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Current prescribing patterns and use of non-benzodiazepine hypnotics in a retail environment

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Chapter 1: Introduction, Aim and Objectives

Insomnia is defined as the "difficulty falling asleep or staying asleep or disturbed sleep patterns resulting in insufficient sleep" (Beers & Berkow, 1999). A distinction is made between primary insomnia, with no underlying cause, and secondary insomnia, which occurs as a result of other disorders, such as depression, anxiety disorders, and stress (Monti, 2004). A further distinction is made between occasional insomnia and chronic insomnia. The latter can continue for many years, and may or may not be attributed to any specific cause. Chronic insomniacs constitute approximately 10% of people complaining of insomnia (Monti, 2004). Persistent chronic insomnia can also contribute to the development of disorders such as depression and anxiety, or alcohol abuse. The prevalence of insomnia is higher in women, and also in the elderly (Holbrook *et al.*, 2000).

Vallières *et al.* reported in 2005 that insomnia affected at least 10% of the adult population in the United States of America, although the prevalence may actually be much higher. A Canadian study using telephone surveys showed that of 2001 adults, over 50% of participants were either dissatisfied with their sleep or had symptoms of insomnia during the previous year (Morin *et al.*, 2006). Although no statistics have been found for South Africa, based on the statistics quoted above, insomnia does occur in the population, and people are increasingly searching for remedies for sleep disorders.

Non-pharmacological remedies are plentiful and vary in different cultures and environments. These include cognitive behavioural therapy, meditation and various stress relief or relaxation techniques. However, these are lifestyle changes, and not a quick cure for insomnia. For severe or persistent insomnia, non-pharmacological treatments may be combined with drug treatment (Morin *et al.*, 2007).

For most people, especially in a retail environment, the first stop is the over-the-counter medication or natural remedies. Natural remedies such as valerian root and chamomile are marketed as sleeping aids. However, these agents are not hypnotics, and do not have dramatic sleep induction effects, but rather are used as relaxants and calming agents, in order to facilitate sleep. In addition, several doses are needed

before benefits are felt (Treben, 2003). Over-the-counter products include natural/herbal remedies, or antihistamines marketed as sleeping aids due to their sedative side effect. These are also not hypnotics and are indicated only for short term use. Furthermore, these drugs have side effects such as dizziness, dry mouth, and daytime fatigue, which negatively influences patient compliance (Gibbon, 2003).

Depending on the severity or duration of insomnia, it may be preferred to take a prescription sedative-hypnotic. In South Africa, such drugs are classed as Schedule 5, and are available only on prescription from a registered medical practitioner (Medicines and Related Substances Act 101 of 1965).

Initially, the barbiturates were widely used as sedative-hypnotics. Barbiturates bind to the GABA receptors to produce hypnotic effect. However, due to the potential for addiction, and serious side effects such as respiratory depression, they are now seldom used as sedative hypnotics. Certain barbiturates are now used only for specific indications, such as in the management of epilepsy (Katzung, 2001).

Barbiturates have been largely replaced by the benzodiazepines. Benzodiazepines also act on the GABA receptor to produce a sedative-hypnotic effect. These drugs are known to cause daytime fatigue, “hangover effect”, withdrawal effects, short term memory loss and, rarely, respiratory depression. An abuse potential does exist and tolerance may develop to the clinical effects (Lippmann *et al*., 2001). Side effects are more pronounced and persistent with the longer acting drugs; flunitrazepam gained notoriety as the “date rape drug” due to its sedative and amnesic effects (Forrester, 2006).

However, the characteristics of efficacy and tolerability can themselves lead to long-term or chronic use of these medications, and may lead to a psychological dependence, which becomes evident on drug withdrawal. In addition to sedative-hypnotic effects are the anxiolytic and muscle relaxing effects, which also aid sleep. These are lost on drug withdrawal, resulting in dysphoria, anxiety and rebound insomnia. (Spiegel, 2003)

Non-benzodiazepine drugs such as zopiclone and zolpidem are alternatives to treatment of insomnia, leading only to sedation without anxiolytic or muscle relaxant properties (Spiegel, 2003).

These two drugs have a lower incidence of producing dependence but are recommended by the South African Medicines Formulary (Gibbon, 2003) only for the short-term treatment of insomnia.

As of January 2006, the inclusion of ICD10 codes on prescriptions became compulsory for the purposes of medical aid claims. A period of adjustment was allowed for the first few weeks of the year; however from March 2006, these codes are mandatory on all prescriptions for a claim to be successful.

From observation in the work place, it has been noticed that zolpidem and zopiclone are widely prescribed and they are used often for extended periods of time, in some cases up to six months of continuous use, which is the maximum length of time that a single prescription may be used for.

This study was conducted to determine the frequency and duration of non-benzodiazepine hypnotic use. The research aimed to investigate whether these hypnotics were indeed used over the long term, as opposed to the recommended short-term treatment, and whether use was continuous or intermittent. In order to do this, the prescribing patterns of these drugs were evaluated, as well as the resulting usage of them by patients. This usage was evaluated in light of the existing recommendations and guidelines for sedative-hypnotic use, to gauge whether these drugs were being used and prescribed appropriately.

The objectives of the study were to investigate the following parameters within the patient population surveyed:

1. the demographic characteristics of patients using zolpidem and zopiclone;
2. the drug and dose distribution;
3. the indications for prescription of these drugs, as given by the ICD10 codes;
4. the type of prescribers who are currently prescribing these drugs;

5. the period of drug use by patients;
6. whether patients are using the drugs continuously or on an “as needed” basis (uninterrupted or interrupted use);
7. the proportion of prescriptions for either one of these hypnotics, as compared to the total number of prescriptions seen in the pharmacy over a retrospective 12 month period;
8. The trade names of the most commonly dispensed formulations of zolpidem and zopiclone over a retrospective 12 month period.

Chapter 2: Literature Review

2.1 Pharmacodynamics, pharmacokinetcis and dosing

Zolpidem and Zopiclone are non-benzodiazepine hypnotic agents. They act on specific subunits of the gamma-aminobutyric acid (GABA) receptor complex, in a similar manner to the benzodiazepines. GABA is the main inhibitory neurotransmitter in the central nervous system. These drugs bind to the receptor complex at different sites to the benzodiazepines, and each other, and upon binding, enhance GABAergic effects, leading to sedation. Greater selectivity in binding may be the reason for greater efficacy and improved side effect profiles of the non-benzodiazepines as compared to the benzodiazepines (Drover, 2004).

Zopiclone has an intermediate duration of action, and should be used for the induction and/or maintenance of sleep in patients who have difficulty in falling asleep or complain of frequent nocturnal awakenings (Sanger, 2004). Side effects seem to be minimal for these drugs, with zolpidem causing visual disturbances in certain patients, and zopiclone causing a dry mouth and metallic taste (Drover, 2004). Zolpidem also causes CNS side effects, most commonly confusion, anterograde amnesia and somnambulism. These side effects are usually seen within a half hour to one hour after the dose is taken (Wortelboer *et al.,* 2002). In patients with sleep apnoea, zolpidem is contra-indicated, although respiration is not significantly affected in other patients (Holm & Goa, 2000).

Zopiclone and zolpidem undergo extensive first pass metabolism and due to hepatic metabolism, there is a potential for drug interactions (Drover, 2004). Zolpidem is metabolized by more than one of the Cytochrome P450 enzyme systems, and interacts with several drugs. Clinically important interactions with zolpidem include those with rifampicin, ketoconazole and cimetidine; its action is reversed by the benzodiazepine antagonist, flumazenil (Hesse *et al.,* 2003). Zopiclone is metabolized mainly by the CYP3A4 enzyme system and clinically important drug interactions include those with rifampicin, azole antifungals, erythromycin and ethanol (Hesse *et al.,* 2003).

Both drugs are found to be equally effective, but zolpidem is found to induce less rebound insomnia on withdrawal than zopiclone (Lee, 2004). Rebound insomnia is a major discouraging factor in the chronic use of hypnotics, especially benzodiazepines, which often leads to the development of tolerance and dependence. However, rebound effects may be psychological as well as physical (Voderholzer *et al.*, 2001). In a double-blind, randomized study conducted across various private practices, Hajak (1999) found a higher incidence of rebound effects in placebo users as compared to users of hypnotic drugs. A perception that drug discontinuation may cause rebound insomnia may contribute significantly to the chronic use of hypnotics, even those which have minimal physical rebound effects.

Recommended doses are zolpidem 10mg and zopiclone 7.5mg, to be taken once nightly. A decrease of dose in zopiclone to 3.75mg nightly is recommended in the elderly, patients with chronic respiratory failure and patients with hepatic or renal dysfunction. Similarly, zolpidem dose should be decreased to 5mg in elderly or debilitated patients, or patients with liver failure (Terzano *et al.*, 2003).

