004). Smith et al (2002) indicate that absence of random assignment is a significant limitation of this meta-analysis. Similarities and differences among BzRAs are discussed in the following section.

BzRA hypnotics result in insignificant decrease sleep latency and a significant increase in total sleep time, when compared with placebo (Holbrook et al., 2000; Holbrook et al., 2001). An exception is zaleplon, which did not increase total sleep time, in most trials (Walsh et al., 2000). Zaleplon has a short half-life (approximately one hour) compared with other hypnotics, and is therefore less effective for treating sleep maintenance (Ebbens and Verster, 2010). Benzodiazepines act to reduce sleep latency, increase total sleep time and reduce the amount of time spent in stage 2 sleep, although they have little effect on the sleep maintenance which is the most common problem in the elderly (McCall, 2005).

Tolerance is the reduced effectiveness of a drug that occurs with continued administration of a constant dose, or alternatively, increasing the dose in order to maintain a particular level of effect (Bélanger et al., 2009). Tolerance to the hypnotic effects of BzRAs has not been reported in the majority of short-term studies for therapeutic doses for a period of 4 weeks (Terzano et al., 2003). Oswald et al (1982) found that two benzodiazepines, lormetazepam and nitrazepam, preserved their hypnotic effect over 24 weeks of continuous therapy as measured by patient self-reports. Other PSG studies demonstrated that zolpidem 10 mg and zaleplon 10 mg retained efficacy for 5 weeks of continuous nightly use (Scharf et al., 1994; Walsh et al., 2000). A study of primary insomniacs reported continued hypnotic efficacy of eszopiclone for 6 months measured by patient self-reports of reduced sleep latency, wakening after sleep onset (WASO), total sleep time, number of awakenings, and sleep quality when given eszopiclone 3 mg or placebo (Krystal et al., 2003). These 6-month findings have been replicated in other studies (Walsh et al., 2007) and assessment of open-label extension data has indicated continued efficacy of eszopiclone for 12 months (Roth et al., 2005). Additional evidence supporting the sustained efficacy following nightly BzRA use includes a 3-month study with indiplon, a non-marketed hypnotic (Scharf et al., 2007). Walsh et al (2000) and Perlis et al (2004) assessed a “when necessary” treatment schedule for zolpidem 10 mg for up
to 12 weeks. Sleep latency, total sleep time, number of awakenings, and sleep quality were all improved on nights when zolpidem was taken when compared with a placebo (Walsh et al., 2000; Perlis et al., 2004). Investigator global ratings, which considered both medication and non-medication nights, indicated a reduced severity of insomnia with zolpidem (Walsh et al., 2000). More recently, Krystal et al (2008) found an extended-release formulation of zolpidem, given to individuals for 3 to 7 nights per week for 6 months, generated similar results.

In addition to clinical trials, some population studies have reported on the use and efficacy of hypnotics. Ohayon et al (1999) reported that 67% of chronic insomniacs with long-term use of hypnotic medications exhibited a significant improvement in sleep quality while 14.4% of patients reported no significant improvement. Balter and Uhlenhuth (1991) interviewed individuals suffering from insomnia or those who had taken a sleep aid. The greatest treatment satisfaction was reported by individuals who took hypnotics with 84% of triazolam users, 82% of flurazepam users, and 74% of temazepam users reporting they would take the medication again to help them sleep (Balter and Uhlenhuth, 1991).

Several long-term, open-label studies examining both middle aged and older adults also contribute to the evidence base about BzRAs effectiveness (Ancoli-Israel et al., 2005; Kummer et al., 1993; Maarek et al., 1993; Roth et al., 2005; Schlich et al., 1991). Patients and physicians expressed a continued benefit regarding BzRAs over a 6-12 month period, without detrimental side effects related to long-term use (Walsh, 2005).

Improvement in the daytime symptoms of insomnia is the primary goal of insomnia treatment (Schutte-Rodin et al., 2008). The few studies that have examined patient-reported daytime measures in patients suffering from primary insomnia usually exhibit improvement (Krystal et al., 2003; Walsh et al., 2007). Two 6-month investigations of primary insomniacs each found a significant improvement in patient reported daytime alertness and ability to function and a stronger sense of wellbeing in the treatment (eszopiclone) group compared to the placebo group (Krystal et al., 2003; Walsh et al., 2007).

Safety in primary insomnia

Detrimental side effects to BzRAs in clinical trials are rare and usually mild (Curry et al., 2006; Hall-Porter et al., 2010). Side effects appear more severe with use of benzodiazepines than with the newer BzRAs (NIH, 2005). The median rate of these side effects in hospital
inpatients treated with any hypnotic was found to be about 1 in every 10,000 doses (Mendelson et al., 1997). Many of the BzRA adverse effects occur as a result of the BzRA sedation mechanism (Ebert and Wafford, 2006a; Roth and Roehrs, 1992). Persistence of the hypnotic effect of the drug after the individual is awake, causes undesirable responses including drowsiness, sleepiness and impairment of psychomotor performance (Vermeeren et al., 2004). The probability of residual sedation occurring is determined by the duration of drug action (Buysse, 2008) and influenced by pharmacokinetic factors such as elimination half-life, administered dose and tissue distribution after a single dose (e.g., lipophilicity) (Zammit, 2009a). The duration of effect is impacted by the half-life when the recommended doses are administered (Zammit, 2009b). The drugs with longer half-lives can accumulate with chronic use, causing accumulation and residual sedation therefore, they are not recommended for older patients due to the increased risk of side effects (Dailly and Bourin, 2008). Theoretically, benzodiazepines with a long half-life may accumulate and produce augmenting sedation; at the same time, tolerance to benzodiazepines may occur, which reduces these effects. However, data on the issue of tolerance were found to be limited and conflicting.

Anterograde amnesia, or memory for information presented following administration of the drug, has the potential to occur with any drug which exhibits sedative activity, including the BzRAs, and barbiturates (Möhler et al., 2002). Benzodiazepines prevent the processing of new information and potentially unpleasant experiences, causing anterograde amnesia (AJHP, 2002). The degree of severity of the amnesia depends on the plasma concentration of the benzodiazepine (Roth et al., 1990; Verwey et al., 2005). The higher the dose (the higher the plasma concentration), the greater the degree of severity of amnesia, leading to a higher frequency of amnesiac events (Roehrs & Roth, 2003). A number case report studies have demonstrate that anterograde amnesia is associated with the use of zolpidem and this behaviour ceased after discontinuation of the zolpidem (Tsai et al., 2007; Hoque & Chesson, 2009). Furthermore, benzodiazepines are vital supplemental drugs in anaesthetics. These drugs can relieve anxiety and prevent the patient from recalling the events of a surgical procedure (Saari et al., 2011). Benzodiazepines have been demonstrated to be far more efficient than other sedative-hypnotic drugs used in anaesthetics, giving better degrees of sedation, reliable amnesia, respiratory and hemodynamic function (Saari et al., 2011). Benzodiazepines (midazolam) also appear to be capable of reducing nausea and vomiting post-surgery (Bauer et al., 2004). A major beneficial use of benzodiazepines is their amnesic
effect in the treatment of nausea and emesis (vomiting), particularly in patients (more notably children) who experience anxiety and anticipatory nausea and emesis linked to chemotherapy (Greenberg et al., 1987; Mori et al., 1993; Potanovich et al., 1993). Kris et al (1985) found the adjunct efficacy of lorazepam used in conjunction with metoclopramide or dexamethasone for the treatment of chemotherapy-induced nausea is equivalent to that of diphenhydramine used with these same drugs, however, the treatment of anticipatory anxiety symptoms using lorazepam is superior. Bishop et al (1984) conducted a randomised, double-blind, crossover study whereby lorazepam was demonstrated to exhibit an enhanced efficacy over placebo when used in conjunction with prochlorperazine for chemotherapy-induced nausea. However, there is no published evidence to advocate the use of benzodiazepines as single or primary anti-emetics (National Cancer Institute, 2011). In addition, there are no definitive guidelines of benzodiazepine doses given in the literature for the treatment of emesis.

The most commonly documented effect which occurs with the discontinuation of BzRAs is rebound insomnia (Pinto et al., 2010). Rebound insomnia is a decline in the quality of sleep as compared to the insomnia experienced by the patient before being treated with BzRAs. Rebound insomnia only lasts for approximately 1-2 nights, after discontinuation of the drug (Zammit, 2009a). Rebound insomnia is different to a withdrawal syndrome, that is, the development of a series of symptoms which were absent before treatment (Zammit, 2009a). Withdrawal symptoms usually last a few days to a few weeks instead of the 1-2 nights for rebound insomnia. Roehrs et al (1990) reported that rebound insomnia becomes apparent when a hypnotic drug is suddenly stopped after 1 or 2 nights of drug use; however, there is no evidence that it increases in severity with the number of repeated nights of use (Merlotti et al., 1991; Roehrs et al., 1990). The frequency of rebound insomnia increases with high doses of short- and intermediate-acting benzodiazepines, but it can be reduced by steadily lowering the dose over a period of a few nights and by decreasing the administration frequency (Budur et al., 2007). Rebound insomnia does not seem to happen with long-acting hypnotics due to the steady decline in plasma concentration, an intrinsic part of the pharmacology of these drugs (Woods et al., 1992). New non-benzodiazepines have been developed which do not appear to produce rebound insomnia, even though the duration of their action is short to intermediate. Silvestri et al (1996) showed that rebound insomnia occurred after the abrupt discontinuation of triazolam but not zolpidem, two short-acting non-benzodiazepines, demonstrating that when administered at an appropriate dose, short-acting non-benzodiazepines may not cause rebound insomnia. Walsh et al (2000) did not find any evidence suggesting that rebound
insomnia occurs when zolpidem 10 mg was self-administered as required over an 8-week period, as subjects’ total sleep time did not change on nights when no medication was taken that immediately followed a night when medication was taken. In an investigation comparing zolpidem-CR to a placebo, rebound insomnia was not detected on the 3 nights after discontinuation of the drug (Erman et al., 2007a; Erman et al., 2007b). Furthermore, other studies have demonstrated that sudden discontinuation of zaleplon does not cause rebound insomnia in adult (Fry et al., 2000; Walsh et al., 2000) or elderly (Ancoli-Israel et al., 1999) patients following time periods of up to 5 weeks of nightly use. One study showed that 2 mg of eszopiclone resulted in rebound insomnia only on the first night after discontinuation of the treatment (Zammit et al., 2004), however another study found that no rebound insomnia (Krystal et al., 2006).