2.2 Use in the elderly

A meta-analysis conducted by Glass *et al.*, (2005) comparing the risks and benefits of short term sedative-hypnotic use in the elderly (including zolpidem and zopiclone) showed that while treatment did result in a statistically significant effect on sleep, the magnitude of that effect was small. In contrast, the magnitude of adverse effects, including cognitive and psychomotor effects, daytime fatigue and increased risk of falls seen was greater in patients over the age of 60, negating any potential benefits of the medications.

Despite their short half-lives as compared to many benzodiazepines, both zolpidem and zopiclone are associated with increased risk of falling and hip fractures in the elderly (Vermeeren, 2004). This is supported by the findings of Allain *et al.* (2005) in a review of existing literature on the association between hypnotic use in the elderly and postural instability, falls and hip fractures.

The majority of studies indicate that increased risk of fall and fractures is seen with benzodiazepine use as compared to zolpidem or zopiclone use. In a post-marketing surveillance of zopiclone amongst over 20 000 patients, with a mean age of 52.3 years, no increased risk of falling was reported (Allain, 1991). Conversely, in a case control study of hip fracture cases, with all subjects above the age of 65 years, and mean age of 82 years, the risk of hip fracture with zolpidem use was significantly increased (nearly double the risk) and comparable to that seen with use of benzodiazepines (Wang *et al.,* 2001).

A study comparing zolpidem 5mg, zopiclone 3.75mg and lormetazepam 1mg with placebo with regards to gait, standing balance and anterograde amnesia in the elderly, it was found that all three hypnotics adversely affected gait and balance. This effect lasted for less than 5 hours with zolpidem, but for more than 8 hours with zopiclone and lormetazepam. In addition, both lormetazepam and zopiclone showed anterograde amnesia of over 8 hours duration (Allain *et al.,* 2003). The effects on balance are dose related, both with benzodiazepines and non-benzodiazepine hypnotics, further highlighting the need for correct prescribing of these drugs in the elderly; it is therefore recommended that the use of hypnotics in the elderly be governed by certain guidelines: half the standard dose should be used initially, and additive effects of other concomitant centrally acting drugs must be taken into account (Allain *et al.,* 2005). If hypnotic use is necessary in the elderly, zolpidem 5mg is the safest (Allain *et al.,* 2003). The dose should be increased to 10mg only if 5mg is not producing the desired hypnotic effect, but is well tolerated (Lee, 2004).

2.3 Impairment of normal functioning

Zopiclone has shown more of a tendency to decrease memory following administration than does the benzodiazepine brotizolam (Silva *et al*., 2003). It has a residual effect up to 16 hours after ingestion; suitability for the patient must be considered. In a standardized highway driving test, zopiclone 7.5mg administered 10-11 hours prior to testing was associated with residual effects similar to blood alcohol levels of 0.5-0.8 g/L. A study in the United Kingdom linking patients' prescription records to police records of road accidents found that an increase in accidents was seen in patients exposed to benzodiazepines and zopiclone (Vermeeren, 2004).

By contrast, zolpidem 10mg, due to shorter duration of action, does not have any residual effect after 8 hours, and can also be used for the induction and maintenance of sleep. However, significant impairment is seen with higher doses, or after 4-5 hours of administration (Vermeeren, 2004).

The effects of zopiclone on driving are further supported by Verster *et al.,* (2004) who conclude that zopiclone impairs driving ability in the same way as do the benzodiazepines. The degree of impairment depends mainly on time of administration and dose taken. Although there is evidence that tolerance may develop to this impairing effect, the process is slow should it occur and appropriate care should be taken in the prescribing and use of this medication. The authors recommend in fact that patients be counseled not to drive in the morning after taking zopiclone. No impairment of driving ability is reported with zolpidem (Verster *et al.,* 2004).

2.4 Abuse, dependence and withdrawal

Animal studies show less of a physical dependence profile and reduced withdrawal symptoms with zolpidem and zopiclone than with the benzodiazepines (Sanger, 2004). Up to 4 weeks of zolpidem or zopiclone use did not lead to withdrawal effects upon discontinuation (Hesse, 2003). Zolpidem does have a marginal tolerance effect with intermediate or long term use (Lee, 2004).

A search for cases of dependence on zolpidem and zopiclone between 1966-2002 found 22 documented cases of dependence on zopiclone, and 36 documented cases of dependence on zolpidem. The key words used in the search were “zolpidem,” “zopiclone,” “abuse,” “dependence” and “addiction.” In all cases patients showed evidence of tolerance and withdrawal effects. A subsequent increase in dose over time was observed, with doses being up to 100 times or 51 times greater than recommended for zolpidem and zopiclone respectively. However, in one case, dependence was reported at the normal dose of zopiclone. The majority of these patients had a history of alcohol or substance abuse. The conclusion reached was that these drugs are safer than the benzodiazepines, but do have potential for abuse and dependence in individuals with a history of substance abuse (Hajak *et al.,* 2003). The

abuse of hypnotics, especially non-benzodiazepine hypnotics, is seemingly rare in non-drug users, who are unlikely to use the medication in a non-therapeutic manner, as evidenced by the low incidence of self-escalation in dosage, or reduction in dosing frequency (Jaffe *et al.,* 2003).

While the cases of abuse and dependence reported were extreme, it is possible that several cases of dependence, possibly at lower or therapeutic doses are either not noticed or not reported (Hajak *et al.,* 2003).

In a study of 300 addicts undergoing treatment in the United Kingdom, participants were asked a series of questions relating to use and abuse of various drugs, including benzodiazepines, non-benzodiazepine hypnotics (zolpidem and zopiclone), antidepressants and sedative antihistamines (Jaffe *et al.,* 2003). The benzodiazepines diazepam, nitrazepam and temazepam had the highest abuse potential. The lowest abuse potential was found with the antihistamines diphenhydramine and chlorpheniramine. Zolpidem and zopiclone were found to have similar abuse profiles and potential as the antidepressants in the study. A significantly larger percentage of users had purchased zolpidem or zopiclone from the street rather than via prescription from a doctor and used the drugs to get high, than was the case with the antihistamines (Jaffe *et al.,* 2003). In South Africa, both diphenhydramine and chlorpheniramine are available at pharmacies without prescription.

2.5 Long term, continuous and "as-needed" use

Despite the excellent safety profiles, there are concerns about tolerance and abuse, and use of these drugs is currently recommended to be limited to a maximum of two to four weeks' duration, and in clinical practice, a tapering down of dose is recommended rather than abrupt withdrawal (Terzano *et al.,* 2003). This is supported by Wortelboer *et al.* (2002) who recommend that if treatment is needed for longer than 2-4 weeks, use should be on an as-needed basis or a controlled-interval schedule.

Although there have been a few studies regarding long term use of hypnotics, they have not been controlled studies (Noble *et al.*, 1998; Harrison & Keating, 2005). It

has, however, been shown that continuous use does not provide long-term benefits. In view of this, and potential safety concerns, and considering that patients with insomnia do not suffer from insomnia every night, zolpidem is recommended for use on an as needed basis (Hajak 2006).

As needed use of hypnotics can be controlled partially or entirely by the patient. In the most nonflexible regimen, the physician determines the days of the week that the patient will use the drug (Cluydts, 2004). This could involve the use of a time table whereby the patient takes the drug for only 3 or 4 specified nights a week. Should medication not be needed on a night when it is scheduled to be taken, it is not necessary to take it. However, medication may not be taken on nights which have not been so designated (Wortelboer *et al.,* 2002).

In a semi-flexible regimen, the patient is given a maximum number of tablets which they are allowed to take weekly, and are then free to choose which days they will be taken, as the need arises. In a fully flexible regimen, the patient uses drug on a completely as needed basis, deciding on both the nights to take medication, and the number of tablets taken weekly (Cluydts, 2004).

The as needed use of hypnotics has several advantages: it more accurately caters to patient needs, as insomnia itself varies in occurrence and severity within individual patients. It also reduces the perceived need for medication in order to sleep, hence lessening the potential psychological dependence on a hypnotic drug, and also lessening the fear of dependence in patients (Cluydts, 2004).

It has been found that non-continuous or “as needed” use of the drug provides similar hypnotic efficacy as continuous use, while decreasing dependence potential and allowing for more long-term treatment (Cluydts *et al*., 2002; Walsh, 2002). Zolpidem seems to continue providing a beneficial effect on sleep for up to one week after drug discontinuation. This allows use of the drug on an as-needed basis with beneficial effects being felt during the initial days of drug-free intervals (Terzano *et al.,* 2003).

Two separate, non-comparative 3-week trials have been conducted to gauge efficacy of zolpidem used on an as needed basis. In the first, patients were allowed a maximum

of 5 tablets per week of zolpidem 10mg. In the second study, patients were given 21 tablets of zolpidem, and instructed to take it as needed. The standard dose of 10mg was used in subjects below the age of 65 years, and 5mg was used in subjects above the age of 65 years. In both studies, the mean tablet consumption per week decreased from week 1 to week 3, with maintained improvement in total sleep time and sleep onset time. Therefore, while long-term use of any hypnotic is not recommended, should there be a need for it, use should be on an as needed basis (Harrison & Keating, 2005).

Three clinical trials quoted by Hajak and Geisler (2004), all in primary care settings, have shown the superiority of zolpidem use as needed over continuous nightly use. In one study conducted, lasting a total of 10 weeks, with 8 weeks of treatment, subjects took either zolpidem 10mg or a placebo for 3-5 nights weekly. They were given flexibility and independence in choosing when to take the drug. The number of tablets taken per week did not increase over the entire study period, suggesting that as needed use of zolpidem, even for prolonged periods of time, does not lead to tolerance or dependence. In addition, no significant rebound insomnia was observed on discontinuation of as needed treatment. In terms of safety, no significant difference was found between the zolpidem and placebo groups (Walsh *et al.*, 2000).

A study in France surveyed 245 drug free, chronically ill insomniac patients over a four week period. Patients were randomly assigned to zolpidem 10mg as needed or placebo as needed. The first week of the study was controlled but for the remaining three weeks, patients were given full flexibility in choosing when and how many tablets to take, on an as needed basis. Again, tablet use did not increase over the weeks, and no significant difference in usage was found between the test group and the control group. However, the zolpidem group did show a marked improvement in insomnia symptoms as compared to the placebo group (Allain *et al.*, 2001).

During a study of 2690 chronic insomniac patients in Germany, patients took zolpidem 10mg as needed in a semi-flexible manner (3-5 tablets weekly). On nights when zolpidem was not used, subjects were encouraged and taught how to use behavioural therapy or stimulus control. This combination treatment was found to be highly effective and well tolerated and the results showed an actual decrease in the

number of tablets taken per week over a three week period. This would suggest that given an option of non-pharmacological relief of insomnia, many patients would prefer this to pharmacological treatment (Hajak *et al.*, 2002). Decrease in hypnotic use with behavioural therapy and long-term efficacy and cost-efficiency of this type of therapy has also been demonstrated by Morgan *et al.* in 2004, who conducted a study providing cognitive-behavioural therapy to subjects in general practice settings.

No studies have been found regarding efficacy and safety of zopiclone on an as-needed or long term basis. Hajak (1999) recommends a maximum treatment duration of 4 weeks at a maximum dose of 7.5mg daily, with half the dose being used initially in the elderly. Data concerning the use of zopiclone in this manner have shown minimal dependence potential and rebound effects. However, this does not necessarily hold true if the drug is used at higher doses or for longer time periods (Hajak, 1999).

2.6 Conclusion

Despite the better safety profiles of zopiclone and zolpidem as compared to the benzodiazepines, the use of hypnotics in the United States and Europe has decreased in the last two decades. Prescribers prefer to use them in the lowest doses possible, for a limited period of time and on an as-needed basis. However, surveys show that most users take hypnotics for a duration of over 1 year (Vermeeren, 2004). To control the problem of excessive hypnotic use, the trend now is to use a low dose of an antidepressant such as trazodone for the treatment of insomnia (Vermeeren, 2004; Jaffe *et al.*, 2003).

Very little research has been done regarding the prescribing patterns and use of drugs in South Africa, and no literature has been found regarding the use of hypnotics in South Africa. It is, therefore, not possible to speculate or comment on trends within the country. However, from casual observation in the workplace, it is apparent that a variety of sedative-hypnotics are used. These include benzodiazepines, zolpidem, zopiclone, antipsychotics, antidepressants and antihistamines. There are no national guidelines on the treatment of insomnia. This research will focus on zolpidem and zopiclone, to quantify the use of these compounds in a retail setting in South Africa.

Chapter 3: Method of research

3.1 Method of data collection

Data was collected from Clicks Rosebank Pharmacy. The pharmacy is situated in the Rosebank Mall based in Rosebank, Johannesburg and is one of very few pharmacies in the area. The pharmacy serves patients from Rosebank Clinic, Rosebank Medical and Dental Centre, various general practitioners and specialist in the Rosebank, Parktown, Parkhurst and surrounding areas, and even patients from Donald Gordon Medical Centre and Johannesburg Hospital. Approximately six hundred prescriptions are processed on a single day, and the variety of patients and prescriptions seen is vast.

The study comprised both prospective and retrospective elements. Prospectively, prescriptions for zolpidem and zopiclone were reviewed for the month of March 2006, until a sample size of one hundred (100) sequential patients had been collected.

The inclusion and exclusion criteria used were as follows:

Inclusion Criteria:

- All new prescriptions for zopiclone or zolpidem received in the month of March 2006, up to a total of 100 prescriptions;
- Prescriptions had to indicate dose and duration of therapy;
- Prescriptions had to contain ICD 10 codes.

Exclusion Criteria:

- No ICD10 code;
- Refills of prescriptions initially issued prior to March 2006.

The data collection instrument is given in Appendix A, page 39.

The 100 patients were followed over a period of seven months from initial presentation to the pharmacy in order to ascertain the patterns of use of these drugs in individual patients. This allowed:

- Monitoring of regularity of refills on a repeat prescription
- Whether patients who were not given a repeat prescription initially, came back subsequently with new prescriptions for these drugs.

Retrospectively, from November 2005 to October 2006, on a monthly basis, total prescriptions received for all drugs were compared to the total number of zopiclone/zolpidem prescriptions received.

All data, prospective and retrospective, was collected from the Unisolv computer system; no patient or doctor interviews were conducted.

3.2 Data collected

Data was collected from each prescription regarding patient demographics such as age and gender of patient, prescriber characteristics (whether general practitioner or specialist prescriber), and ICD10 code.

The dates of dispensing of the original prescription, as well as any repeats were recorded. This was to indicate dosing frequency, and hence show continuous versus "as needed" use, and to indicate duration of use, whether short-term or long-term use.

The total number of prescriptions dispensed monthly by the pharmacy over the period November 2005 to October 2006 was recorded. The number of prescriptions for zolpidem and zopiclone dispensed monthly during this period was also recorded. The brand names of the formulations dispensed were recorded, as well as the corresponding active ingredient, zolpidem or zopiclone.

The study was completely anonymous. The patient's name, address, identity number or any other identifying characteristic remained confidential. The names of the

prescribers were not recorded. Only the category of prescriber (general practitioner or specialist) was used.

3.3 Data analysis and presentation

As this was an exploratory study of the prescribing patterns and use of these two drugs, the statistical data analysis is mainly of a descriptive nature with graphical representations. Patient demographics have been summarised and quantified using descriptive statistics, such as mean and modes. The proportion of male and female users is compared at a 5% level of significance. ICD10 codes were recorded to give the reason for prescription of these drugs, and the different ICD10 codes seen have been summarised by description and frequency counts. The use of the various commercially available brands has been summarised.

The duration of therapy indicated on the original prescription, including repeats, if any, determined the duration of use. Original prescriptions of longer than one month duration, where the repeats were dispensed regularly on a monthly basis were seen as continuous use of hypnotics. Where refills of repeats were irregular, with a period of over one month between refills, this was classified as “as needed” use. The same classification applied to patients presenting with several different prescriptions over the seven month period, with more than one month’s interval between the dates of the current and previous prescriptions.

Short term versus long term users are given as proportions of the total sample, based on the duration of treatment indicated in the first prescription presented. Continuous versus “as needed” use has been classified as interrupted or uninterrupted use. The proportion of patients who used the two drugs on an uninterrupted basis as compared to an interrupted basis has been expressed at a 5% level of significance.

During the period November 2005 to October 2006, the number of zolpidem/zopiclone prescriptions dispensed were presented as a proportion of total prescriptions dispensed during that time. This was done for individual months and the monthly usage of these drugs compared to establish whether there was any seasonal

variation in use. The most commonly used brands of the two drugs over the one year period were tabulated, showing the preferred commercial formulations.

3.4 Postgraduate and ethics clearance

Approval to conduct the research was given by the University Postgraduate Research Committee in May 2006. Approval from the ethics committee was issued in October 2006. Copies of these approvals are found in Appendices D and E, pages 42 and 43 respectively.