The major concern with using BzRA hypnotics is dependence (Ebert et al., 2006). Epidemiologic data suggests that most insomnia patients do not continue treatment with hypnotics for extended time periods, with approximately 70% using these drugs for up to 2 weeks (Mellinger et al., 1985; Roehrs et al., 2002). Of patients taking prescription hypnotics, approximately 36% report regular use, that is, longer than one month, (Johnson et al., 1998) however it is improbable that this persistent use as reported in this study reflects physical or psychological drug dependence. Studies examining the self-administration of hypnotics by patients with insomnia suggest that these patients do not increase the dose of the drug (Roehrs et al., 1996), daytime use is uncommon (Roehrs et al., 2002a) and the frequency of self-administration changes depending on the severity of the insomnia (Roehrs et al., 2002b). Other investigations demonstrate that BzRAs have a low-to-moderate behavioural dependence liability, indicating that hypnotic self-administration in patients suffering from insomnia is best explained as therapy-seeking behaviour, instead of drug dependence (Roehrs et al., 2002; Roehrs et al., 1996; Roehrs et al., 1992).

Several studies have examined the risk of incurring a fall in elderly patients being treated with a BzRA (Joester et al., 2010; Rhalimi et al., 2009; Wang et al., 2001). However, it is difficult to attribute any increased risk of falling to this class of drugs alone, as these patients exhibit other physical or psychiatric conditions which may affect their risk of falling. Moreover, the clinical studies that have been conducted have a small sample size. However, a few studies suggest that insomnia and sleep disturbance, but not the use of hypnotic such as BzRAs, lead to an increased risk of incurring a fall in elderly individuals (Brassington et al., 2000; Latimer et al., 2007; Avidan et al., 2005), although these findings cannot be taken as definitive
evidence. This is due to the fact that these studies did not use sufficient sample size, did not adjust for the large number of potential covariates, and did not employ a longitudinal design.

Individual side effects have been reported following treatment with BzRA hypnotics, including somnambulism and sleep-related eating disorders (AMH, 2012). Zolpidem is the only documented BzRA to cause both of these conditions (Hoque and Chesson, 2009; Sharma and Dewan, 2005; Sansone and Sansone, 2008). Somnambulism (Liskow and Pikalov, 2004; Yang et al., 2005) and sleep-related eating disorder (Morgenthaler and Silber, 2002; Vetrugno et al., 2006) occurs when zolpidem was administered at two to three times the clinical dose. The first reported a case of sleepwalking following administration of zolpidem was recorded by Mendelson (1994). Since then, several cases of somnambulism after zolpidem intake for treatment of insomnia have been reported (Harazin & Berigan, 1999; Morgenthaler and Silber, 2002; Sansone and Sansone, 2008; Sattar et al., 2003; Sharma and Dewan, 2005; Yang et al., 2005). These behaviours were not apparent in patients before commencement of treatment with zolpidem. Furthermore, those with a history of childhood sleepwalking or alcohol abuse or have incurred previous brain injury, seem to be more susceptible to sleepwalking following administration of zolpidem (Mendelson, 1994; Yang et al., 2005).

**Melatonin Receptor Agonist**

The first melatonin receptor agonist officially approved by the FDA to treat insomnia was ramelteon (Pandi-Perumal et al., 2011). However, it is not available in Australia. Ramelteon is used to treat insomnia characterized by sleep-onset difficulty and is rapidly absorbed by and eliminated from the body (Hibberd and Stevenson, 2004; Karim et al., 2006). Ramelteon is 1,000 times more selective for the melatonin-1 (MT1) receptor than for the MT2 receptor, suggesting that ramelteon may be more effective for insomnia characterized by difficulty falling asleep (Hirai et al., 2003) as (MT1) receptors impede the wake-promoting activity of the SCN, thereby inducing sleep (Mitchell and Weinshenker, 2010). MT2 receptors appear to be involved in sleep-wake cycling (Dubocovich et al., 2003; von Gall et al., 2002).

Data from polysomnographic and subjective reports show that ramelteon at doses between 4 and 32 mg decreases sleep latency in adult (Erman et al., 2006) and elderly (Roth et al., 2006; Roth et al., 2007) primary insomniacs. Ramelteon efficacy studies show that improvements in sleep latency are sustained following 5 weeks (8 and 16 mg) (Zammit et al., 2007), 6 months (8 mg) (Mayer et al., 2009), and 1 year (8 and 16 mg) (DeMicco et al., 2006) of treatment. There are only small improvements in total sleep time and sleep efficiency
which may be explained by the decrease in sleep latency, without disrupting other sleep maintenance variables including wake after sleep onset (Roth et al., 2007). One study suggests that ramelteon may exhibit chronobiotic properties when administered at doses from 1-4 mg, allowing a shift in the phase of the circadian rhythm, determined as melatonin offset following morning awakening, when individuals experienced a 5-hour phase advance in their sleep-wake cycles (Richardson et al., 2008). Despite the data suggesting that ramelteon may be successful in the treatment of insomnia, there are no published studies which directly compare the effectiveness and safety of ramelteon with other sleep-inducing drugs, nor has it been assessed in clinical settings (Sateia et al., 2008).

The most frequent adverse effects which occur when taking ramelteon are headache, somnolence, dizziness, fatigue, and nausea (Borja and Daniel, 2006). Several clinical trials have tested different doses to determine whether residual sedation or cognitive impairment occurs, finding no evidence of either (Erman et al., 2006; Griffiths et al., 2005; Roth et al., 2005). Furthermore, no evidence has been found of the development of rebound insomnia or withdrawal symptoms following discontinuation of ramelteon (Roth et al., 2006; Zammit et al., 2005). Due to the low potential for abuse of the substance (Griffiths et al., 2005; Johnson et al., 2006), ramelteon may be a suitable candidate for the treatment of insomnia in patients who exhibit a history of chemical dependence. However, there is no evidence to support this claim.

**Antihistamines**

Antihistamines are expansive class of pharmacologic agents including the first-generation, central acting histamine H1 receptor antagonists. Antihistamines act as competitive antagonists at histamine receptors, thus lessening congestion, sneezing, coughing, and allergy symptoms. Histamine is one of the most important alerting central neurotransmitters which promote wakefulness, and inactivation of histamine in the central nervous system has been shown to cause sedation and disturbed wakefulness patterns (Mignot et al., 2002). Antihistamines also have a sedative effect and thus are commonly used as non-prescription sleep aids in Australia as they can be purchased in a community pharmacy without a prescription. The evidence gathered from the literature seems to suggest that antihistamines may be effective in the short-term treatment of insomnia, for a period of 1–2 nights, but is not effective in the treatment of chronic insomnia (Richardson et al, 2002). First-generation H1 antihistamines, also known as sedating antihistamines, obtain their sedative ability as they are
capable of penetrating the blood–brain barrier (BBB) to cause their effects (Mahdy and Webster, 2011). Thus, they are used as non-prescription sleeping aids. Conversely, second-generation H1 antihistamines lack sedative activity as they are unable to cross the BBB (Mahdy and Webster, 2011).

**Diphenhydramine**

In 1982, the FDA approved diphenhydramine hydrochloride and diphenhydramine citrate as active ingredients in non-prescription sleep aids (Randall *et al.*, 2008). Also, diphenhydramine hydrochloride is approved by the TGA as a temporary sleep aid (Therapeutic Goods Adminstration, 2012). Diphenhydramine is also used for a range of other medical problems such as alleviating allergies, and motion sickness (Simons and Simons, 2011). When used to treat sleep problems, diphenhydramine is administered in doses ranging between 25–50 mg which should be taken 30–60 minutes before bedtime (Bender *et al.*, 2003; Kudo and Kurihar, 1990). While its primary intended use is for the relief of allergies, diphenhydramine is frequently used as a sleep aid (Randall *et al.*, 2008). Diphenhydramine products often contain an analgesic such as paracetamol or ibuprofen (Morin and Benca, 2012), which can be used to provide pain relief and assist sleep induction if the insomnia is due to pain (Morin and Benca, 2012).

Despite the common use of diphenhydramine, the number controlled studies published in the literature providing evidence in support of its efficacy is limited, and they lack objective data (Estivill *et al.*, 2003; Nichols *et al.*, 2007). Many studies demonstrate that diphenhydramine exhibits sedative properties (Kudo and Kurihara, 1990; Meuleman *et al.*, 1987; Rickels *et al.*, 1983).

Diphenhydramine is an ethanolamine which has anticholinergic activity (Skidgel & Erdos, 2006). Its half-life is 3-12 hours (Husain *et al.*, 2010; Lippmann *et al.*, 2001). As a result, diphenhydramine is commonly associated with the development of mild-to-moderate side effects the following day, most notably residual morning sedation, dry mouth, grogginess, and malaise (Bender *et al.*, 2003; Kudo and Kurihar, 1990). Even though diphenhydramine produces mild-to-moderate side effects, it is the active ingredient in multiple Australian over-the-counter products marketed as sleep aids.

Rickels et al (1983) conducted a double blind, placebo-controlled, crossover study into the use of diphenhydramine (50 mg) as a treatment for insomnia. A symptom shared by all
patients was a difficulty in sleep-initiation (Rickels et al, 1983). Result showed that diphenhydramine was more effective than placebo at enhancing all sleep parameters, including sleep latency, frequency of awakenings, wake time, sleep duration, and quality of sleep, based on self-completed daily sleep-log responses (Rickels et al., 1983).

In a double-blind study conducted by Kudo and Kurihara (1990), 144 psychiatric patients complaining of symptoms characteristic of insomnia were randomly allocated to receive either a particular dose of diphenhydramine (12.5 mg, 25 mg, and 50 mg) or placebo for 2 weeks. Several self-reported sleep measures were improved such as sleep quality, duration of sleep and severity of insomnia symptoms (Kudo and Kurihara, 1990). Enhanced sleep was considerably better in patients who had not previously been treated for insomnia (Kudo and Kurihara, 1990). This implies drug tolerance, cross-drug tolerance or treatment resistance.