Chapter 4: Results

4.1 Demographic characteristics of subjects

Of the 100 patients, 62 (62%), were female, while 38 were male (38%). In a one-sample hypothesis test for proportion, at a 5% level of significance, a z-value of 2.4 was calculated. The proportion of female users was significantly greater than 50%, in other words there was a significantly high number of female as compared to male users within the patient sample.

The age of patients varied considerably. A graphical representation of the age distribution of all 100 patients is given below in Figure 4.1.1.

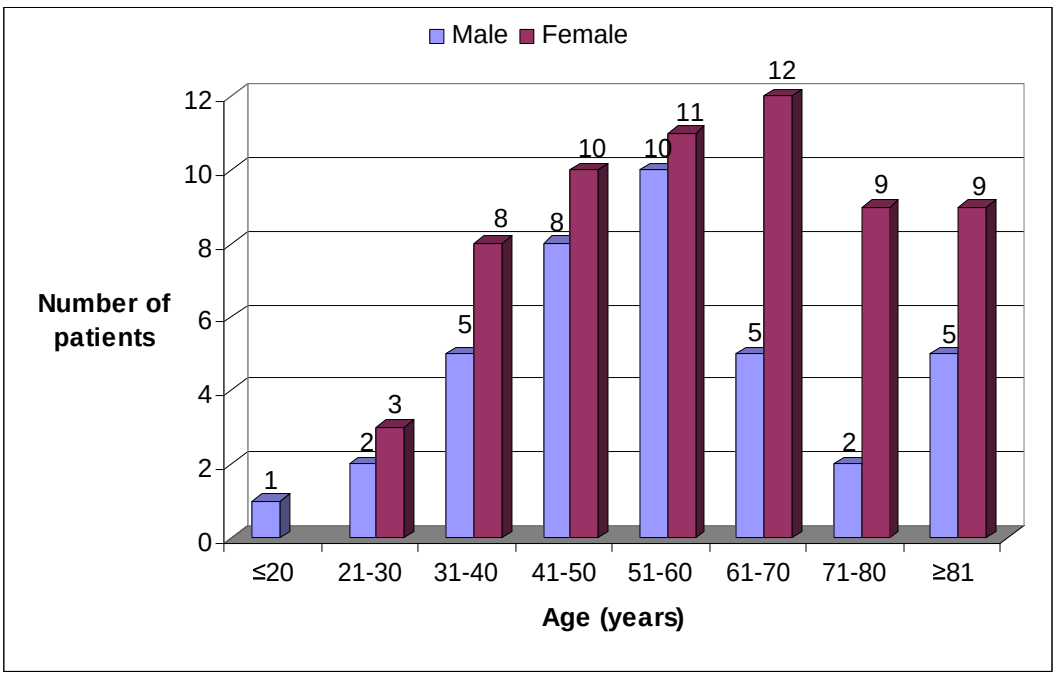


Figure 4.1.1: Age and gender distribution of 100 users of the non-benzodiazepine hypnotics zolpidem and zopiclone

The most common users were in the 51-60, 41-50 and 61-70 age brackets respectively. Amongst males, the modal class of users was the 51-60 years age bracket, while in females it was the 61-70 years age bracket. In each age group, excluding 20 years and below, the number of females was greater than males. Between the ages of 21 and 80 years, the mean age of female patients was 54.6 years,

while the mean age of male patients was 50.8 years. The mean age of all patients between the ages of 21 and 80 years was 53.1 years, coinciding with the overall modal age bracket of 51-60 years.

When calculating the Pearson correlation coefficient, r, for the relationship between age and percentage of users, a value of 0.418 (41.8%) was obtained, indicating poor correlation between age and frequency of use over the entire age range of 21 to 80 years. However, this is to be expected as percentage of users decreases after the age brackets 61-70 years and 51-60 years for females and males respectively.

The racial distribution of patients indicated that 91% of patients were Caucasian, 6% were African and 3% were Asian. However, due to the design of the study, there was no personal contact with any of the patients. Information as to the patients' ethnic background is therefore restricted to information available from patient records, which may not always be accurate with regards to race. Hence, the above racial distribution of patients is seen to show that of the 100 patients, the majority were Caucasian, while a minority belonged to various other racial backgrounds. This may not be significant as the racial demographics of the general patient population in Rosebank also show a majority of patients to be Caucasian.

4.2 Drug and dose distribution for zolpidem and zopiclone amongst the 100 subjects

The specific drug and dose used by individual patients also varied. Zolpidem was the more frequently prescribed and dispensed hypnotic of the two, with 61 patients (61%) using zolpidem, 36 (36%) using zopiclone, and 3 (3%) of patients switching from one drug to the other. Of the 100 patients, 57 (57%) used zolpidem 10mg and 28 (28%) used zopiclone 7.5mg. These are the standard doses as well as the strength of all commercially available formulations of the two drugs. Six patients used half the standard dose: 5mg of zolpidem or 3.75mg of zopiclone, and six patients used double the standard dose: 20mg zolpidem or 15mg zopiclone. This information is summarised below in Figure 4.2.1.

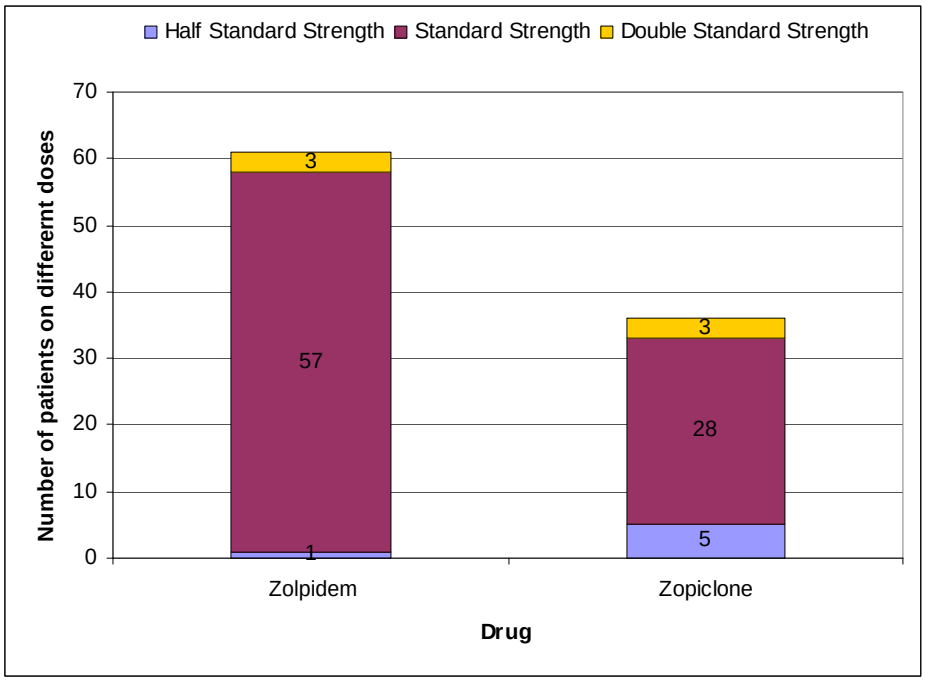


Figure 4.2.1: Drug and dose distribution for 97 users of zolpidem and zopiclone

Two patients changed medication from zopiclone 7.5mg to zolpidem 10mg. In addition, one patient was initially on zopiclone 7.5mg for a period of two months. She then changed to zolpidem 10mg for one month and finally returned to using zopiclone 7.5mg for a further three months.

4.3 Indications for prescription of zolpidem or zopiclone on the 100 initial prescriptions

On the 100 initial prescriptions, a total of only four different ICD10 codes were observed; these are given in Table 4.3.1 below, with their meanings and the number of prescriptions bearing those codes.

Table 4.3.1: ICD10 codes seen on the 100 initial prescriptions

ICD 10 Code	Definition	Number of prescriptions (%)
G47.0	Disorders of initiating and maintaining sleep [insomnias]	52
G47.9	Sleep disorder, unspecified	42
G47.8	Other sleep disorders	5
F33.1	Recurrent depressive disorder, current episode moderate	1

From the above table it can be seen that only little more than a half (52%) of the patients were prescribed a hypnotic for the recommended indication, i.e. insomnia. In the case of 48 (48%) of patients, with prescriptions indicating ICD10 codes of G47.9, G47.8, and F33.1, the particular sleep disorder was not specified.

4.4 Prescriber characteristics

Information on whether the prescriber is a General Practitioner or Specialist is available from an original prescription. Of the 100 initial prescriptions, 68 (68%) were prescribed by General Practitioners, while 32 (32%) were prescribed by Specialists. A total of 206 original prescriptions were received over the seven months for the 100 patients. This was due to renewal of expired scripts and/or interrupted use of a hypnotic on an as-needed basis. The majority of these prescriptions, 149 of 206 (72.3%), were prescribed by General Practitioners, while 57 prescriptions (27.7%)

were prescribed by Specialists. In a one-sample hypothesis test for proportion, at a 5% level of significance, a z-value of 4.46 was calculated. The proportion of scripts prescribed by General Practitioners constituted significantly more than 50% of the total 206 prescriptions. Therefore, in this study, prescriptions of hypnotic drugs were prescribed significantly more often by general practitioners as opposed to specialist prescribers.

4.5 Total period of use of either hypnotic by the study subjects

The total time of use of either zopiclone or zolpidem by each patient over the seven month period is given in Figure 4.5.1. Thirty of the 100 patients (30%) used one of the drugs for the full seven months. Twenty two patients (22%) used one of the drugs for a period of one month or less, in other words only brought in one script over the seven month period. The remaining 48 patients (48%) used a hypnotic for a total of two to six months.

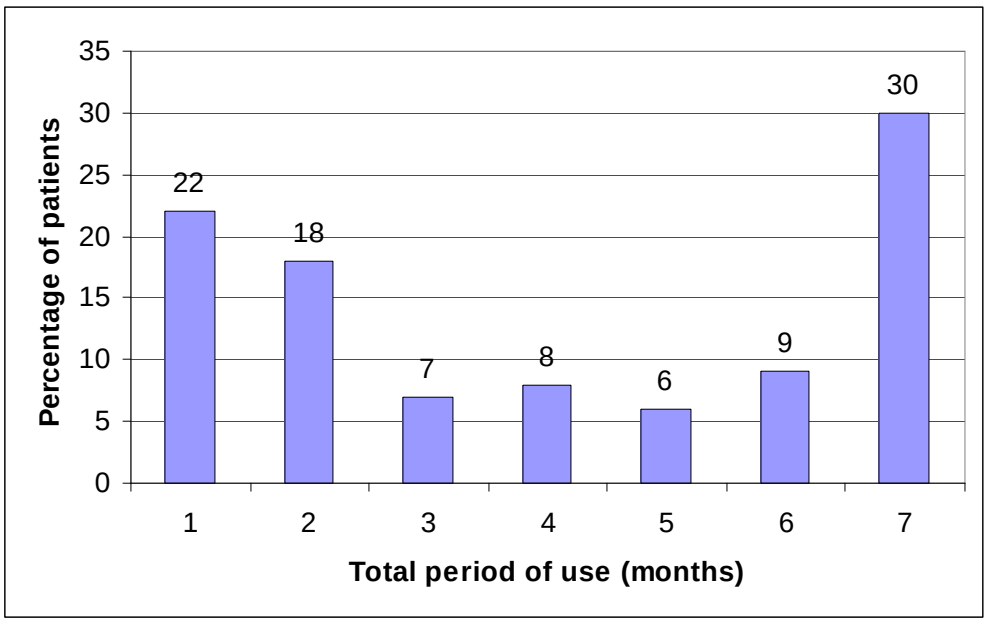


Figure 4.5.1: Total period of use of zolpidem or zopiclone by 100 patients over a 7 month period

4.6 Period of use classified as interrupted or uninterrupted

Use for the full seven months (30% of patients) can be seen as uninterrupted. Nine patients (9%) used a hypnotic for six months, and six patients (6%) used a hypnotic for five months, indicating a one or two month abstinence from hypnotic use respectively. It must be stressed here that while usage is interrupted, of the two separate periods of use, at least one period will be longer than one month duration, indicating both long-term use and uninterrupted use. Amongst patients who used a hypnotic for three or four months, some used the drugs for an uninterrupted three- or four month period, while others had interruptions between periods of use. Table 4.6.1 shows the number of patients who used a hypnotic either in an interrupted or uninterrupted manner, giving the total period of use over the seven months.

Table 4.6.1: Number of patients using zolpidem or zopiclone in an interrupted or uninterrupted manner, over a period of 7 months

	Number of patients using zolpidem/zopiclone:		
Total period of use (months)	**Uninterrupted**	**Interrupted**	**Total**
7	30	0	30
6	0	9	9
5	0	6	6
4	4	4	8
3	4	3	7
2	6	12	18
1	0	22	22
Total	44	56	100

In the case of four-, and three-month users, if interrupted, the separate individual periods of use are not necessarily longer than one month. If an individual period of use is longer than one month, it is classified as a period of long-term use, and that individual period of use can also be seen as uninterrupted use. However, if individual periods of use do not exceed one month, then use can truly be classified as interrupted or as-needed. Hence, in these cases, determining the length of the individual periods of use is essential before usage can be classified as interrupted or uninterrupted. Table

4.6.2 shows the number of patients who used a hypnotic for four and three months, in an apparently interrupted manner, with the individual periods of use given.

Table 4.6.2: Patients who used zolpidem or zopiclone for a total of three or four months, in an apparently interrupted or as needed manner

Total period of use (months)	Number of patients who used hypnotic in apparently interrupted fashion	Separate periods of use for individual patients (interruption indicated with /)
4	4	**Patient 1:** 2 months/ 1 month /1 month **Patient 2:** 1 month/ 3 months **Patient 3:** 2 months/ 2 months **Patient 4:** 1 month/ 2 months/1 month
3	3	**Patient 1:** 2 months/ 1 month **Patient 2:** 2 months/ 1 month **Patient 3:** 2 months/ 1 month

Table 4.6.2 indicates all of the patients who used a hypnotic for a total of three or four months, in an interrupted manner, had at least one individual period of use that was longer than one month. Hence, these seven patients had at least one period of long-term, uninterrupted use.

Patients who used a hypnotic for a total of two months, if interrupted, each period would be one month long, indicating true short term and interrupted usage pattern. This applies to 12 (12%) of the patients.

From this data it can be summarised that of the 56 patients in Table 4.6.1 who seemingly used a hypnotic in an interrupted manner, those who use it for three, four, five or six months had at least one period of use of greater than one month duration. Therefore they had at least one period of uninterrupted use. The patients who used a hypnotic in an interrupted manner were those who used a drug for either a single or separate periods, with each period of use being one month or less duration. True short term interrupted use was therefore limited to patients who used a hypnotic for only one month in the total seven months (22 patients) plus patients who used a hypnotic for a total of two months, interrupted (12 patients). This gives a total of 34 patients (34%) who used a hypnotic on an as-needed, interrupted basis. Sixty six (66%) of patients used a hypnotic for at least one period of long-term uninterrupted use.

To test the hypothesis that the proportion of patients using a hypnotic in an uninterrupted manner is greater than 50%, a one-sample hypothesis test for proportion, at a 5% level of significance, was performed. A z-value of 3.2 was calculated. It can be said that significantly greater than 50% of the 100 patients used a hypnotic in an uninterrupted manner.

4.7 Proportion of non-benzodiazepine hypnotic prescriptions as compared to total prescriptions issued over a one year period: November 2005 to October 2006

Over a 12 month period, from November 2005 to October 2006, a total of 99 649 prescriptions were issued at the pharmacy. Of this number, 3163 prescriptions were of either zolpidem or zopiclone, representing 3.17% of total prescriptions. Of this number, 1682 prescriptions (53.18%) were for zolpidem and 1481 (46.82%) were for zopiclone. Table 4.7.1 shows the use of the two drugs over the 12 month period, as compared to all prescription medication used.

Table 4.7.1: Number of zolpidem and zopiclone prescriptions as compared to all prescriptions issued in the pharmacy over a 12 month period, November 2005 to October 2006

	Nov 05 (%)	Dec 05 (%)	Jan 06 (%)	Feb 06 (%)	Mar 06 (%)	Apr 06 (%)
Zolpidem	133 (1.60)	126 (1.52)	126 (1.54)	120 (1.49)	120 (1.46)	163 (1.92)
Zopiclone	141 (1.70)	127 (1.53)	117 (1.43)	108 (1.34)	112 (1.36)	118 (1.39)
Total	8310	8274	8206	8053	8213	8492

	May 06 (%)	Jun 06 (%)	Jul 06 (%)	Aug 06 (%)	Sep 06 (%)	Oct 06 (%)
Zolpidem	148 (1.77)	129 (1.55)	160 (1.91)	148 (1.78)	155 (1.85)	154 (1.83)
Zopiclone	129 (1.54)	134 (1.61)	119 (1.42)	120 (1.44)	129 (1.54)	127 (1.51)
Total	8356	8298	8377	8316	8358	8396

The percentage of patients who use zolpidem as compared to all medication used varies between a low of 1.46% in March 2006 and a high of 1.92% in April 2006, a difference of 0.46% during the year. Similarly the percentage of patients who use zopiclone as compared to general use varies between a low of 1.34% in February 2006 and a high of 1.70% in November 2005, a difference of 0.36% during the year. The range of variation in both cases is less than 0.5%, almost negligible. The proportion of zolpidem/zopiclone, therefore, remains a constant proportion of total prescriptions throughout the 12 month period. There is no significant seasonal fluctuation in hypnotic use.