Significant increases in daytime sleepiness measured by Multiple Sleep Latency Tests has been demonstrated to occur with diphenhydramine (50 mg 3 times daily) versus a placebo (6.7 ± 2.6 vs 10.3 ± 3.3; P< .02) (Roth et al., 1987). This is not surprising because the dose used in this study exceeded the recommendations for sedative use which 50 mg at night. (AMH, 2012).

Shapiro et al (1969) collated observational data from a program which monitored drug use in order to assess the effectiveness of four hypnotics (chloral hydrate, diphenhydramine hydrochloride, secobarbital, and pentobarbital). This study examined 4177 patients and found that 2405 (58%) were given one or more of these drugs when admitted to hospital (Shapiro et al, 1969). Diphenhydramine was administered to 512 patients, however of these, 213 (42%) were concurrently given one or more of the other hypnotics (Shapiro et al, 1969). Patients were administered different diphenhydramine dosages (Shapiro et al, 1969). The authors did not specify how these doses were determined (Shapiro et al, 1969). 46 patients were given 100 mg, 440 patients were given 50 mg, 24 patients were given 25 mg while 2 patients received a dose other than those mentioned (Shapiro et al, 1969). Physicians rated the effectiveness of these drugs and found dose related effects (Shapiro et al, 1969). Specifically, in 259 patients, efficacy rated ‘good’ (50.6%), ‘fair’ in 42 patients (8.2%), ‘poor’ in 54 patients (10.5%), and ‘undetermined’ in 157 patients (30.7%) (Shapiro et al, 1969). What was not examined in this study was the possibility of an additive effect when a combination of hypnotic agents was taken.
Derbez and Grauer (1967) found no difference in total hourly observational wake versus sleep recordings in elderly patients with insomnia who were either administered a placebo or 25 mg diphenhydramine hydrochloride. However, a drastic improvement was observed in patients who were given Mandrax™ (methaqualone base and diphenhydramine), chloral hydrate, and methaqualone base (Derbez and Grauer, 1967). However, it must be noted that all participants suffered from psychiatric disturbances (Derbez and Grauer, 1967). Therefore, the concurrent use of hypnotics, neuroleptics, or antidepressants may have confounded the results obtained.

A randomised, double-blind, crossover study investigated the efficacy of temazepam 15 mg, diphenhydramine 50 mg, and placebo for 5 nights and found that insomniacs experienced shorter sleep latency when administered diphenhydramine than the placebo (Meuleman et al., 1987). On the fifth night diphenhydramine was more effective at prolonging the duration spent asleep than temazepam (Meuleman et al., 1987).

Richardson et al (2002) found tolerance to diphenhydramine’s hypnotic effects in both objective and subjective sleep measures following 3-4 days of taking diphenhydramine. Thus only short-term use of diphenhydramine is recommended due to the development of tolerance (Mumford et al., 1996; Richardson et al., 2002).

In the series of trials conducted by Shapiro et al (1969), adverse effects to diphenhydramine were reported in 9 out of 512 participants (1.8%) while treatment was discontinued in 8 of the 512 participants (1.6%). These side effects included vomiting and depression (Shapiro et al, 1969). Most of the participants received a dose of 50 mg diphenhydramine, and two were given 100 mg (Shapiro et al, 1969).

In a study conducted by Kudo and Kurihara (1990), the authors demonstrated that the occurrence of these side effects may be dose-dependent. In the group taking 12.5 mg diphenhydramine, no adverse side effects were reported in 95.8% of participants, while this percentage decreased in the group given 25 mg diphenhydramine (88%) and the group given 50 mg diphenhydramine (82.6%) (Kudo and Kurihara, 1990). Diphenhydramine may also cause drowsiness, dizziness, groginess, dry mouth, tiredness and weakness (Rickels et al., 1983).

Agostini et al (2001) conducted a study involving elderly hospitalised patients suffering from disturbed sleep, prophylaxis for blood transfusions, or allergic reactions in which 27% of patients received diphenhydramine. They found that diphenhydramine-treated patients
exhibited a 70% increase in the risk of developing impaired cognition, which may be dose-dependent (Agostini et al., 2001).

In children, the only reported adverse side effect from use of diphenhydramine hydrochloride was mild drowsiness (Kudo et al., 1990). The potential for abuse for dimenhydrinate, a combination of diphenhydramine and 8-chlorotheophylline, is high due to the hallucinogenic and excitatory properties it causes on the CNS when taken at a higher dosage than prescribed (Halpert, et al., 2002). Other side effects which act on the CNS are sedation, dizziness, stimulation, euphoria, nervousness, and extrapyramidal reactions (Cirillo and Tempero, 1976). Other studies demonstrate that gastrointestinal complaints, voiding difficulties, impotence, and headaches may also occur (Cirillo and Tempero, 1976). Antihistamines have been shown to increase intraocular pressure and therefore antihistamines should not be prescribed to patients with narrow angle glaucoma (Tripathi et al., 2003). These reported side effects are not surprising as antihistamines are well documented to produce anticholinergic effects (Yanai, 2012). Overdosages of antihistamines cause hallucinations, tachcardia, and convulsions (Worthley, 2002). In more severe cases, coma may occur followed by death usually as a result of hypotension or cardiac arrest (Cirillo and Tempero, 1976).

**Doxylamine**

Doxylamine succinate is an FDA and TGA approved active ingredient in over-the-counter sleep aids (AMH, 2012; Neubauer, 2007). Doxylamine succinate mediates its activity through histamine antagonism at H₁ receptors (AMH, 2012). Doxylamine has a slow onset of action as it requires a relatively long time period to reach maximum plasma concentration (Randall et al., 2008). Following oral administration, sleep is achieved after 45-60 minutes (Randall et al., 2008). To reach the peak plasma concentration, doxylamine requires 2-3 hours after administration (Krystal et al., 2006). Rickel et al (1984) found that sleep latency was significantly decreased following administration of doxylamine at a dose of 25 mg for 1 week. Also, they found that ratings given by the patient were more in favour of doxylamine in terms of sleep latency, nocturnal awakenings, sleep duration, sleep quality and morning restfulness (Rickel et al., 1984).

Mizoguchi et al (2007) conducted a randomized, double-blind, placebo-controlled, multi-center, parallel design study on 432 subjects (224 in test group, 208 in placebo group). A single night dose of syrup containing 7.5 mg doxylamine, 600 mg paracetamol, 15 mg dextromethorphan and 8 mg ephedrine sulfate was administered (Mizoguchi et al., 2007).
Subjects were asked to complete night-time symptom relief and sleep satisfaction assessments (Mizoguchi et al., 2007). The results confirmed that subjects who took test syrup had better control of cold symptoms and 25-68% confirmed better quality of sleep, indicating that the sedative effects of doxylamine could give better quality of sleep for patients with common cold (Mizoguchi et al., 2007).

This combination has different active ingredients as ephedrine was used to relief nasal congestion, dextromethorphan as an antitussive, paracetamol as an analgesic and doxylamine as a sedating agent.

The elimination half-life of doxylamine is 10 hours (Krystal et al., 2006). Therefore, upon waking, doxylamine is still present in plasma and can cause residual daytime sedation, a well-known side effect (Neubauer, 2007). Other potentially serious side effects following doxylamine overdose include rhabdomyolysis and secondary acute renal failure, exhibiting a frequency of 19% (Young-Il et al., 2007). Therefore, patients at greater risk of these side effects (eg. elderly) taking doxylamine should be carefully monitored as early identification and treatment of side effects is important (Leybishkis et al., 2001). Due to possible anticholinergic properties, H1 antihistamines are not recommended for use by the elderly which may cause or worsen mental confusion, urinary retention and constipation (Fick et al., 2003). The mechanism of action of doxylamine is the same as diphenhydramine and there is also the potential for tolerance to the sedative effects of doxylamine to develop (Randall et al, 2008).

**Doxepin**

Low-dose doxepin (3 mg and 6 mg) has recently (2010) received FDA approval for use in the treatment of insomnia characterized by difficulty in sleep maintenance. Doxepin has long been used as an antidepressant (doses from 10-150 mg) and an off-label sleep aid (Neubauer, 2008). When administered at extremely low doses, the primary pharmacologic activity of doxepin appears to be antagonism of H-1 receptors (Krystal et al., 2010; Weber et al., 2010). The issues regarding the safety of doxepin taken in high doses do not appear to apply when administered at these very low doses (Krystal et al., 2010). This is primarily due to the fact that the anticholinergic activity of this drug at low doses is negligible (Lankford et al., 2012; Roth et al., 2007).
There are few published studies regarding the use of low dose doxepin in the treatment of insomnia (Owen, 2009; Roth et al., 2007; Scharf et al., 2008). These studies are acute administration PSG studies, and show that, in adult and elderly patients suffering from primary insomnia, that 3 mg and 6 mg doses are capable of significantly reducing wakenings after sleep onset (WASO) during the sleep period and increase the total sleep time (TST) (Owen, 2009; Roth et al., 2007; Scharf et al., 2008). The 6 mg dose of doxepin is effective at decreasing sleep latency (Roth et al., 2007; Scharf et al., 2008). Even though there was a decrease in WASO, residual sedation did not occur (Roth et al., 2007; Scharf et al., 2008). It is thought that this is related to the circadian pattern of histamine release within the body, with elevated histamine levels at approximately the time of awakening, thus prevailing over the antagonistic effect of doxepin (Roth et al., 2007). The findings deduced from PSG studies are supported by subjective data (Roth et al., 2007). The type and prevalence of detrimental side effects were more or less similar to those reported in placebo groups within these trials (Owen, 2009; Roth et al., 2007; Scharf et al., 2008). Studies involving administration of nightly doxepin for three months demonstrate a similar reduction in WASO and increase in TST, without observed tolerance or safety concerns (Owen, 2009).

The longest clinical study conducted to assess the safety of doxepin lasted 3 months. More than 2% of patients taking doxepin complained of mild to moderate side effects including somnolence/sedation, nausea, and upper respiratory tract infection (Weber et al., 2010).

Tolerance of doxepin appears to be better at hypnotic doses of between 3 mg and 6 mg, than at antidepressant doses ranging from 50 to 300 mg per day (Goforth, 2009; Roth et al., 2007; Scharf et al., 2008). However, there are no published studies in the literature that directly compare to two dose ranges. Furthermore, psychomotor function, measured using Digit-Symbol Substitution Test (DSST) and Symbol-Copying Task (SCT), and sedation the following day, measured using Visual Analogue Scale (VAS), was the same for both patients receiving hypnotic doses of doxepin and those receiving placebo (Krystal et al., 2010; Roth, 2007). One study recorded significant differences SCT and VAS when 6 mg of doxepin was taken (Roth et al., 2010).