4.8 Most commonly used brands of zolpidem and zopiclone

There are various different brands available for the two drug compounds; Table 4.8.1 shows a comparison in use of the various generics of the two drugs, for the months of November 2005 to October 2006.

Table 4.8.1: Use of the various brands of zopiclone and zolpidem over a 12 month period, November 2005 to October 2006

Drug	Brand name	Number of patients using drug	Total
Zolpidem	Stilnox (original)	817	
	Ivedal	97	
	Zolnoxs	16	
	Zolpihexal	123	
	Adco-Zolpidem	629	1682
Zopiclone	Imovane (original)	460	
	Zopimed	602	
	Alchera	86	
	Sandoz-zopiclone	243	
	Z-Dorm	9	
	Zopivane	81	1481

In the case of zolpidem, the original brand Stilnox® was the most popular, despite higher cost of original products in general. In the case of zopiclone, the generic Zopimed® was the most commonly used brand.

In summary, the results show that while the hypnotics are being used for the correct indications, they are being used for periods longer than is indicated in the existing literature and are being used in a predominantly uninterrupted or continuous manner.

Chapter 5: Discussion

There was a positive correlation between hypnotic use and increasing age, but only up to age brackets 51-60 years and 61-70 years for men and women respectively. Thereafter, use of hypnotics declined. 42% of all 100 patients were 61 years or above and 25% were 71 years and above.

It was found that significantly more females used zolpidem or zopiclone than males, suggesting either that females suffer more from insomnia or that they seek treatment more often. It is not known whether the demographic distribution of the entire patient population shows a majority of female patients; therefore conclusions as to the gender distribution of hypnotic users may be difficult to draw. However, the prevalence of female users was maintained across all age groups, excluding the age group below 20 years of age, where there was only 1 user. The more frequent use of hypnotics in these two populations is in line with existing literature; insomnia has been shown to be more common in females and in the elderly (Holbrook *et al.*, 2000).

Brownlee *et al.*, (2003) looked at gender differences in the prescribing of hypnotics for insomnia. The medications included zopiclone, antidepressants, benzodiazepines, antihistamines and no medication. There were 887 male respondents and 1487 female respondents. No difference in prescribing between men and women was found for any of the classes of medication. No differences were found also for duration and frequency of use. A significant relationship between age and hypnotic prescribing was seen for both men and women, with both genders more likely to get benzodiazepines if in the eldest age group (45 years and above). For men, marital status and income also affected the choice of drug. This suggests that the greater use of hypnotics, and psychoactive drugs in general, by women is not due to gender alone, but that several factors contribute to prescribing patterns.

The racial distribution, although not precisely quantifiable, showed a majority of users to be Caucasian. This does not necessarily mean that Caucasians suffer from insomnia more, but perhaps that they are more likely or able to seek treatment for it. In addition, the race distribution of the particular area will have affected these findings; the general patient population in Rosebank was predominantly Caucasian. In the retail

sector, costs of consultation with a medical practitioner and of the medication itself may be higher than what is affordable to the general population. There may also be cultural aspects to consider, for example, the use of traditional or alternative therapies, or the perception of insomnia in different cultures and the perceived need for treatment for it.

The drug and dose distribution showed 85% of patients using the standard dose of zolpidem or zopiclone, 10mg or 7.5mg nocte, respectively. There were 25 patients above the age of 75 years. Of these 25, a minority of only 2 patients (8%) used half the standard dose, as is recommended. The proportion of patients using zolpidem, 61%, exceeded that of patients used zolpidem, only 36%. In addition, of the three patients who changed drugs, two changed from zopiclone to zolpidem. This may be due to differing adverse effect profiles of the two drugs, which may influence both patient and prescriber preference.

The ICD codes provided the reason or indication for prescription of a hypnotic. Botvinik *et al.* (2004) found twelve separate reasons for the prescription of antipsychotics in specific patients, with some patients having up to four different indications or reasons for use. It was found that the use of antipsychotics in a private inpatient psychiatric setting was not limited to treatment of psychotic symptoms but also included depression, anxiety and agitation, and control of difficult behaviour (Botvinik *et al.*, 2004).

As opposed to antipsychotics, both the hypnotics zolpidem and zopiclone are indicated solely for the treatment of insomnia. The most frequently recorded ICD 10 code (52%) was for “disorders of initiating and maintaining sleep (insomnias)”. This correlates with the pharmacokinetic and pharmacodynamic properties of zopiclone and zolpidem, and their indication for use in the induction and maintenance of sleep. A further 47% of prescriptions pointed to a sleep disorder, which was not specified, but which would presumably include insomnia. One patient (1%) used a hypnotic for a psychiatric indication, specifically depression, possibly to treat insomnia either due to or leading to a depressive disorder. This implies that within this patient group in general, the drugs were being prescribed and used for the correct indications.

Significantly more than half of the prescriptions seen over the seven month period, 72.3%, were prescribed by general practitioners. This is despite the fact that insomnia, especially if occurring chronically, may be associated with other mental or physical conditions (Monti, 2004), which often warrant the need for specialist treatment. Only 27.7% of prescriptions seen were written by specialists, suggesting that patients with secondary insomnia may not always receive the specialist care they require.

The study did not include patient or prescriber interviews, and data was presented in a descriptive manner. Similar studies have been completed, although not with zolpidem and zopiclone. A survey of the use of antidepressants by general practitioners and psychiatrists in Australia concluded that 86% of antidepressants were prescribed by general practitioners and only 10% by psychiatrists. Confusion with wording of the indications for use may have led to the prescribing of antidepressants inappropriately (McManus *et al.,* 2003).

Research conducted by Jureidini and Tonkin in 2006, by means of a literature review of several databases, regarding the overuse of antidepressants in the treatment of depression found a significant increase in the prescribing of antidepressants to various age groups over the last two decades. The increase in prescriptions coincided with the introduction of Selective Serotonin Re-uptake Inhibitors (SSRIs), which have fewer serious side effects and are much safer in cases of overdose. The authors concluded that antidepressants were being over used and inappropriately prescribed, which would negate the benefits of these drugs for the population.

A similar scenario may be occurring with hypnotic drugs, with the newer non-benzodiazepines which have been shown to be safer than benzodiazepines in terms of side effects, dependence and withdrawal. This research has found that zolpidem and zopiclone were often prescribed for a longer term period than the recommended maximum of four weeks. The total period of use of a hypnotic during the seven month period was greater than one month in 78% of the patients surveyed. This shows that the great majority of hypnotic users either used a hypnotic continuously, or frequently if use was on an “as needed” basis. Furthermore, it points to longer term use as opposed to the recommended short term use.

It was found that 66% of patients used the drugs in an uninterrupted manner over an extended period of time. While the use of hypnotics is not recommended over the long term, should long term pharmacotherapy be required, it is recommended that drugs be used on an as needed basis. The results would suggest that only 34% of patients use the drugs on an as needed basis. This figure must be looked at in the context of the limitations of the study, Chapter 6 (page 31). However, it can be said that patients who use one of these hypnotics either over a short term or in an interrupted manner are a minority.

Of the total number of prescriptions seen over one year, 3.17% were for one of the two hypnotics, possibly suggesting overuse of these medications. A seasonal fluctuation in zolpidem and zopiclone use alone was not expected, and was not found. However, due to potential seasonal fluctuations in total number of prescriptions, there was the possibility of a seasonal variation in proportion of zolpidem/ zopiclone use, as compared to total prescription drug use. Surprisingly, this was not the case.

While there is no difference in the active ingredients, dose, and mechanism of action of the different commercial formulations available of the two drugs, a favourite in brand was seen with both zolpidem and zopiclone. In the case of zolpidem, the original brand, Stilnox®, remained the most popular, despite the availability of several generics. In the case of zopiclone, the generic Zopivane® was the most popular. Reasons for these findings may include patient perceptions regarding original and generic products, cost differences, and familiarity of patients and prescribers with certain established brands, perhaps based on how long a product has been on the market.

Very little research was found regarding the use and prescribing patterns of various drugs in South Africa. One research was conducted concerning the prescribing patterns of methylphenidate in South African primary care patients. The researcher obtained data from a medical aid administrator, showing records of patients receiving methylphenidate over a one year period, during the year 2002. The total number of prescriptions dispensed, the average number of prescriptions used per patient and patient demographics were presented (Truter, 2005).

Chapter 6: Limitations

This study did have some limitations. These are as follows:

1. Patients who had prescriptions with multiple repeats indicated, may have requested their prescriptions to be returned to them. If these patients then obtained subsequent monthly repeats at another pharmacy, these records would be unavailable. This was considered a minor limitation as the pharmacy where the research was undertaken is one of very few pharmacies in the area. The majority of patients request that their prescriptions be retained in one place, and repeats stored on the system for the sake of convenience.

2. Patients may have donated medication to friends or family members. If this occurred continuous use would be difficult to establish. This limitation applies to any database used for any medication being surveyed.

3. Patients may have filled a script for one of the drugs, prescribed at the standard strength, but taken only a half a tablet nightly. They may then have filled a repeat prescription later than expected, giving an impression of interrupted or as-needed use when this was not the case. This limitation also applies to any database used for any medication being surveyed.

4. The causes of the insomnia and reasons for seeking treatment are not known. This data could be obtained only through patient interviews. Analysis of existing co-morbidities and other medications taken may also provide greater understanding of the problem.

Chapter 7: Conclusion

In terms of demographics, a higher percentage of female users supports findings in other studies regarding psychoactive mediation, and the increased incidence of insomnia in women. The frequent use of hypnotics in the elderly may be expected as they are also more likely to suffer from insomnia. However, the prolonged use and perhaps the doses used should be questioned, especially in light of potential adverse effects directly or indirectly as a result of medication. The drugs were mostly used at the standard doses, except in the elderly, where a higher dose than recommended was often used. A preference for zolpidem was seen over zopiclone.

The indications used to prescribe these medications were acceptable. However, they are misleading in that except for one patient, it would seem that none of the patients had any other illness, whether physical or mental, that may have caused the development of insomnia. The majority of prescriptions were prescribed by general practitioners, including the long-term repeat prescriptions.

The total period of use exceeded one month in the majority of patients. Patients generally used a hypnotic for an extended period of time, in other words over a long term, and in an uninterrupted manner, which is not recommended.

Approximately 3% of total prescriptions reviewed retrospectively over one year were for either zolpidem or zopiclone, with no seasonal variation seen in the use of a hypnotic. Several generics are available for both drugs. The original product remained the preferred alternative in the case of zolpidem, while a generic was preferred in the case of zopiclone.

While these drugs are classed as schedule 5, there is nothing in the law that prohibits any medical practitioners from prescribing hypnotics. It may also be expected that the initial use of a hypnotic by a patient is as a result of prescription from a general practitioner, as the family or personal doctor is usually the first to be consulted when seeking help. Additionally, there are a greater number of general practitioners, and they are generally more accessible than are the specialists, who are fewer in number. It is recommended, however, that as with the tranquilisers and analgesics, perhaps

some restriction should be imposed to limit the use of hypnotics, and a clearer definition and guidelines may be needed as to the details of prescribing. Specifically, it may be useful to compile guidelines concerning who may prescribe such medications, who may continue long term treatment, how patients will be evaluated for the need for long term treatment and the use of as needed therapy if long term treatment is indicated.

A study in Britain found that the use of cefuroxime tablets declined significantly after reinforcement of prior-authorisation, requiring physicians to obtain approval to prescribe the drug. This was found to be an effective means of controlling drug use and encouraging rational prescribing, possibly through what was called a "sentinel effect," where physicians decrease the use of certain medications or services because they are being monitored (Kahan *et al.*, 2006). This may be a practical method of controlling hypnotic drug prescribing by general practitioners, especially if trying to control the duration of use, and develop more appropriate usage of drugs.

While the newer non-benzodiazepine hypnotics are safer than benzodiazepines, and indeed the older hypnotics, there is still concern and doubt about long-term safety. This study found that despite numerous cautions in the literature, these medications are still being prescribed and used in a manner contrary to existing guidelines. The majority of patients used one of the two hypnotics in an uninterrupted manner, and over a long term period.

References

Allain, H. 1991. Postmarketing surveillance of zopiclone in insomnia: analysis of 20,513 cases. *Sleep*, 14, 5, 408-413.

Allain, H, Arbus, L, Schück, S. 2001. Efficacy and safety of zolpidem administered 'as needed' in primary insomnia: results of a double-blind, placebo-controlled study. *Clinical Drug Investigation,* 21, 6, 391-400.

Allain, H, Bentué-Ferrer, D, Tarral, A, Gandon, J. 2003. Effects on postural oscillation and memory functions of a single dose of zolpidem 5 mg, zopiclone 3.75 mg and lormetazepam 1 mg in elderly healthy subjects. A randomized, cross-over, double-blind study versus placebo. *European Journal* of *Clinical Pharmacology*, 59, 3, 179-188.

Allain, H, Bentué-Ferrer, D, Polard, E, Akwa, Y, Patat, A. 2005. Postural instability and consequent falls associated with use of hypnotics in the elderly: a comparative review. *Drugs & Aging*, 22, 9, 749-765.

Beers, MH & Berkow, R.1999. *The Merck Manual of Diagnosis and Therapy,* Merck Research Laboratories, NJ, 1410.

Botvinik, L, Ng, C, Schweitzer, I. 2004. Audit of antipsychotic prescribing in a private psychiatric hospital. *Australasian Psychiatry* 12, 3, 227-233.

Brown, AF, Perez-Stable, EJ, Whitaker, EE, Posner, SF, Alexander, M, Gathe, J, Washington, AE. 1999. Ethnic differences in hormone replacement prescribing patterns. *JGIM*, 14, 663-669.

Brownlee, K, Devins, GM, Flanigan, M, Fleming, JAE, Morehouse, R, Mosovitch, A, Plamondon, J, Reinish, L, Shapiro, CM. 2003. Are there gender differences in the prescribing of hypnotic medications for insomnia? *Human Psychopharmacology,* 18, 69-73.

Cluydts, R, Heyde, K, De Volder, I. 2002. Polysomnographic findings during non-continuous administration of zolpidem. *Sleep Medicine Reviews*, 6, 1, S13-S19.

Cluydts, R. 2004. Zolpidem "as needed": Methodological issues and clinical findings. *CNS Drugs*, 18, 1, 25-33.

Drover, DR. 2004. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: Zaleplon, zolpidem and zopiclone. *Clinical Pharmacokinetics,* 43, 4, 227-238.

Forrester, MB. 2006. Flunitrazepam abuse and malicious use in Texas, 1998-2003. *Substance Use & Misuse,* 41, 3, 297-306.

Gibbon, CJ (ed.). 2003. *The South African Medicines Formulary,* 6th edn., Health and Medical Publishing Group, South Africa, 438-439.

Glass, J, Lanctot, KL, Herrmann, N, Sproule, BA, Busto, UE. 2005. Sedative hypnotics in older people with insomnia: Meta-analysis of risks and benefits. *British Medical Journal,* 331, 7526.

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

Hajak, G, Bandelow, B, Zulley, J, Pittrow, D. 2002. 'As needed' pharmacotherapy combined with stimulus control treatment in chronic insomnia – assessment of a novel intervention strategy in a primary care setting. *Annals of Clinical Psychiatry,*14, 1, 1-7.

Hajak, G. 2006. New paradigms in the pharmacological treatment of insomnia. *Sleep Medicine,* 7, 1, s20-s26.

Hajak, G, Geisler, P. 2004. Experience with zolpidem "as needed" in primary care settings. *CNS Drugs,* 18, 1, 35-43.

Hajak, G, Muller, WE, Wittchen, HU, Pittrow, D, Kirch, W. 2003. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: A review of case reports and epidemiological data. *Addiction,* 98, 1371-1378.

Harrison TS & Keating GM. 2005. Zolpidem: A review of its use in the management of insomnia. *CNS Drugs,* 19, 1, 65-89.

Hesse, LM, von Moltke, LL, Greenblatt, DJ. 2003. Clinically important drug interactions zopiclone, zolpidem and zaleplon. *CNS Drugs,* 17, 7, 513-532.

Holbrook, AM, Crowther, R, Lotter, A, Cheng, C, King, D. 2000. The diagnosis and management of insomnia in clinical practice: A practical evidence-based approach. *Canadian Medical Association Journal,* 162, 2.

Holm KJ & Goa KL. 2000. Zolpidem: An update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs,* 59, 4, 865-889.

Jaffe, JH, Bloor, R, Crome, I, Carr, M, Alam, F, Simmons, A, Meyer, RE. 2003. A postmarketing study of relative abuse liability of hypnotic sedative drugs. *Addiction,* 99, 165-173.

Jureidini J & Tonkin A. 2006. Overuse of antidepressant drugs for the treatment of depression. *CNS Drugs*, 20, 8, 623-632.

Kahan, NR, Chinitz, DP, Waitman, D, Kahan, E. 2006. When gatekeepers meet the sentinel: The impact of a prior authorization requirement for cefuroxime on the prescribing behaviour of community-based physicians. *British Journal of Clinical Pharmacology*, 61, 3, 341-344.