Withdrawal and rebound insomnia were investigated in a randomized, double-blind, parallel-group, placebo-controlled trial lasting 35 days conducted on adults suffering from chronic insomnia (Krystal et al., 2011). After discontinuation of 3 mg and 6 mg of doxepin, no signs of withdrawal syndrome have been recorded (Krystal et al., 2011).
**Aims**

The aims of this study were to determine:

The characteristics of patients requesting antihistamines as sleep aids; and

The actual usage and perceived efficacy of antihistamine therapy for insomnia in a sub-sample of the study population.
Chapter 2: Methodology

OVERVIEW

This study was conducted to determine the characteristics of consumers who received an antihistamine for the treatment of a sleep condition in a community pharmacy, and a more detailed exploration in these consenting to a follow-up telephone interview. The study period was February to April 2012.

PROJECT DESIGN

Project Site

Community pharmacies located throughout the Australian Capital Territory were approached to participate in this study. Written agreement to participate was obtained from each participating pharmacy.

Participants

The study was based on a convenience sample of community pharmacy clients seeking an antihistamine product as a sleep aid. It was conducted in 7 community pharmacies around the Australian Capital Territory (ACT) metropolitan area. Patients attending a participating pharmacy requesting or recommended an antihistamine for insomnia and aged 18 years or older were eligible for recruitment. Eligible patients were asked by the pharmacist or pharmacy assistant (using a standardised script) if they would participate in the study and complete an anonymous written survey regarding their treatment of insomnia. Verbal informed consent was obtained from all participants before the survey form was provided. The bottom of the survey form contained an optional part where patients could choose to provide their first name and a contact telephone number. This option was to allow a researcher (FA) to contact these patients after two weeks to conduct a telephone follow-up survey regarding the effectiveness of the antihistamine and other factors for their insomnia. The survey form was placed in a locked box in the pharmacy upon completion. A researcher (FA) visited each pharmacy to empty the locked box once per week during the study period. Individuals who provided their contact details were contacted approximately 2 weeks after completing the initial survey. Informed verbal consent was obtained from each participant before commencing the telephone interview. A second survey instrument was used to collect data on other factors affecting insomnia and subjective data related to the effectiveness of the antihistamine for the patient’s insomnia.
**Pharmacy staff**

The researcher visited each pharmacy to provide training on the study protocols. Inclusion criteria were described and a sample script (Appendix A) provided to assist in recruiting patients into the study.

**Instruments**

This study consisted of two phases: 1) recruitment and in-pharmacy survey (Appendix B); and 2) follow-up telephone interview (Appendix C). The questions in both the survey and telephone interview were adapted from the COPSAT sleep survey tool developed at the University of Queensland.

COPSAT is a sleep survey tool developed at the University of Queensland which is based on the Insomnia Severity Index (ISI) and Epworth Sleepiness Scale (ESS) which are validated instruments to quantify perceived insomnia severity. The COPSAT survey not included in the appendix because it is currently an unpublished tool, uncovered through peer networks.

**Phase 1: Recruitment and in-pharmacy survey**

A single page in-pharmacy survey was used as the initial data-gathering instrument for this study. This survey assessed a number of sociodemographic characteristics of respondents that have been examined in previous studies of risk factors for insomnia. These include age, gender and highest education level. Other questions explored previously used insomnia treatments and participant characterisation of their insomnia. Tick boxes were used to guide patient categorisation and limit investigator interpretation of open patient comments.

**Phase 2: Follow-up telephone survey**

The follow-up telephone survey consisted of 17 open-ended questions to assess the effectiveness of the antihistamine used in the treatment of insomnia, and other factors related to causes of insomnia, such as caffeine and/or alcohol consumption and smoking status. The researcher (FA) collated participants’ open responses into the categories used in the COPSAT for ease of data analysis.
Data Processing and Analysis

All the completed in-pharmacy survey responses were tabulated and depicted graphically. Statistical analyses were performed using Microsoft Excel™ computer software and SPSS 19 software. The Pearson chi-square test was then used for cross-tabulated variables. For all statistical tests, the a priori value for statistical significance was set at p < 0.05.

Ethics

Ethical approval for this study was obtained from the Committee for Ethics in Human Research, Faculty of Health, University of Canberra (Approval number 11-132).
Chapter 3: Results

Seventy-three people completed in the Pharmacy questionnaire of whom 48 agreed to participate in a more detailed telephone follow-up survey 2 weeks after the pharmacy questionnaire to assess efficacy of the antihistamine provided.

Part 1: Pharmacy Questionnaire

Seventy-three participants (47 (63.5%) female) over 18 years of age completed a brief questionnaire administered by pharmacy staff. The initial survey contained questions about the individual’s demographic characteristics (age, gender, and education level), sleep patterns and treatments already tried. All subjects identified symptoms of insomnia.

Age distribution

Age was categorized into 10-year bands from 18 -66 years or more, except the 18-25 and 66+ groups. The age distribution is shown in Figure 1. If the 18-25 age group is removed, the remaining distribution appears to approximate a normal distribution. However, this sample is not normally distributed because it is a self-selected group who sought treatment for self-identified symptoms of insomnia in a community pharmacy.

The study sample consisted of 47 women (63.5%) and 26 men (36.5%). All subjects were seeking treatment for insomnia in a community pharmacy.
The age-gender breakdown (Tables 4&5) show an inversion in the male/female split between those participants aged 18-35 years (60.7% male) and those over 35 years (80.0% female) (p= 0.000021).

**Table 4. Age and Gender Cross tabulation**

<table>
<thead>
<tr>
<th>Age</th>
<th>Male n (% )</th>
<th>Female n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>10 (22.6%)</td>
<td>9 (47.4%)</td>
<td>19</td>
</tr>
<tr>
<td>26-35</td>
<td>7 (77.8%)</td>
<td>2 (22.2%)</td>
<td>9</td>
</tr>
<tr>
<td>36-45</td>
<td>3 (23.1%)</td>
<td>10 (76.9%)</td>
<td>13</td>
</tr>
<tr>
<td>46-55</td>
<td>4 (28.6%)</td>
<td>10 (71.4%)</td>
<td>14</td>
</tr>
<tr>
<td>56-65</td>
<td>2 (16.7%)</td>
<td>10 (83.3%)</td>
<td>12</td>
</tr>
<tr>
<td>66+</td>
<td>0 (0.0%)</td>
<td>6 (100.0%)</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>26 (35.6%)</td>
<td>47 (64.4%)</td>
<td>73</td>
</tr>
</tbody>
</table>

**Table 5. Condensed Age and Gender Cross tabulation**

<table>
<thead>
<tr>
<th>Age</th>
<th>Male n (% )</th>
<th>Female n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-35</td>
<td>17 (60.7%)</td>
<td>11 (39.3%)</td>
<td>28</td>
</tr>
<tr>
<td>36+</td>
<td>9 (20.0%)</td>
<td>36 (80.0%)</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>26 (35.6%)</td>
<td>47 (64.4%)</td>
<td>73</td>
</tr>
</tbody>
</table>

**Education Level**

Participants were asked to indicate the highest education level they had achieved: diploma or less, bachelor degree, and postgraduate study. The largest group of participants had achieved a diploma or less (Figure 2), suggesting those with a higher education level either may have less trouble with insomnia, are less likely to seek assistance in a community pharmacy, or are less likely to participate in point of care research. No differences were found in the gender mix between education levels (Figure 2) (p=0.443).
Figure 2. Education levels of participants

The gender distribution by education level was quite even (Figure 3).

Figure 3. Distribution of highest education level by gender

How often do you think you have difficulties falling asleep?

Almost one third of participants (30.1%) identified difficulty initiating sleep 5-7 times per week with equal proportions of 23.3% each identifying difficulty falling asleep less than once per week, 1-2 times per week and 3-4 times per week.
When cross-tabulated with age, the maximum frequency of difficulty falling asleep increased with increasing age (shaded cells, Table 6) (p=0.006). A higher proportion of older participants reported more frequent difficulty falling asleep.

Table 6. Difficulty falling asleep and age cross tabulation

<table>
<thead>
<tr>
<th>Difficulty falling asleep</th>
<th>18-25</th>
<th>26-35</th>
<th>35-45</th>
<th>46-55</th>
<th>56-65</th>
<th>66+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per week</td>
<td>Count</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>29.4%</td>
<td>17.6%</td>
<td>29.4%</td>
<td>23.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>Count</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>52.9%</td>
<td>23.5%</td>
<td>11.8%</td>
<td>0%</td>
<td>11.8%</td>
<td>0%</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>Count</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>11.8%</td>
<td>0%</td>
<td>17.6%</td>
<td>35.3%</td>
<td>23.5%</td>
<td>11.8%</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>Count</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>13.6%</td>
<td>9.1%</td>
<td>13.6%</td>
<td>18.2%</td>
<td>27.3%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
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<td>9</td>
<td>13</td>
<td>14</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>26%</td>
<td>12.3%</td>
<td>17.8%</td>
<td>19.2%</td>
<td>16.4%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

How often do you think you have difficulty staying asleep?
The largest proportion (32.9%) of participants reported interrupted sleep 5-7 times per week (Table 7). It is not known if an answer of 7 times per week was an occurrence of each night or more awakenings on fewer nights. Interestingly, the second most frequent response (30.1%) was less than once per week. Recall bias could be a factor in these data.

Table 7. Frequency of staying asleep

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per week</td>
<td>30.1</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>13.7</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>23.3</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>32.9</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Similar to the “difficulty falling asleep” above, the maximum frequency of difficulty staying asleep also increased with increasing age (shaded cells, Table 8) when cross-tabulated (p=0.004).
Table 8. Difficulty staying asleep and age cross tabulation

<table>
<thead>
<tr>
<th>Difficulty staying asleep</th>
<th>Age</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per week</td>
<td>18-25</td>
<td>9</td>
<td>40.9%</td>
<td>5</td>
<td>27.2%</td>
<td>3</td>
<td>13.6%</td>
<td>4</td>
<td>18.2%</td>
<td>1</td>
<td>4.5%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>26-35</td>
<td>5</td>
<td>40.9%</td>
<td>2</td>
<td>10%</td>
<td>2</td>
<td>10%</td>
<td>1</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>36-45</td>
<td>3</td>
<td>60%</td>
<td>2</td>
<td>20%</td>
<td>1</td>
<td>10%</td>
<td>2</td>
<td>10%</td>
<td>0</td>
<td>0%</td>
<td>13.7%</td>
</tr>
<tr>
<td></td>
<td>46-55</td>
<td>4</td>
<td>40%</td>
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<td>20%</td>
<td>1</td>
<td>10%</td>
<td>1</td>
<td>5.9%</td>
<td>17</td>
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<tr>
<td></td>
<td>56-65</td>
<td>1</td>
<td>11.8%</td>
<td>6</td>
<td>35.3%</td>
<td>5</td>
<td>29.4%</td>
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<td>9.2%</td>
<td>6</td>
<td>29.4%</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>66+</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>6</td>
<td>20.8%</td>
<td>1</td>
<td>3.3%</td>
<td>1</td>
<td>3.3%</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>19</td>
<td>26%</td>
<td>9</td>
<td>12.3%</td>
<td>13</td>
<td>17.8%</td>
<td>14</td>
<td>19.2%</td>
<td>12</td>
<td>16.4%</td>
<td>6</td>
</tr>
</tbody>
</table>

How often do you think you have frequent awakening from sleep?

Maintenance of sleep, once established, followed a similar pattern to the previous question of difficulty staying asleep (Table 9), with the largest proportion reporting 5-7 times per week (34.2%) followed by less than once per week (26.0%). This is not surprising given the similarity in the two questions. There was a trend towards increased incidence of this factor with increasing age (shaded cells, Table 10), however, it did not quite reach statistical significance (p=0.083).

Table 9. Frequency of awakening from sleep

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per week</td>
<td>26.0</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>16.4</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>23.3</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>34.2</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 10. Awakening from sleep and age cross tabulation

<table>
<thead>
<tr>
<th>Awakening from sleep</th>
<th>Age</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per</td>
<td>18-25</td>
<td>8</td>
<td>42.1%</td>
<td>4</td>
<td>21.1%</td>
<td>3</td>
<td>15.8%</td>
<td>3</td>
<td>15.8%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>week</td>
<td>26-35</td>
<td>5</td>
<td>41.7%</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>16.7%</td>
<td>1</td>
<td>8.3%</td>
<td>4</td>
<td>33.3%</td>
<td>0</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>36-45</td>
<td>3</td>
<td>17.6%</td>
<td>3</td>
<td>17.6%</td>
<td>3</td>
<td>17.6%</td>
<td>5</td>
<td>29.4%</td>
<td>2</td>
<td>11.8%</td>
<td>1</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>46-55</td>
<td>3</td>
<td>17.6%</td>
<td>2</td>
<td>20%</td>
<td>5</td>
<td>20%</td>
<td>6</td>
<td>24%</td>
<td>6</td>
<td>16%</td>
<td>4</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>56-65</td>
<td>3</td>
<td>12%</td>
<td>2</td>
<td>8%</td>
<td>5</td>
<td>20%</td>
<td>5</td>
<td>24%</td>
<td>12</td>
<td>16%</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>66+</td>
<td>19</td>
<td>26%</td>
<td>9</td>
<td>12.3%</td>
<td>13</td>
<td>17.8%</td>
<td>14</td>
<td>19.2%</td>
<td>12</td>
<td>16.4%</td>
<td>6</td>
</tr>
</tbody>
</table>

How often do you think you have frequent awakening from sleep?
How often do you feel that your sleep is refreshing?

Over one third of respondents (37.0%) stated their sleep was not refreshing on most nights (Table 11). This complements the results above, and is not surprising, given the population for this study is those people seeking a sleep aid in a community pharmacy. When the nature of the population is considered (ie seeking a sleep aid), this result could be considered low.

Table 11. Frequency of self-reported refreshing sleep

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per week</td>
<td>37.0</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>27.4</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>19.2</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>16.4</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

No significant association was found between the frequency of refreshing sleep and age (Table 12) (p=0.332).

Table 12. Refreshing sleep and Age Cross tabulation

<table>
<thead>
<tr>
<th>Refreshing sleep</th>
<th>Age 18-25</th>
<th>Age 26-35</th>
<th>Age 36-45</th>
<th>Age 46-55</th>
<th>Age 56-65</th>
<th>Age 66+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per week</td>
<td>Count 5</td>
<td>Count 4</td>
<td>Count 7</td>
<td>Count 6</td>
<td>Count 3</td>
<td>Count 2</td>
<td>Count 27</td>
</tr>
<tr>
<td></td>
<td>% 18.5%</td>
<td>% 14.8%</td>
<td>% 25.9%</td>
<td>% 22.2%</td>
<td>% 11.1%</td>
<td>% 7.4%</td>
<td>% 37.0%</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>Count 8</td>
<td>Count 2</td>
<td>Count 2</td>
<td>Count 5</td>
<td>Count 2</td>
<td>Count 1</td>
<td>Count 20</td>
</tr>
<tr>
<td></td>
<td>% 40%</td>
<td>% 10%</td>
<td>% 10%</td>
<td>% 25%</td>
<td>% 10%</td>
<td>% 5%</td>
<td>% 27.4%</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>Count 5</td>
<td>Count 1</td>
<td>Count 2</td>
<td>Count 1</td>
<td>Count 4</td>
<td>Count 1</td>
<td>Count 14</td>
</tr>
<tr>
<td></td>
<td>% 35.7%</td>
<td>% 7.1%</td>
<td>% 14.3%</td>
<td>% 7.1%</td>
<td>% 28.6%</td>
<td>% 7.1%</td>
<td>% 19.2%</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>Count 1</td>
<td>Count 2</td>
<td>Count 2</td>
<td>Count 2</td>
<td>Count 3</td>
<td>Count 2</td>
<td>Count 12</td>
</tr>
<tr>
<td></td>
<td>% 8.3%</td>
<td>% 16.7%</td>
<td>% 16.7%</td>
<td>% 25%</td>
<td>% 16.7%</td>
<td>% 16.7%</td>
<td>% 16.4%</td>
</tr>
<tr>
<td>Total</td>
<td>Count 19</td>
<td>Count 9</td>
<td>Count 13</td>
<td>Count 14</td>
<td>Count 12</td>
<td>Count 6</td>
<td>Count 73</td>
</tr>
<tr>
<td></td>
<td>% 26%</td>
<td>% 12.3%</td>
<td>% 17.8%</td>
<td>% 19.2%</td>
<td>% 16.4%</td>
<td>% 8.2%</td>
<td>% 100%</td>
</tr>
</tbody>
</table>

Have you tried any other treatment?

Almost 80% of participants (79.5 %) had previously tried at least one different type of treatment before seeking the treatment that qualified them for inclusion in this study.

Which product(s) have you tried for insomnia?

More than half the respondents reported using a herbal and/or an over the counter product and (52.1% and 50.6% respectively) (Table 13). Approximately one quarter used a prescription medication (26.0%) and almost one-fifth had used alcohol as a sleep aid (19.2%). Natural
activities were also taken in consideration, having 12.3% for behavior therapy, 32.9% for relaxation, and 37.0% for exercise.

Table 13. Product (s) previously used for insomnia

<table>
<thead>
<tr>
<th>Product that has been used</th>
<th>Percentage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal</td>
<td>52.1%</td>
</tr>
<tr>
<td>OTC</td>
<td>50.7%</td>
</tr>
<tr>
<td>Exercise</td>
<td>37.0%</td>
</tr>
<tr>
<td>Relaxation</td>
<td>32.9%</td>
</tr>
<tr>
<td>Prescription Medicine</td>
<td>26.0%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>19.2%</td>
</tr>
<tr>
<td>Behavior</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

*Participants could indicate more than one choice

Relaxation (11.0%), over the counter products (8.2%) and exercise (8.2%) were more commonly used by younger participants (18-25 years) while prescribed medications were rarely used (1.37%) (Table 14). In the 26-35 year age group, over the counter medication was the most commonly used sleep aid (5.5%). Herbal remedies were commonly used by participants aged 36-45 (12.3%). Over the counter medication was the most common sleep aid (13.7%) used by patients aged 46-55. Equal proportions of 11.0% of participants aged 56-65 years had used either over the counter and/or herbal products.

Table 14. Other treatments used by participants by age group

<table>
<thead>
<tr>
<th>Age Range</th>
<th>OTC</th>
<th>Herbal</th>
<th>Alcohol</th>
<th>Behavior</th>
<th>Prescription</th>
<th>Relaxation</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>6.9%</td>
<td>8.2%</td>
<td>5.5%</td>
<td>2.7%</td>
<td>1.4%</td>
<td>8.2%</td>
<td>11%</td>
</tr>
<tr>
<td>26-35</td>
<td>5.5%</td>
<td>4.1%</td>
<td>2.7%</td>
<td>1.4%</td>
<td>2.7%</td>
<td>4.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>36-45</td>
<td>9.6%</td>
<td>12.3%</td>
<td>2.7%</td>
<td>1.4%</td>
<td>4.1%</td>
<td>8.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>46-55</td>
<td>13.7%</td>
<td>12.3%</td>
<td>4.1%</td>
<td>4.1%</td>
<td>5.5%</td>
<td>9.6%</td>
<td>12.3%</td>
</tr>
<tr>
<td>56-65</td>
<td>10.9%</td>
<td>10.9%</td>
<td>4.1%</td>
<td>2.7%</td>
<td>6.9%</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>66+</td>
<td>4.1%</td>
<td>4.1%</td>
<td>0%</td>
<td>0%</td>
<td>5.5%</td>
<td>1.4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Total</td>
<td>50.7%</td>
<td>52.1%</td>
<td>19.2%</td>
<td>12.3%</td>
<td>26.1%</td>
<td>32.9%</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

Highest result in each row (by age)
Highest result in each column (by treatment)
Result if highest in a particular row & column together

How often you have used antistamine as a sleep aid?

The majority of respondents (60.2%) identified that they had previously used an antihistamine as a sleep aid (Figure 4). Of the 44 respondents who had previously used an antihistamine,
almost three quarters (72.8%) had used it on an as required basis, 13.6% once weekly and 13.6% used it a couple of times a week.

![Pie chart showing frequency of using antihistamine](image)

**Figure 4. Frequency of using Antihistamine**

**Which product was recommended for treatment of your insomnia?**

All participants (100%) used doxylamine for the treatment of insomnia complaints.

**Part 2: Telephone interview survey**

Forty-eight of the original 73 participants opted to complete a follow up telephone interview to evaluate the effectiveness after using antihistamine by providing contact details. Participants who elected to participate in this additional interview were asked more detailed questions about other factors which might impact on their sleep patterns.

**Participant demographics**

Three quarters of this sub-sample (36, 75.0%) were women. The age distribution for this part was skewed to the 36-65 bracket (Figure 5), however, the education distribution was similar to the total study population with half the participants in this part of the study (50.0%) having achieved a diploma or less (Figure 6).
Figure 5. Age group for Part 2 telephone survey

Figure 6. Education level of respondents for Part 2 telephone survey
Effect of caffeine consumption on falling asleep

Participants were asked about their caffeine consumption (tea, coffee or soft drink beverage) to explore the association between daily caffeine intake and patient’s ability to fall asleep. The majority of respondents (61.2%) stated that they consumed caffeine 2 to 3 times a day (Table 15), with a further 26.5% having caffeine once a day. Only 4.1% of participants stated they did not consume caffeine.

Table 15. Frequency of caffeine consumption

<table>
<thead>
<tr>
<th>Caffeine Consumption</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>4.1</td>
</tr>
<tr>
<td>Less than once a day</td>
<td>2.0</td>
</tr>
<tr>
<td>Once a day</td>
<td>26.5</td>
</tr>
<tr>
<td>2 to 3 times a day</td>
<td>61.2</td>
</tr>
<tr>
<td>More than 4 times a day</td>
<td>6.1</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

No significant relationship was found between caffeine consumption and difficulty falling asleep variables, however, there was a trend towards increased incidence of difficulties falling asleep with increasing caffeine consumption (shaded cells, Table 16) (p=0.063).

Table 16. Caffeine consumption and difficulty falling asleep Cross tabulation

<table>
<thead>
<tr>
<th>Caffeine Consumption</th>
<th>Difficulty Falling Asleep Frequency</th>
<th>1-2 times per week</th>
<th>3-4 times per week</th>
<th>5-7 times per week</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than once per week</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>50%</td>
<td>0%</td>
<td>5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Never</td>
<td>Count</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>50%</td>
<td>0%</td>
<td>5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Less than once a day</td>
<td>Count</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Once a day</td>
<td>Count</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>16.7%</td>
<td>25%</td>
<td>50%</td>
<td>25.0%</td>
</tr>
<tr>
<td>2 to 3 times a day</td>
<td>Count</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>10%</td>
<td>16.7%</td>
<td>30%</td>
<td>62.5%</td>
</tr>
<tr>
<td>More than 4 times a day</td>
<td>Count</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>6</td>
<td>9</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>12.5%</td>
<td>18.8%</td>
<td>31.3%</td>
<td>37.5%</td>
</tr>
</tbody>
</table>

Most respondents consumed caffeine containing beverages 1-3 times a day with highest proportion was seen within age group 36-55 consuming caffeine two to three times a day (Table 17).
### Table 17. Caffeine consumption with age group Cross tabulation

<table>
<thead>
<tr>
<th>Caffeine consumption</th>
<th>Age</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-25</td>
<td>26-35</td>
<td>36-45</td>
<td>46-55</td>
<td>56-65</td>
<td>66+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Less than once a day</td>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Once a day</td>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>2 to 3 times a day</td>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>More than 4 times a day</td>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.6%</td>
<td></td>
</tr>
</tbody>
</table>

**Alcohol Consumption**

Respondents were asked about their alcohol consumption status and frequency (Table 18). Sixty percent stated that they drank alcohol 2-3 times a week, with 25.0% drinking more than 4 times a week.

### Table 18. Frequency of alcohol drinking per week

<table>
<thead>
<tr>
<th>Alcohol Drinking Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>10.4</td>
</tr>
<tr>
<td>Once a week</td>
<td>4.2</td>
</tr>
<tr>
<td>2 to 3 times a week</td>
<td>60.4</td>
</tr>
<tr>
<td>More than 4 times a week</td>
<td>25.0</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

No statistically significant relationship was found between frequency of alcohol consumption and difficulties falling asleep. However, consuming alcohol 2-3 times a week appears to increase the incidence of all frequencies of difficulty falling asleep. The amount of alcohol consumed was not requested.
Table 19. Difficulties Falling Asleep and Alcohol Consumption Cross tabulation

<table>
<thead>
<tr>
<th>Difficulties Falling Asleep</th>
<th>Alcohol Consumption</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>Once a week</td>
</tr>
<tr>
<td>Less than once per week</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>12.5%</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>16%</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6.3%</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>32%</td>
</tr>
<tr>
<td>5-7 times per week</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10.45%</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>100%</td>
</tr>
</tbody>
</table>

Smoking status

Participants were classified as smokers if they reported smoking of any kind (cigarette, pipe or cigar) and as non-smokers otherwise. A narrow majority of respondents (47.9%) were smokers (Table 20). Smokers were significantly more likely than non-smokersto report more frequent difficulties falling asleep (p=0.003).

Table 20. Smoking and Difficult falling asleep Cross tabulation

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Frequency of difficulties falling asleep</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than once per week</td>
<td>1-2 times per week</td>
</tr>
<tr>
<td>Non smoker</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>Smoker</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>%</td>
</tr>
</tbody>
</table>

Effects of antihistamine on sleep latency

Table 21 shows a clear difference in sleep latency between pre- and post-antihistamine use (p=0.002). When the respondents were not using an antihistamine, the sleep latencies were higher than when using antihistamines. Given antihistamines are used for sleep disturbances, this finding shows their efficacy.
Table 21. Sleep latency time before and after using antihistamine

<table>
<thead>
<tr>
<th>Sleep latency time</th>
<th>Before using antihistamine</th>
<th>After using antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1/2 hour</td>
<td>0</td>
<td>77.1</td>
</tr>
<tr>
<td>1/2 - 1 hour</td>
<td>0</td>
<td>18.8</td>
</tr>
<tr>
<td>1 - 2 hours</td>
<td>39.6</td>
<td>4.2</td>
</tr>
<tr>
<td>2 - 3 hours</td>
<td>47.9</td>
<td>0</td>
</tr>
<tr>
<td>More than 3 hours</td>
<td>12.5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Quality of sleep before and after using antihistamine

Participants were asked to assess the quality of their sleep before and after antihistamine use (Table 22). Before treatment, the vast majority rated their sleep quality as “poor” or “very poor” (85.5%), whereas after (or during) treatment with an antihistamine, 93.7% rated their sleep as “good” or “very good”.

Table 22. Quality of sleep before and after using antihistamine

<table>
<thead>
<tr>
<th>Quality of sleep before using antihistamine</th>
<th>Quality of sleep after Using antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Very poor</td>
<td>29.2</td>
</tr>
<tr>
<td>Poor</td>
<td>56.3</td>
</tr>
<tr>
<td>Average</td>
<td>12.5</td>
</tr>
<tr>
<td>Good</td>
<td>2.1</td>
</tr>
<tr>
<td>Very good</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Nap time before and after using Antistamine

The responses to the question about napping did not change with antihistamine use (Table 23), therefore, antihistamine use was not associated with any change in day time subjective sleepiness.
Table 23. Nap length time before and after using antihistamine

<table>
<thead>
<tr>
<th>Nap length time</th>
<th>How long do you nap during the day before antihistamine?</th>
<th>How long do you nap during the day after antihistamine?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not nap</td>
<td>79.2%</td>
<td>79.2%</td>
</tr>
<tr>
<td>0-15 minutes</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>16-30 minutes</td>
<td>14.6%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Longer than 30 minutes</td>
<td>6.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

**Effect of Antihistamine on awakening after sleep onset**

Participants were asked about fragmentation characteristics include mid-sleep awakening, wakening after sleep onset and time delay to fall asleep again after awakening.

Table 24, shows a significant impact of antihistamine usage where 95.8% of participants who experienced awakening before antihistamine (of varying duration) did not wake after using an antihistamine (p=0.017).

Table 24. Wake time after sleep onset before and after using antihistamine Cross tabulation

<table>
<thead>
<tr>
<th>How long does it take fall asleep again when you wake you up at night before antihistamine?</th>
<th>How long does it take fall asleep again when you wake you up at night after antihistamine?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>No awaking</td>
<td>Between 1/2-1 hour</td>
</tr>
<tr>
<td>less than half hour</td>
<td>15</td>
<td>100%</td>
</tr>
<tr>
<td>Between 1/2-1 hour</td>
<td>14</td>
<td>100%</td>
</tr>
<tr>
<td>1 to 2 hours</td>
<td>14</td>
<td>93.3%</td>
</tr>
<tr>
<td>2 to 3 hours</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>More than 3 hours</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>95.8%</td>
</tr>
</tbody>
</table>

**How long and you how often you have used an antihistamine as a sleep aid?**

The range of time participants used an antihistamine as a sleep aid was 2 to 14 days with a mean of 5 days.
Respondents were also asked about how frequently they have used antihistamine as a sleep aid. Half (50.0%) reported using an antihistamine every night while 33.3% reported using one on a “when necessary” basis and 16.7% used one more regularly, rated as “a couple of times a week” (Figure 7).

**Figure 7. Frequency of taking antihistamine**

### Effect of Antihistamine on daytime sleepiness

Respondents were asked if using an antihistamine was associated with daytime sleepiness. Almost three-quarters (72.9%) reported no chance (Table 25), 20.8% reported slight chance and 6.3% a moderate chance of daytime drowsiness. These data correlate well with the daytime napping question (Table 26).

**Table 25. Effect of antihistamine on daytime sleepiness**

<table>
<thead>
<tr>
<th>Antihistamine effects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chance</td>
<td>72.9</td>
</tr>
<tr>
<td>Slight chance</td>
<td>20.8</td>
</tr>
<tr>
<td>Moderate chance</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

### Effect of Antihistamine on ability to stay awake during the day

Respondents were asked if using an antihistamine affected their ability to stay awake during the day. Similar to table 25 above, 72.9% stated not at all (Table 26), 16.7% a little, 4.2% somewhat affected and 6.3% reported they were very much affected.
Table 26. Effect of Antihistamine on ability to stay awake during the day

<table>
<thead>
<tr>
<th>Antihistamine effect</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>72.9</td>
</tr>
<tr>
<td>A little</td>
<td>16.7</td>
</tr>
<tr>
<td>Somewhat</td>
<td>4.2</td>
</tr>
<tr>
<td>Very much</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Effect of antihistamine on work performance**

When asked if using an antihistamine has affected their ability to perform their work, more impact was reported (Table 27). In response to this question, the “Not at all” response (39.6%) almost half that of the previous question (72.9%, Table 27)%.

Table 27. Effect of antihistamine on work performance

<table>
<thead>
<tr>
<th>Antihistamine effect</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>39.6</td>
</tr>
<tr>
<td>A little</td>
<td>18.8</td>
</tr>
<tr>
<td>Somewhat</td>
<td>18.8</td>
</tr>
<tr>
<td>Much</td>
<td>16.7</td>
</tr>
<tr>
<td>Very much</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Side effects of antihistamines**

Almost one third (31.1%) stated that an antihistamine did not cause any side effects (table 28). Over half the respondents reported drowsiness (54.2%), 12.6% dry mouth and only 2.1% said that antihistamine caused nausea.

Table 28. Side effects of antihistamine

<table>
<thead>
<tr>
<th>Side effects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No side effects</td>
<td>31.1</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>54.2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Patient's opinion on antihistamines as a sleep aid

As an overall subjective assessment, 97.9% of respondents reported that an antihistamine was helpful for treating their sleep problem.
Chapter 4: Discussion and Conclusion

This study recruited a range of people seeking treatment for insomnia in community pharmacies in the Australian Capital Territory. The collated data showed that younger people (18-25 years) exhibited a high frequency of seeking a sleep aid in a community pharmacy compared to other age groups. A possible explanation for this observation is the fact that older patients can experience a range of other health issues that require medical attention, compared to younger individuals (Australian Institute of Health and Welfare [AIHW], 2010). It is logical to extrapolate that older individuals experiencing one or more other health issues are more likely to seek medical treatment and therefore could be more likely to seek medical treatment of insomnia rather than self-medication in a community pharmacy.

Overall, this study concurs with the findings of several previous studies (Arber et al, 2009; Groeger et al, 2004; Lindberg et al. 1997; Middelkoop et al, 1996) which reported a higher frequency of insomnia in females than males independent of age. One age category was an exception to this (26-35 years), where males had a higher incidence of insomnia than females. After the age of 35 years, the difference between men and women becomes more apparent which is consistent with Polish study findings that the incidence of insomnia increased with age more rapidly in women aged 35 years and over than men (Kiejna et al, 2003). Johnson et al (2006) found that the rate of insomnia was the same for boys and girls until a girl’s menes, when the risk of developing insomnia increased almost three-fold and continued to increase throughout life. Although our participants were aged over 18, these data support the reported higher incidence of insomnia in females than males. Hormones (Kravitz et al, 2005), pregnancy (Santiago et al, 2001), menopause, stress, medical conditions, and complex home life (Meltzer & Mindell, 2006) may all be factors which contribute to the higher prevalence of insomnia in females. Furthermore, Ohayon (2006) reported that 80% of women experiencing severe hot flashes also reported chronic insomnia.

One of the aims of this study was to explore the symptoms and frequency of insomnia in those receiving antihistamine treatments in a community pharmacy. While difficulty initiating sleep, difficulty maintaining sleep and frequent awakening all increased with increasing age, subjective expression of restorative sleep did not show a clear age-related pattern. These findings are supported in the literature (Hoffmann, 1999; Klink et al, 1992; Ohayon & Smirne, 2002; Ancoli-Israel & Roth, 1999) where non-restorative sleep is usually reported by
younger individuals (Ohayon & Bader, 2010; Ohayon & Smirne, 2002). The higher rate of insomnia observed in the older participants involved in this study could be due to multiple medical problems which they are more likely to experience, polypharmacy, and environmental factors such as institutionalisation and the absence of a daily schedule, however, these issues were not explored. Older adults who are healthy and active with a good social life have been reported to not have higher rates of insomnia (Benca et al, 2004; Foley et al, 1999; Janson et al, 2001; Ohayon et al, 2001).

The findings of the present study suggest that the relationship between age and insomnia may be explained by various other factors. In recent years, the relationship between increasing age and the risk of developing insomnia has been investigated and a positive correlation found (Komada et al, 2011; Morphy et al, 2007; Paparrigopoulos et al, 2010; Klink & Quan, 1987; Ohayon, 1996; Weyerer & Dilling, 1991). Foley et al. (1999) showed that in a 3-year longitudinal study involving 6,800 older people, increasing age was not linked with insomnia in healthy individuals. Foley et al. (1999) suggested that other factors such as chronic disease, physical disability, depressed mood, poor perceived health, widowhood, and use of sedatives were more likely explanations for the incident insomnia. Comorbidities were not investigated in this study; therefore it is difficult to draw a comparison with Foley et al’s (1999) work. However, future research could investigate the causal links in more detail.

However, other studies have determined that there is not a clear correlation between increasing age and the development of insomnia. (Liljenberg et al, 1988; Ohayon et al, 1997). The results of this study concur with that published by Palleson et al. (2001) who showed that problems maintaining sleep were more frequent in the elderly participants, with daytime impairment less common.

**Education Status**

Education level was found to have an inverse relationship with the risk in experiencing insomnia with no difference found between genders. This result is supported in the literature where individuals of lower education status were significantly more likely to experience insomnia compared to more highly educated individuals (Frisoni et al, 1993; Gellis et al, 2005; Hartz et al, 2007). The explanation of this association could be that the higher the education level achieved by an individual, the greater their knowledge concerning sleep hygiene practices and how improved sleep can be achieved. Hislop & Arber (2003) also suggested that more educated individuals may be more willing to be involved in attempts to
use various strategies to overcome their insomnia symptoms, and also recognise the benefits of sleep for health and well-being (e.g. through awareness from media sources).

**Treatments for Insomnia**

The results of this study suggest that the use of both pharmacological and non-pharmacological treatments for insomnia is a relatively common practice among participants. Herbal-based supplements were the most commonly used treatment reported (52.1%), with prescription medicines used by 26.0%. This appears to be much greater than the prescription hypnotic use in other countries such as France (9.8%), the US (8%) the UK (3.6%) and Germany (2.4%) (Ohayon, 2001; Roehrs et al, 2002). However, the international hypnotic use rates are sourced from the general population, whereas this study interviewed people who self-identified insomnia and were seeking treatment in a community pharmacy, therefore a higher rate of hypnotic use is not unexpected.

The proportion of individuals surveyed who used OTC medications was 50.7%. This result is much higher rate than USA where 10% OTC sleep aid use has been reported (Roehrs et al, 2002). Also, alcohol use was almost double (19.2%) that of insomniacs in the USA (10%) (Roehrs et al, 2002). The AIHW reported that 7.2% of the Australian population over 12 years of age consumed alcohol daily in 2010 (AIHW, 2011) this is just less than half the rate found for respondents with a sleep problem. Whether these clear differences between countries in the use of medications or a healthcare intervention reveal differences in cultural or economic status is unclear and requires further investigation. Finally, 82.2% of individuals surveyed in this study used a range of self-help methods to treat insomnia including relaxation, exercise or other behavioural strategies. This result shows that insomniacs may use a variety of such self-help remedies for a considerable period of time before seeking professional help. This result is consistent with the findings of Morin et al (2006).

A majority of participants (60.2%) had used an antihistamine previously (at the time of survey) as a sleep aid. Pillitteri et al (1994) found that among college students who reported sleep problems, 6.4% of men and 11.4% of women reported using OTC sleep aids, although this is a younger age group, and almost 20 years old. The age of these data is important as restrictions on pharmaceuticals have been eased over this timeframe, making antihistamines more accessible now than they were in 1994.
Of the respondents who had previously used an antihistamine, the majority (72.7%) reported using it as required, with 13.6% each reporting once weekly use or “a couple of times a week”. High proportions of individuals who experience transient insomnia self-medicate for short periods of time (less than 1 week) with OTC products (Johnson et al, 1998). Ohayon et al (1998) showed that most of the subjects used antihistamine at least 3 days per week (53.7%) and had been doing so for over 1 month (57.6%). These results appear conflicted, however, countries place different restrictions on antihistamines – for example, they require a prescription in the USA. Self medication of antihistamine could be enhanced by the low cost and ease of obtaining OTC medication in Australia rather than visiting a physician. Diminished physician involvement in the prescription of OTC medication and freedom to move between community pharmacies reduces patient follow-up and may lead to the misuse of these medications, potentially leading to dependence. Ancoli-Israel (1999) and Roth (1999) reported that it is rare for insomniacs to see a physician about their sleep problem with 40% of insomniacs preferring to self-medicate with either OTC medications or alcohol.

**Caffeine consumption**

There was a trend towards an increased incidence of difficulty falling asleep with increasing caffeine consumption; however, the results were not statistically significant. The timing, nature and amount of caffeine consumption were not investigated and these could also be reasons for the spread of results. This concurs with Youngberg et al (2011) who found that low to moderate caffeine consumption during the morning hours has little effect on subjective or polysomnographic sleep measures in individuals with primary insomnia.

**Smoking Status**

Smoking was also linked to an increased frequency of difficulty falling asleep compared to non-smokers. This is consistent with several studies which have found a strong relationship between smoking and insomnia (Peters et al., 2011; Pomerleau et al., 2000; Soldatos et al., 1980; Wetter and Young, 1994; Zhang et al, 2006). Furthermore, people who smoke during the night have greater sleep disturbance than those who do not (Peters et al., 2011). This is not surprising given that nicotine acts as a stimulant in the central nervous system (Saint-Mleux et al, 2004).
Alcohol consumption

No statistically significant difference between frequency of alcohol consumption and difficulties falling asleep were found. However, 77.8% of the respondents reported problems falling asleep 5-7 times per week after consuming 2 to 3 units of alcohol within the same period. Studies into this issue have varied findings. In the Medical Outcomes Study, there was no significant association between insomnia and alcohol use in patients with a chronic disease (Katz & McHorney, 1998; Kuppermann et al, 1995). However, several studies have shown that moderate alcohol consumption detrimentally effects sleep (Tsutsumi et al, 2000; Young et al, 2002).

Doxylamine

The most frequently administered nonprescription medications are doxylamine and diphenhydramine, two sedating antihistamines (Ramakrishnan & Scheid, 2007; Ringdahl et al, 2004). Doxylamine has been shown to induce sedation (AMH, 2012), leading to its use as a sleep aid.

In this study carried out on patients seeking treatment for insomnia in community pharmacies, doxylamine was the antihistamine used by all respondents. It produced significantly more improvement than previous treatment in several sleep parameters, including sleep-onset latency (which is the target symptom for OTC products), maintenance of sleep and quality of sleep as measured by patient’s subjective reports. Comparing pre- and post-treatment responses, 97.9% stated that the antihistamine they received (doxylamine) was helpful in treating their insomnia symptoms. To my knowledge, there is little published literature in English addressing the use of doxylamine as a sleep aid. Rickels et al (1984) concur by concluding that doxylamine consistently produced a significant improvement in sleep. The results in this study are from a smaller sample size and only subjective appraisals of efficacy.

Side effects reported included anticholinergic effect of dry mouth, nausea, sluggishness, and a hangover effect. These were not unexpected as they are common side effects of doxylamine (AMH, 2012), which was the product taken by all participants in this study. Doxylamine is effective at inducing drowsiness when taken at before going to sleep, however, having a half-life of up to 10 hours, doxylamine is still present in plasma on awakening, causing residual daytime sedation (Krystal et al., 2006). This poses a risk to elderly patients and those taking other anticholinergic medications (antidepressants, antipsychotics) (Neubauer, 2007). One
such risk of an anticholinergic-based antihistamine is tachycardia and other cardiac effects which may aggravate angina (Hayes et al, 2007). Furthermore, concurrent use of antihistamines with any of phenothiazines, nitroglycerin, nifedipine, prazosin, and diuretics significantly impairs responsiveness and sensitivity of baroreceptors, leading to an increased risk in developing postural hypotension (Hayes et al, 2007).

The answers to the question regarding how long participants nap did not change with antihistamine use indicating no change in subjective day time sleepiness. The reason for this lack of napping may be due to participants’ professional duties or perhaps it was advised by healthcare professionals to avoid napping during the day. Alternatively, a possible reason is because napping is not a strong part of Australian culture, few people actually nap. The exact reasons are uncertain as the survey did not address this question.

Respondents were asked about the period of time in which they used doxylamine as a sleep aid and the frequency. The duration was between 2 to 14 days with a mean of 5 days. In regards to the frequency of use, half (50%) reported using an antihistamine every night. The development of tolerance to the sedative effects of antihistamines is possible (Richardson et al, 2002). It is the responsibility of pharmacists to ensure that patients do not extend this period of use. Pharmacists should discuss the risks of misusing antihistamines.

This study also examined the association between using antihistamines (doxylamine) and the reports of excessive sleepiness, tiredness, or drowsiness. Few patients reported residual effects such as sleepiness, tiredness or drowsiness following antihistamine use. To my knowledge, these associations have never been examined in past general population surveys.

Almost three-quarters of the surveyed individuals (72.9%) who used an antihistamine reported no daytime sleepiness, 20.8% reported slight chance while 6.3% a moderate chance (Table 26). The respondents were also asked whether antihistamine use affected their ability to stay awake during the day with 72.9% stating “not at all”. Respondents were also asked whether antihistamine use affected their ability to perform their work duties. These results were different with 39.6% reporting not at all, indicating a possible low grade of drowsiness, or affect on mental alertness. Since doxylamine is a potent sedative with a long half-life it is not surprising to find that some users experienced these effects.

Comparing before and after treatment, 97.9% of patients rated an antihistamine as helpful as a sleep aid for the treatment of insomnia. For those people who rated it not helpful, a possible
explanation that may develop tolerance as tolerance can develop (Richardson et al, 2002) and abrupt withdrawal can lead to rebound insomnia (Morin & Benca, 2012).

The main strength of this study is that the data are reliable in terms of what the researcher can control; it was collated from a survey distributed to patients exhibiting symptoms of insomnia and followed up by the researcher with one-on-one telephone interviews rather than surveying individuals who do not present such symptoms. As Hajak states that, strict diagnostic criteria are required to ensure that the study sample ‘undoubtedly (requires) treatment’ (Hajak, 2001). This study used participant self diagnosis as this criterion, leading to potential misdiagnosis and also over diagnosis.

However, there are also some limitations to this study. Firstly, the collated data was self-reported and therefore may have been affected by recall and other biases. Secondly, as the study was conducted in community pharmacies, this requires participants to be able to reach these locations and as such, the data collated may be biased against the frail, ill or institutionalised. Thirdly, the sample size employed in this study was not large enough to ensure the data were completely robust and the short data collection window would not account for any seasonal variation in presentations. Finally, the data collated was of a subjective nature, that is, data was not objective as it explored opinions and beliefs.

This study has linked some of the individual research processes previously used in sleep disorder and insomnia research into a practical study reflective of real world practice and issues. The findings show that antihistamines are used as a sleep aid with quite good efficacy.

**Conclusion**

Despite the limitation of the study, the prevalence of insomnia complaints associated with many factors. Increasing age affected sleep patterns. The findings of this study showed that antihistamine (Doxylamine) is effective for primary insomnia. This treatment leads to significant improvements in subjective sleep parameters.
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Ohayon, M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews, 6(2), 97-111.


Ohayon, M., & Smirne, S. (2002). Prevalence and consequences of insomnia disorders in the general population of Italy. *Sleep Medicine, 3*(2), 115-120.


Appendix A

Recruitment script for Pharmacy Staff

This pharmacy is participating in a University of Canberra study for people who are taking this antihistamine as a sleep aid.

The study involves you completing this anonymous 1 page survey about your sleep (*show questionnaire*). If you want to, you can add your first name and phone number so a researcher from the University can contact you to see how well this product worked.

No-one from the pharmacy will see your completed form because I will ask you to put it in this locked box (*show box*). Only the University researcher has the key.

If you have any questions about the study, the researcher’s phone number is here on the form (*show phone number*).
Appendix B

Using Antihistamines as a sleep Aid Questionnaire

University contact: Greg Kyle (02) 6201 2567


- Gender  □ Male  □ Female

- What is your highest education level?
  □ High School or less  □ Diploma  □ Bachelor degree  □ Postgraduate study

- Which product was recommended today for your insomnia?

- Have you tried any other treatments for your insomnia?  □ Yes  □ No

- If so which one(s) have you used: (tick as many as apply).
  □ Over The Counter medicine  □ Behavior therapy (eg counseling)
  □ Prescribed medication  □ Relaxation therapy (eg yoga)
  □ Exercise  □ Alcohol
  □ Herbal products

- Please tick the appropriate box for your opinion on the following statements:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Less than once per week</th>
<th>1 – 2 times per week</th>
<th>3 – 4 times per week</th>
<th>5 – 7 times per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- How often do you think you have difficulty falling asleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2- How often do you think you have difficulty staying asleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3- How often do you think you have frequent awakenings from sleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4- How often do you feel that your sleep is refreshing?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Have you ever used an Antihistamine for sleep before?  □ Yes  □ No

- How often have you have used antihistamine as a sleep aid?
  □ Once weekly  □ Couple of times a week  □ Whenever you need

*The researcher would like to telephone you in two weeks to ask about factors that influence your sleep and how effective this treatment has been. The telephone interview has 15 questions about the effectiveness of the treatment and should only take a maximum of 10-15 minutes. If you are happy to be contacted, please include your first name and telephone number below.

*You do NOT need to provide your name and phone number if you do not want to be contacted.

- Do you wish to complete the second part of this survey?  □ Yes  □ No

Contact phone number……………………………………………  First name……………………………………………

Thank you for taking the time to contribute to this research.

This study has been approved by the Human Ethics Research Committee at the University of Canberra (Approval No.: 11-132)
Appendix C

Q1. How often (if ever) do you consume caffeine?
- Never
- Less than once a day
- Once a day
- 2-3 times a day
- 4+ times a day

Q2. When you consume caffeine, what do you drink and how much?
.............................................................................................................................................
.............................................................................................................................................

Q3. How often (if ever) do you drink alcohol?
- Never
- Less than once a week
- Once a week
- 2-3 times a week
- 4+ times a week

Q4. When you consume alcohol, what do you drink and how much?
.............................................................................................................................................
.............................................................................................................................................

Q5. How often (if ever) do you smoke tobacco/ cigar/ pipe?
- Never
- Rarely
- 1-10 cigarettes a day
- 11-20 cigarettes a day
Q6. How long does it usually take you to fall asleep on the nights you have a problem falling asleep?

<table>
<thead>
<tr>
<th></th>
<th>Before antihistamine</th>
<th>After antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; ½ hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>½ - 1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q7. How would you rate your sleep quality overall?

<table>
<thead>
<tr>
<th></th>
<th>Before antihistamine</th>
<th>After antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q8. On a typical day, how long do you nap for in total?

<table>
<thead>
<tr>
<th></th>
<th>Before antihistamine</th>
<th>After antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>I don’t take naps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-15mins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-30mins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer than 30mins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q9. How much time do you usually spend awake at night on the nights you have trouble sleeping?

<table>
<thead>
<tr>
<th></th>
<th>Before antihistamine</th>
<th>After antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; ½ hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between 1/2 – 1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One to two hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 – 3 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 3 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q10. How long does it usually take you to get back to sleep once you wake up at night?

<table>
<thead>
<tr>
<th></th>
<th>Before antihistamine</th>
<th>After antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; ½ hour</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>More than 3 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Q11. How long you have used Antihistamine as a sleep aid? (Total time = days or weeks)
...................................................................................................................................................
.......................................................................................................................................................

Q12. How often you have used Antihistamine as a sleep aid?
- Once weekly
- Couple of times a week
- Every night
- Whenever you need

Q13. How much do you think taking the sleep aid has affected your ability to fall asleep during the daytime without intending to, or that you would struggle to stay awake while you were doing things?
- No chance
- Slight chance
- Moderate chance
- High chance

Q14. How much do you think taking the sleep aid has affected your ability to stay awake during the day?
- Not at all
- A little
- Somewhat
- Very much
Q15. How much do you think taking the sleep aid has affected your ability to get through your work?
- Not at all
- A little
- Somewhat
- Much
- Very much

Q16. Do you think the sleep aid is causing any side effects? If yes what are these effects?

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Q17. What do you think of this product as a sleep aid?

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