Katzung, BG (ed.). 2001. *Basic and Clinical Pharmacology, 8th edn.*, The McGraw-Hill Companies, Inc., United States of America, 364-381.

Lee, Y. 2004. Overview of the therapeutic management of insomnia with zolpidem. *CNS Drugs*, 18, 1, 17-23.

Lippmann, S, Mazour, I, Shahab, H. 2001. Insomnia: therapeutic approach. *Southern Medical Journal*, 94, 9.

McManus, P, Mant, A, Mitchell, P, Britt, H, Dudley, J. 2003. Use of antidepressants by general practitioners and psychiatrists in Australia. *Australian and New Zealand Journal of Psychiatry*, 37, 184-189.

Medicines and Related Substances Act 101 of 1965, as amended. 2003. *Pharmaceutical Society of South Africa Law Compendium,* Volume 1, LexisNexis Butterworths, South Africa.

Monti, JM. 2004. Primary and secondary insomnia: Prevalence, causes and current therapeutics. *Current Medical Chemistry- Central Nervous System Agents*, 4, 119-137.

Morgan, K, Dixon, S, Mathers, N, Thompson, J, Tomeny, M. 2004. Psychological treatment for insomnia in the regulation of long-term hypnotic drug use. *Health Technology Assessment*, 8, 8, 1-68.

Morin, AK, Jarvis, CI, Lynch, AM. 2007. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy*, 27, 1, 89-110.

Morin, CM, LeBlanc, M, Daley, M, Gregoire, JP, Merette, C. 2006. Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Medicine*, 7, 2, 123-130.

Noble, S, Langtry, HD, Lamb, HM. 1998. Zopiclone: An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs*, 55, 2, 277-302.

Sanger, DJ. 2004. The pharmacology and mechanisms of action of new generation, non-benzodiazepine hypnotic agents. *CNS Drugs*, 18, 1, 9-15.

Silva, A, Collao, A, Orellana, M, Melendez, J, Caviedes, P, Cardenas, AM. 2003. Zopiclone, but not brotizolam, impairs memory storage during sleep. *Neuroscience Research*, 47, 2, 241-243.

Spiegel, R. 2003. *Psychopharmacology, an Introduction, 4th edn.,* John Wiley and Sons Ltd., West Sussex, England.

Terzano, MG, Rossi, M, Palomba, V, Smerieri, A, Parrino, L. 2003. New drugs for insomnia: Comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety,* 26, 4, 261-282.

Treben, M. 2003. *Health Through God's Pharmacy,* Ennsthaler, Austria, pp. 16, 22.

Truter, I. 2005. Methylphenidate: Prescribing patterns in a South African primary care patient population. *Journal of Clinical Pharmacy and Therapeutics,* 30, 59-63.

Vallières, A, Morin, CM, Guay, B. 2005. Sequential combinations of drug and cognitive behavioral therapy for chronic insomnia: An exploratory study. *Behaviour Research and Therapy,* 43, 12, 1611-1630.

Vermeeren, A. 2004. Residual effects of hypnotics: Epidemiology and clinical implications. *CNS Drugs,* 18, 5, 297-326.

Verster, JC, Veldhuijzen, DS, Volkerts, ER. 2004. Residual effects of sleep medication on driving ability. *Sleep Medicine Reviews,* 8, 4, 309-325.

Voderholzer, U, Riemann, D, Hornyak, M, Backhaus, J, Feige, B, Berger, M, Hohagen, F. 2001. A double-blind, randomized and placebo-controlled study of the polysomnographic withdrawal effects of zopiclone, zolpidem and triazolam in healthy subjects. *European Archive of Psychiatry and Clinical Neuroscience,* 251, 17-123.

Walsh, JK. 2002. Zolpidem "as needed" for the treatment of primary insomnia: A double-blind, placebo-controlled study. *Sleep Medicine Reviews,* 6, 1, S7-S11.

Walsh, JK, Roth, T, Randazzo, A, Erman, M, Jamieson, A, Scharf, M, Schweitzer, PK, Ware, JC. 2000. Eight weeks of non-nightly use of zolpidem for primary insomnia. *Sleep,* 23, 8, 1087-1096.

Wang, PS, Bohn, RL, Glynn, RJ, Mogun, H, Avorn, J. 2001. Zolpidem Use and Hip Fractures in Older People. *Journal of the American Geriatrics Society,* 49, 12, 1685-1690.

Wortelboer, U, Cohrs, S, Rodenbeck, A, Ruther, E. 2002. Tolerability of hypnosedatives in older patients. *Drugs & Aging*, 19, 7, 529-539.

Appendix A: Data Collection Instrument

Patient Number: (1 – 100)

Age of patient:

Gender of patient:

Race:

Month	Prescription drug	Dose	Duration of treatment	Single or repeat prescription	ICD10 code	Prescriber (GP or specialist)
1 Date:						
2 Date:						
3 Date:						
4 Date:						
5 Date:						
6 Date:						
7 Date:						

Appendix B: Letter requesting permission to conduct research in Clicks Pharmacy, Rosebank

Jonathan Herson
Manager, Clicks Rosebank Pharmacy
Rosebank Mall

23 February 2006

Dear Mr. Herson

Re: Permission to collect data for Msc(Med) research report

I am currently enrolled for an MSc(Med) Pharmacotherapy degree at the University of the Witwatersrand. Part of the requirements of the degree is the submission of a research report. I will be doing a report on the usage and prescribing patterns of the hypnotic drugs zolpidem and zopiclone.

I would like to request your permission to collect data from your pharmacy. Data collected will include patient, prescriber and prescription characteristics and will be obtained directly from the Unisolv computer system. Patients or doctors will not be approached. No other person will be involved in data collection and details such as patient name, profile or identity number will not appear in the final report and will be accessible only to myself. **All patient details will remain completely confidential**; the final report will reflect only the statistical findings.

I am attaching a copy of my proposed method of research for you to gain insight into exactly what my methods will be, and the time frame involved.

Please do not hesitate to contact me if you have any further queries.

Yours Sincerely

Gauri Jain

Telephone (cell): 0726360063

Email: gauri.jain@gmail.com

Appendix C: Letter from the manager of Clicks Pharmacy, Rosebank, granting permission to conduct research in the pharmacy

24/02/06

Dear Ms Jain

I have received and read over your letter and research method. I have no objection to your collecting data from this pharmacy. I will be happy to provide any assistance you may need. I wish you the best of luck in your endeavour.

ROSEBANK
P. O. BOX 2344
PARKLANDS 2121
TEL: 880-7682/3/4

Jonathan Herson
Pharmacy Manager, Clicks Pharmacy Rosebank

Appendix D: University of Witwatersrand Postgraduate Research Committee Approval

Faculty of Health Sciences
UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

7 York Road PARKTOWN Johannesburg 2193 Telegrams WITSMED Telex 4-24655.SA
FAX 643-4318 TELEPHONE 717-2075/2076
E-MAIL healthpg@health.wits.ac.za

MISS G JAIN
PRINCE ALFRED HOUSE
P/BAG 1025
GRAHAMSTOWN
6140

APPLICATION NUMBER 0515926K
STATUS (DEG 75) (MM044) PZZ

2006-08-15

Dear Miss Jain

Approval of protocol entitled Current prescribing patterns and use of non-benzodiazepine hypnotics in a retail environment

I should like to advise you that the protocol and title that you have submitted for the degree of Master Of Science In Medicine (Part-Time).(Coursework) have been approved by the Postgraduate Committee at its recent meeting. Please remember that any amendment to this title has to be endorsed by your Head of Department and formally approved by the Postgraduate Committee.

Prof AG Gous, Dr. GJ Lowndes has/have been appointed as your supervisor/s. Please maintain regular contact with your supervisor who must be kept advised of your progress.

Please note that approval by the Postgraduate Committee is always given subject to permission from the relevant Ethics Committee, and a copy of your clearance certificate should be lodged with the Faculty Office as soon as possible, if this has not already been done.

Yours sincerely

S Benn (Mrs)
Faculty Registrar
Faculty of Health Sciences

Telephone 717-2075/2076

Copies - Head of Department_____Supervisor/s

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The University seeks to serve South Africa by furthering access to equal opportunity while striving for excellence in teaching, learning and research

Appendix E: University of Witwatersrand Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Jain

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060962**
PROJECT	Current Prescribing Patterns and Use of Non-Benzodiazpeine Hypnotics
INVESTIGATORS	Ms G Jain
DEPARTMENT	Pharmacy & Pharmacology
DATE CONSIDERED	06.09.29
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr G Lowndes

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES