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***Acute pharmacological effects of temazepam,
diphenhydramine and valerian in healthy elderly
subjects***

By

Jennifer R. Glass

***A thesis submitted in conformity with the requirements for the degree of
Master of Science.
Graduate Faculty of Pharmaceutical Sciences in the School of Graduate Studies,
University of Toronto***

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***ACUTE PHARMACOLOGICAL EFFECTS OF TEMAZEPAM, DIPHENHYDRAMINE AND VALERIAN
IN HEALTHY ELDERLY SUBJECTS***

BY JENNIFER R. GLASS

**Thesis for M.Sc in the Graduate Faculty of Pharmaceutical Sciences in the School of
Graduate Studies, University of Toronto, September 2001**

ABSTRACT

A randomized, double-blind, placebo-controlled, crossover study was performed to compare the acute single-dose effects of temazepam (15 and 30 mg), diphenhydramine (50 and 75 mg) and valerian (400 and 800 mg) in 14 healthy elderly volunteers.

Treatment or placebo were received in random order. Subjective sedation and mood were measured using visual analogue scales and psychomotor impairment was measured using the digit symbol substitution and manual tracking tests at baseline, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose. Temazepam elicited a dose-dependent effect on subjective sedation, mood and psychomotor ability that had a consistent time-course of effect.

Diphenhydramine elicited sedation in a non-dose-dependent fashion, but much less psychomotor impairment than temazepam. No differences in sedation, psychomotor ability or side effects were noted with valerian compared to placebo. Results from this study may impact how sedative-hypnotics are recommended for elderly patients.

In memory of Keith Grant Glass, my grandfather.

For Agnes Glass, and Andy & Ruth Padmos, all of whom have taught me that dignity and respect should be ubiquitous in the lives of all people, for the duration of their lives.

And for my parents, the most generous, understanding, helpful and solid people in my life.

“To achieve the impossible dream, try going to sleep.” Joan Klempner

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LIST OF ACRONYMS

DIMS.....	Difficulty Initiating or Maintaining Sleep
ICD-10.....	International Classification of Disorders, 10 th edition
ARCI.....	Addiction Research Centre Inventory
OTC.....	Over The Counter
GABA.....	γ -aminobutyric acid
CNS.....	Central Nervous System
Cl ⁻	chloride ions
BZ.....	Benzodiazepine
H1, H2, H3.....	Histamine receptors type 1, 2 and 3, respectively
IP ₃	Inositol triphosphate
Ca ²⁺	Calcium ions
cAMP.....	cyclic Adenosine MonoPhosphate
US.....	United States
Hrs.....	hours
AM.....	Active Metabolite
5-HT.....	5-Hydroxy-Tryptophan
DSM-IV.....	Diagnostic and Statistics Manual, 4 th edition
DSM-III-R.....	Diagnostic and Statistics Manual, 3 rd edition, Revised
y.o.....	years old
I.V.	intravenous
ARF.....	Addiction Research Foundation
ICH.....	International Conference of Harmonization
JG.....	Jennifer Glass
CAMH.....	Centre for Addiction and Mental Health
ANOVA.....	Analysis of Variance
ANCOVA.....	Analysis of Covariance
Pla.....	Placebo
Tem 30.....	30 mg temazepam
Tem 15.....	15 mg temazepam
Dph 75.....	75 mg diphenhydramine
Dph 50.....	50 mg diphenhydramine
Val 800.....	800 mg valerian
Val 400.....	400 mg valerian
AUC.....	Area Under the Curve
MTT.....	Manual Tracking Test
DSST.....	Digit Symbol Substitution Test
VAS.....	Visual Analogue Scale
CFFT.....	Critical Flicker Fusion Threshold

SECTION I - INTRODUCTION

IA STATEMENT OF THE PROBLEM

The elderly often use pharmacological remedies for promoting sleep. Many different treatments are employed, despite the lack of evidence of efficacy or sound scientific evidence that these remedies are useful.¹ There are also very different regulations surrounding the use of these treatments, despite evidence that this is necessary or rational.² This study was performed to investigate the differential human pharmacology of three sedative-hypnotic medications in an elderly population.

IB OBJECTIVES

The objective of this study is to compare the acute pharmacological effects of three hypnotic medications that are frequently used by elderly individuals; a benzodiazepine (temazepam), an antihistamine (diphenhydramine), and an herbal medication (valerian). To date, there are no published data on the comparative effects of these three medications in the elderly.

IC HYPOTHESIS AND RATIONALE FOR THE HYPOTHESIS

The *a priori* hypothesis was that there would be significant objective and subjective effects of these three medications compared with placebo. Furthermore, temazepam was expected to have the most robust sedative effect, followed by diphenhydramine. The least sedative effect was expected with valerian treatment. These effects were expected to show a dose-dependent magnitude of effect, and have a time-course of effect.

Dependent variables employed included objective sedation measured by validated psychomotor tasks and subjective sedation and changes in mood, measured by a variety of well-validated instruments.

Temazepam is a benzodiazepine that has been on the market in North America since the 1980s. There have been several studies evaluating the safety and efficacy of temazepam, in both younger³⁻⁵ and older adults⁵⁻⁹, and therefore this will serve as the positive control for the study, i.e., as a benchmark to compare other, less well-studied medications.

Diphenhydramine is a sedating antihistamine. Clinicians have known of its somnolescent effects since the 1940s. Some clinical studies have demonstrated its effectiveness as a sedative medication, but there are others that have demonstrated little effect, making the efficacy of this medication a contentious issue. There are few studies that have examined the effect of diphenhydramine in an elderly population.

Published clinical studies assessing valerian as a sedative were not well controlled, have generally had small sample sizes, and the assessments and sleep ratings are not well explained. Some researchers found valerian to be a mildly effective sedative compound, but others found that treatment had no effect on sleep. We therefore expect valerian to be the least sedating of the three experimental compounds.

The assessments that are used in this study have been used in many instances in the past and have proven to be accurate measures of psychomotor impairment and subjective feelings of sedation and mood.^{10, 11}

SECTION II - REVIEW OF THE LITERATURE

IIA INSOMNIA IN ADULTS

Insomnia or “difficulty initiating and/or maintaining sleep” is often overlooked because of its generality – nearly everyone experiences poor sleep at some point in his or her life. At any one time, the prevalence of insomnia is estimated to range between 10 and 30% among adult community residents¹²⁻¹³ and this estimate increases to 45-66% in the elderly.¹⁴ Symptoms of insomnia tend to be recurrent or persistent in both clinical and community samples.^{15, 16}

Lack of sleep is the most common cause of impaired daytime functioning^{17, 18}, and can lead to injurious or fatal motor vehicle or workplace accidents.^{15, 19, 20} For example, insomniacs are found to be 2.5 times more likely to report fatigue-related vehicle accidents.¹ Sleep problems have also been shown to cause debilitating daytime fatigue, irritability, diminished ability to cope, impaired productivity, and/or depression and anxiety.²¹⁻²⁴ Sufferers have been shown to be significantly greater consumers of alcohol, which may lead to abuse.¹ Moreover, insomnia is often comorbid with other health problems, such as states of pain or discomfort, substance abuse disorders, depression, stress, or anxiety.^{14, 21, 25} Inability to sleep is comorbid with Alzheimer’s disease and other syndromes of impaired cognition.²⁶

II B DIAGNOSIS AND CLASSIFICATION OF INSOMNIA

Insomnia is often referred to as ‘difficulties initiating or maintaining sleep’ (DIMS). This can mean difficulty achieving sleep, often marked by an overly long sleep onset latency; nocturnal awakenings with difficulty resuming sleep, or premature early morning

awakenings with an inability to return to sleep. For a sleep disturbance to afford the title of insomnia as per DSM-IV classification, this sleep disturbance must continue for at least one month and cause significant distress, daytime fatigue, and/or impairment of social, occupational, or other areas of functioning.²⁷

Insomnia is further divided into 3 separate categories based on duration of symptoms (see Table 1).²⁸ These are transient (lasting 2-3 days), short-term (less than 3 weeks), and chronic or long-term (greater than 3 weeks).

Chronic or long-term insomnia includes what DSM-IV calls Primary Insomnia (307.42), which may be due to behavioural reasons, primary sleep disorders such as sleep apnea or restless legs syndrome, or chronic medical problems. In many cases primary insomnia is not associated with an identifiable stressor or event, and therefore any clinical investigation should include examination of subjects' sleep habits, use of drugs and alcohol, and underlying mental, physical and psychiatric conditions.^{21, 22} Primary insomnia is often psychological in nature - usually initiated during a time of psychological, mental, or physical stress, and persisting due to heightened arousal at bedtime and negative conditioning.^{24, 27} These negative associations, such as associating the bed and bedroom with anxiety or sleeplessness, perpetuate the inability to sleep beyond its original cause, thus leading to insomnia independent of any psychological or medical cause, or primary insomnia. The ICD-10 refers to this paradoxical stimulation associated with bedtime as "Persistent Psychophysiological Insomnia".[Organization, 1992 #246]

TABLE 1. Classification of Insomnia by Duration

Type of Insomnia	Duration	Probable Cause
Transient	2-3 days	Environmental factors, acute stressors (e.g. excessive noise, temperature, jet lag etc.)
Short-term	less than 3 weeks	personal stress, grief, injury (e.g. death in family, work or financial problems)
Long-term	more than 3 weeks	medical, psychiatric, pharmacological, or substance abuse condition; psychophysiological

IIC INSOMNIA IN THE AGED

The estimated point prevalence of insomnia is increased from approximately 10-30% in younger adults to 40-66% in elderly populations (depending on ambulatory vs. institutionalized and concomitant conditions).^{1,2} Older individuals are more likely to report decreased sleep quality and quantity, and increased daytime sleepiness.^{1, 16, 25, 26, 29-34} It has been shown that the architecture of sleep changes with age. The amount of deep sleep and total sleep time are decreased while the number of nocturnal awakenings is increased.^{20, 35}

Sleep apnea is a condition that leads to the cessation of breathing alternating with waking for periods of time in the night, which causes unrestful sleep. This condition becomes more common as people age, and as many as 20% of older individuals may suffer from some degree of sleep apnea.^{26, 36, 37}

There are many potential reasons for the increased prevalence of insomnia in older individuals. Changes in lifestyle or routine, such as retirement and/or decrease in activity & exercise may affect sleep patterns.^{32, 38, 39} Ohayon et al (2001) demonstrated that dissatisfaction with social life was the most important predictor of insomnia in individuals

and that this was more likely with elderly persons.³⁰ Psychiatric conditions such as anxiety and depression are more common in elderly individuals, due in part to life-changes (such as loss of independence, decreased social activities, loneliness) and/or increase in medical illnesses.^{40, 41} Dementia, distress, psychoses and delirium are also conditions that are suffered more commonly by elderly individuals and have been linked to insomnia.²⁶

An increase in comorbid physical or pharmacological conditions may compromise the ability to sleep fitfully. Some examples of conditions that are more common in the elderly and that are known to negatively affect sleep are: aforementioned sleep apnea or respiratory impairment; gastro-intestinal conditions; conditions causing nocturia; grief and/or mourning. Pharmacological treatments can also interfere with sleep, such as: caffeine; theophylline; nicotine; beta-adrenergic blockers; thyroid medications; or steroid hormones.^{20, 25, 38, 42} As individuals age they are more likely to use more prescription and non-prescription medications that might interfere with sleep.^{33, 43, 44}

Hormonal changes that occur as individuals age and that affect sleep are decreases in melatonin production;⁴⁵ dihydroepiandrosterone (DHEA); and reproductive hormones such as estrogen, prolactin and testosterone.^{46, 47} Melatonin is a circadian hormone that is thought to elicit general relaxation and sedation at the end of the day. Declines in melatonin levels may be associated with waning in normal circadian rhythm.^{45, 48} This may result in individuals sleeping for shorter periods of time at night, or experiencing long periods of nocturnal wakefulness.

Despite the increased prevalence of these physiological, psychological and sociological changes, and the increased prevalence of sleep disorders with increased age, sleep requirements do not decrease with age.³² Logically then, the repercussions of lack of sleep in elderly individuals are similar to younger individuals; such as decreased

productivity and quality of life. The elderly chronic insomniac is at a significantly higher risk for motor vehicle accidents, compromised ability for self-care, memory problems, falling, difficulty in accomplishing daily tasks and coping with daily stresses.^{15, 49} Older people may be even more prone to these effects than their younger counterparts.^{33, 50} Lack of sleep is also thought to be comorbid with psychiatric and psychological problems, dementia and delirium, states that elderly individuals are at greater risk for.^{50, 51}

IIb ECONOMIC IMPACT OF INSOMNIA

It has been estimated that direct costs associated with insomnia in 1990 were \$10.9 billion US dollars,⁴⁹ and \$13.93 billion in 1995.⁵² A substantial proportion of this cost is associated with nursing home care for the elderly, which is estimated to cost \$9.0 billion (1990). Simon et al (1997) report that the cost for health services for insomnia sufferers in primary care was approximately 60% greater than in non-sufferers.⁵³ These estimates do not include indirect costs such as reduced productivity, health and property costs related to accidents, or medical costs associated with comorbid conditions; which may increase costs up to \$77 – \$92 billion US dollars per year (1990 dollars).⁴⁹ Costs that are difficult, if not impossible, to accurately estimate include increased mortality, catastrophic accidents, and academic and job failures. Interestingly, in a study done in 1990, the estimated cost for substances used to promote sleep was \$1.1 billion, or approximately 10% of the total estimated cost. Less than half of this estimated \$1.1 billion was spent on prescription medications.⁴⁹

In summary, inability to sleep can affect work, relationships, health, and therefore contributes to an appreciably decreased quality of life in individuals of all ages. Elderly

persons tend to suffer more often from insomnia, and the repercussions can be more pronounced in this population.⁵⁴

IIe PHARMACOLOGICAL TREATMENTS FOR INSOMNIA

Treatment for short-term acute episodes of insomnia is usually pharmacological.⁵⁵ Pharmacological treatments are prescription (usually benzodiazepines), over the counter, (usually antihistamines), or herbal remedies. Pharmacological remedies for insomnia that are marketed in Canada are listed in Table 2.

Benzodiazepines are strictly regulated by Health Canada as “targeted substances”, subject to the Controlled Substances Act⁵⁶- in contrast to antihistamines, which are readily available without a prescription. Therefore, although pharmacists are required to strictly document receipt, dispensing and stocking of benzodiazepine substances, antihistamines can be bought without any controls on quantity or frequency of purchases. As with benzodiazepines, there are some reports of abuse of antihistamines by psychiatric patients, youths, and drug users,^{57, 58} and that induced sedation may impair driving ability.⁵⁹⁻⁶¹ One study that compared the abuse liability of diphenhydramine to lorazepam found that scores on the Addiction Research Centre Inventory (ARCI), a well-validated measure of drug effects, were similar for doses with comparable sedative effects.⁶² There is not much evidence that this contrast in regulatory measures is justified.

Herbal preparations are not subject to the same regulations as drugs since the Canadian government maintains herbal products in the same regulatory category as dietary supplements, although new regulations are said to be forthcoming in 2001.[Products, 1998 #266] Unlike drugs, it is not necessary for natural health products, such as herbal

medications, to undergo clinical trials or toxicological testing, as with drugs.[Sibbald, 2000 #265; Products, 1998 #266] Therefore, there are no regulations surrounding the use of natural health products, nor are there strict regulations on their sale in Canada currently. Natural products that are recommended for sleep are listed in Table 3, and discussed further in Section IIN, page 35.

Table 2. Pharmacological treatments for insomnia that are marketed in Canada

DRUG	DOSE RANGE (mg)	HALF-LIFE (hrs)	INDICATION	ACTIVE METABOLITE
PRESCRIPTION DRUGS				
Flurazepam	15-30	2.5 AM 50-160	Insomnia	Yes
Temazepam	15-30	3-25	Insomnia	No
Triazolam	.125-.05	1.5-5	Insomnia	No
Zopiclone	3.75-7.5	3.8-6.5	Insomnia, Anxiety	No
Zaleplon	5-20	1.0	Insomnia	No
OTC DRUGS				
Diphenhydramine	25-75	2.4-9.3	Allergies, sedative	No
Doxylamine	25	10	Allergies, sedative	No

Table 3. Herbal and Natural Products used to promote sleep

HERB OR PRODUCT	DESCRIPTION	USED FOR	ACTIVE INGREDIENTS
MELATONIN	Hormone released by pineal gland at night, cues circadian rhythm	Disturbances in circadian rhythm, jet lag, shift wor	Melatonin
KAVA KAVA (<i>Piper methysticum</i>)	Plant product from Polynesia, Micronesia – used in religious ceremonies and diet	Anxiety, nervousness, stress, muscle relaxation, sleep disorders associated with anxiety	Kavapyrones and/or kavalactones
VALERIAN (<i>Valeriana officinalis</i>)	Dried roots and rhizomes of <i>Valeriana officinalis</i> , found in Europe, N. America	Insomnia, stress	Sesquiterpines, valpotriates, valerian
TRYPTOPHAN	Amino acid obtained from diet, precursor to 5-HT	Depression, sleep disorders associated with depression	Tryptophan – Precursor to 5-HT

II F BENZODIAZEPINES AND NON-BENZODIAZEPINE ALLOSTERIC MODULATORS OF THE GABA_A RECEPTOR

In the 1960s, prescription benzodiazepines quickly took over the barbiturates' place as the drug of choice for the treatment of short-term insomnia because of their efficacy, relatively safety and low abuse potential.⁶³ However, it was not until the late 1970s that

researchers discovered that the benzodiazepines enhanced the inhibitory effect of gamma-amino-butyric-acid (GABA), and that they were binding at specific sites in the CNS.⁶⁴

Benzodiazepines work as allosteric modulators at the γ -aminobutyric acid-type A (GABA_A) receptor. The GABA system is the major inhibitory neurotransmitter system in the central nervous system.⁶⁵ The GABA_A receptor is an ionophoric Cl⁻ channel; binding of GABA induces influx of Cl⁻ into the cell, resulting in hyperpolarization. Hyperpolarization of the cell has an inhibitory effect on production of action potentials, the mode of fast communication in the CNS.

There are three subtypes of the GABA receptor in human brain, GABA_A, GABA_B, and GABA_C. The GABA_A receptor is the receptor that is affected by sedative-hypnotic medications.^{65, 66} The GABA_A receptor is a pentameric protein; 5 protein moieties come together and form in a rosette shape to create a central pore that is permeable by Cl⁻ ions⁶⁷. There are at least 16 different genes and 5 different families of subunit proteins that make up the receptor.⁶⁸ There are six different alpha subunits (1-6); four beta subunits (1-4); three gamma (1-3); and one of each delta and rho. GABA binds to the beta subunit of the protein, for example, and a conformational change allows Cl⁻ to enter the cell.⁶⁹ The subunits can come together in many different combinations, and this may confer different pharmacology.^{70, 71} The most common combination of subtypes for the GABA_A receptor seems to involve alpha-1, beta-2 and gamma-2; this particular combination is expressed by over 50% of GABA_A receptors in the human brain and these particular subtypes are important determinants of receptor pharmacology.⁷² Figure I depicts an example of the pentameric structure of the receptor and the pertinent binding sites (Figure I, page 21).

Benzodiazepines work by potentiating the action of GABA, or increasing the inhibitory action at the GABA_A receptor site. They bind to the alpha subunit of the receptor

and when both a benzodiazepine and GABA bind to the receptor, more Cl^- will enter the cell than with GABA alone. As a result, benzodiazepines are sometimes called “positive allosteric modulators” of the GABA_A receptor. The resultant effects are sedative, anxiolytic, anti-convulsant, amnesic, and muscle-relaxant.⁷³ Compounds may also bind to this receptor with the opposite effect, i.e. as negative allosteric modulators – decreasing the inhibitory action of GABA and decreasing the degree of hyperpolarization. These compounds are proconvulsive, anxiogenic, and may enhance memory.^{68, 69, 74, 75} There has been speculation that endogenous moieties may exist that are expressed in response to stress, but conclusive evidence has not been demonstrated.⁷⁵

There are 6 isomers of alpha subunits that may be found in GABA_A receptors, and it is probable that the composition of the alpha subunit determines the receptors' benzodiazepine pharmacology.⁷⁰ Because it is where the benzodiazepine drugs bind and cause their pharmacological effect, the alpha subunit of the pentameric GABA receptor is known as the benzodiazepine receptor (BZ receptor), or the ω receptor (Figure I, page 20). Three distinct subtypes of the BZ receptor have been found to exist in humans: BZ1; BZ2; and BZ3.⁷⁶ The BZ1 receptor (or the alpha 1 subunit) is associated with somnolence, whereas BZ2 and BZ3 receptors are thought to be related to the anticonvulsant, muscle relaxant, and anxiolytic properties of benzodiazepines.^{68, 70}

Figure I. Structure of the GABA_A receptor.⁷⁷ Binding sites for GABA, the barbiturates, benzodiazepines (BZ), steroids (e.g. steroid hormones), ethanol, Zinc (Zn²⁺) and picrotoxin (PTX) have been labeled. Cl⁻ ions enter the cell through the central pore in the receptor.

More recently, non-benzodiazepine entities that modulate the GABA_A receptor in the same way as benzodiazepines have been introduced as sedative-hypnotic medications.

These are zopiclone, zaleplon, and zolpidem. These medications are also BZ receptor agonists but target specifically the BZ1 receptor subtype, and are therefore thought to target sleep problems more efficiently. Functionally, their pharmacology is remarkably similar to benzodiazepines.^{21, 78-80}

BZ receptor agonists differ mainly in their kinetics and can be broken down into 3 subtypes depending on their duration of action. Long-acting benzodiazepines, such as flurazepam (Dalmane®), have half-lives in the range of 40 – 160 hours because of active metabolites that are excreted much more slowly than the parent compound. When the

shorter-acting compounds were discovered in the 1980s, these long-acting sedatives fell out of favour for the treatment of insomnia because of residual sedation and morning hangover effects. . An example of an intermediate-acting hypnotic is temazepam (Restoril®), with a mean half-life of 9 hours in healthy adults.⁸¹ Short-acting BZ receptor agonists such as triazolam (Halcion®) and the non-benzodiazepines have very short half-lives and may be used to alleviate sleep problems such as sleep onset latency, but are not as effective for nocturnal awakenings or early morning awakening.^{36, 79} Concerns about effects on memory also prompted the decreased prescribing of triazolam.⁷⁸ Benzodiazepines with high affinity for the BZ receptor are thought to be more likely to have reinforcing effects. Triazolam has a high affinity for the BZ receptor compared to temazepam. All have been used extensively as sedative-hypnotics clinically, however – for a comprehensive review see Mitler, (2000), and/or a meta-analysis by Holbrook et al (2000) that provides a good review of benzodiazepine efficacy for sleep.⁵⁵ Review of the clinical data from studies with benzodiazepines will focus here on temazepam, the most commonly prescribed benzodiazepine sedative-hypnotic in Canada for the past three years.⁸²

TEMAZEPAM

Temazepam is a 1,4-benzodiazepine. It is absorbed quickly when taken orally with peak plasma concentrations occurring in 2-3 hours and significant blood levels and sedative effects after 30 minutes in most patients.⁸¹ It is metabolized mainly in the liver by glucuronide conjugation, and eliminated as glucuronide-temazepam in the urine.

Temazepam has been shown to demonstrate differential elimination half-life and volume of distribution in elderly female subjects as compared to younger female adults.⁷ Furthermore, elderly females compared to elderly males have been found to have longer elimination half-lives and total oral clearance in elderly individuals.⁷ While some studies have found that

temazepam may accumulate in older individuals,^{7,9} others report no accumulation in elderly subjects.⁸³ In general, accumulation of drugs is dependent of their half-lives – the longer the half-life, the more the drug will accumulate. The half-life of temazepam has been found to range from 10-20 hours in younger subjects,⁵ to 8-38 hours with both young and elderly subjects (age was found to have no effect on half-life in this study).⁸⁴

There have been several studies evaluating the safety and efficacy of temazepam, in both younger³⁻⁵ and older adults.⁵⁻⁹ A post-marketing study done in 12,350 patients prescribed 10-30 mg of temazepam indicated that 80% of respondents rated the drug as effective after 2 weeks. Further follow-up with 3062 patients at 3 months indicated that 92% rated the drug as effective.⁸⁵

Effective doses generally range from 7.5 to 45 mg⁵; the Canadian Compendium of Pharmaceuticals and Specialties' recommended dose is 15-30 mg for adults, where 15 mg is the recommended dose for patients over the age of sixty-five⁸¹. However, in another post-marketing study, doses of temazepam up to 80 mg were found to be safe and effective in "about 80-90% of more than 10 000 general practice patients with insomnia that did not respond to low dose temazepam or other hypnotics".⁵ These results indicate that temazepam is a reliable, safe and efficacious sedative, even at higher doses. Furthermore, because it has been in use for several years, and has been used in several clinical studies, it was chosen as a positive control or verum for this study.

II.G EPIDEMIOLOGY OF USE OF BZ-RECEPTOR AGONISTS

Drug-use studies have reported a wide range of use of benzodiazepine sedative-hypnotics in elderly patients. For example, Egan et al (2000) found that 19.8% of the population over 65 years of age in Quebec had used a benzodiazepine continuously over the

past year.⁸⁶ In Italy, a study of adult general practice patients (i.e. study was not limited to elderly patients), indicated that 14.0% of patients used benzodiazepines at the time of survey. Users of benzodiazepines are generally older (i.e. 57% of long term users in Italy were over 65); and are more likely to be female (72.8% of users in Italy). As well as use for sleep disorders, benzodiazepines are prescribed for generalized anxiety disorders, panic disorder, obsessive-compulsive disorder, personality disorders such as avoidant personality or social phobia, posttraumatic stress disorders, mania, acute psychosis, and agitation and/or distress associated with dementia or distress associated with events such as bereavement, and acute alcohol or drug withdrawal syndromes.⁶⁹

It is recommended that when used as sedative-hypnotics, benzodiazepines should not be used for longer than 30 days.^{81, 87} However, it has been demonstrated repeatedly that prescribing of sedative-hypnotics for long periods of time is common in western society.⁸⁸⁻⁹¹ Barnas et al (1991) interviewed customers filling prescriptions for benzodiazepines in a community pharmacy in Austria and found that the average duration of use was 4.5 years.⁹² Tamblyn et al (1994) found that, of 65 349 elderly patients in Quebec, 36% received benzodiazepines for longer than 30 consecutive days.⁸⁹ It has been shown that many hospital patients receive prescriptions for sedative-hypnotic medications while in hospital and continue to utilize these drugs after discharge without proper indication.⁹³

III OTC SEDATIVES - ANTIHISTAMINES

Sedative drugs that are available over the counter (OTC) in Canada are antihistamines, such as Nytol® (diphenhydramine) or Unisom® (doxylamine). They are also sold in allergy preparations, such as Benadryl® (diphenhydramine) as anti-emetics such as Gravol® (dimenhydratate), or in cough and cold preparations, such as Neo Citran®

(pheniramine maleate). Surveys have indicated that individuals use antihistamine preparations that are indicated as anti-emetics or cold medications, for their sedative properties.^{94, 95}

The antihistamines have a very different pharmacology from the benzodiazepines. Histamine is a neurotransmitter that has both agonistic activities at a histamine receptor, as well as modulating effects in other neurotransmitter systems.⁹⁶ Histamine receptors H1, H2 and H3 are G-protein-coupled receptors that are found in peripheral tissue as well as in the posterior hypothalamus of the brain in humans, with cell bodies in the tuberomammillary nucleus and projections throughout CNS. When stimulated by an agonist, such as histamine, intracellular stores of Ca^{2+} are mobilized through various pathways, including inositol 1,4,5-triphosphate (IP_3), protein kinase C and cyclic AMP (cAMP).⁹⁷ Functionally, histamine is a widely distributed neurotransmitter that controls vigilance during the waking hours by promoting precise transmission in thalamocortical relay neurons and by processing sensory inputs and cognition.⁹⁸ As a modulatory amine, currents may be enhanced by actions at the N-methyl-D-aspartate receptor, or the muscarinic cholinergic receptor.^{96, 99} Antihistamines act antagonistically at these receptor sites, blocking stimulation by histamine both peripherally and centrally at histamine receptors and centrally at muscarinic cholinergic receptors.⁹⁹ Peripherally, antihistamines block allergic or anaphylactic reactions such as bronchial constriction and capillary dilation.⁸¹

Antihistamines were first developed in the 1940s for the treatment of allergic disorders such as rhinitis, conjunctivitis, and urticaria. The most pertinent side effect of treatment was thought to be sedation.¹⁰⁰ Positron emission tomography (PET) studies indicate that the sedative effect of antihistamines is likely due to binding in the frontal cortex in humans.¹⁰¹ Increased binding at this site was found to correlate with increased subjective

sleepiness, impaired cognition, and decreased reaction time. More recently, newer antihistamines that have larger and less lipophilic molecular structures and therefore do not cross the blood brain barrier as readily as these prototype entities have been developed, such as acrivastin, terfenadine, fexofenadine, cetirizine, and loratadine.^{60 98, 102, 103} Because they do not reach the brain as readily as older antihistamines, there is less sedation with these newer moieties.

However, antihistamines can be and are purchased over the counter (OTC) to be used for what was originally thought to be their most debilitating side effect – sedation. Diphenhydramine (Nytol®, Sleep-Eze® and Sleep-Eze-D®, Sominex®) and doxylamine (Unisom®) are marketed as sedatives in Canada. Review of the clinical data from studies with antihistamine sedatives will focus here on diphenhydramine because of the extensive research that has been conducted using this entity.

DIPHENHYDRAMINE

Diphenhydramine is the prototypical antihistamine entity. It was developed in the 1940s and has been on the market since 1945.¹⁰⁴ It is metabolized by P450 enzymes in human hepatocytes by N-demethylation to monodesmethyl-diphenhydramine.¹⁰⁵ First-pass effects in part determine bioavailability, which ranges from approximately 43 to 72%. The half life of diphenhydramine has been shown to be longer for aged individuals than younger adults – Simons et al (1990) report half lives of 9.2 +/- 2.5 hours for adults and 13.5 +/- 4.2 hours for elderly individuals. Higher peak serum concentrations of diphenhydramine were found in elderly individuals, as well as slower elimination rates.⁹⁸ Differences in pharmacokinetics in aged individuals are most likely due to decreased hepatic drug oxidizing capacity with advancing age.^{98, 105} Diphenhydramine kinetics have been found to

be altered in different ethnic groups (e.g. Oriental vs. Caucasian)¹⁰⁶, and in individuals with liver disease.¹⁰⁷

In clinical trials, some studies have demonstrated a significantly higher degree of sedative effects (objective and subjective measures) with diphenhydramine compared to placebo,¹⁰⁸ while some have shown no difference in somnolence.^{109, 110} Studies that have examined the effects of antihistamine sedatives in geriatric subjects or patients demonstrate conflicting results.¹¹¹ For example, Scavone et al. (1998) studied the effects of a single low dose (25 mg) diphenhydramine in young and elderly volunteers and found that there was no significant difference in psychomotor performance, sedation, memory impairment or mood between this dose of diphenhydramine and placebo.¹⁰⁵ Other studies have shown that 50 mg/70 kg and 50 mg doses of diphenhydramine did not induce significant sedation, psychomotor impairment, confusion or arousal in elderly, but did impair younger adults compared to placebo.¹¹² No age-related changes in the plasma kinetics of diphenhydramine were found at 25-mg oral, 50 mg/70 kg IV and oral doses.¹¹³ In contrast to the findings of these studies, Katz et al. (1998) evaluated cognitive performance after diphenhydramine 50-mg administration in older volunteers and found that there were significant effects of impairment on five test measures of psychomotor performance and cognitive ability.¹¹⁴ Simons et al (1998) also found significant impairment using objective measures of cognitive processing and subjective measures of somnolence in a similar single-dose study with 50-mg diphenhydramine.⁹⁸ Meuleman et al (1987) compared temazepam 15 mg to diphenhydramine 50 mg, each over 5 nights in elderly individuals in a crossover design and found that diphenhydramine was as efficacious as temazepam, and better than placebo at these doses.¹¹⁵

III PATTERNS OF ANTIHISTAMINE USE

Data from surveys have indicated that individuals, including the elderly, often self-medicate with antihistamine medications that can be purchased over the counter.¹¹⁶⁻¹²⁰ Some reports indicate that the use of OTC medications for sleep surpasses prescription medications.^{44, 95, 118, 121} For example, Pillitteri et al (1994) found that 17.8% of a sample of university students had used an OTC medication as a sleep aid in the past month.⁹⁵ One study found that 12% of a sample of 60-74 year-olds had used an OTC sedative-hypnotic preparation in the past year.¹²¹ Another study, conducted in a rural US elderly population found that only approximately 1% used antihistamines at the time of survey.¹¹⁸ Studies have shown that users of OTC sedative-hypnotics are more likely to be female and more likely to have a higher level of psychological distress.^{116, 122, 123} Surveys have indicated that a large proportion of individuals that use OTC medications fail to inform their physician and/or pharmacist of alternative drugs usage, and many tend to take OTC medications along with prescription medications, other OTC medications, and/or alcohol.^{43, 116} Polypharmacy concerns are especially worrisome in the elderly, because they are more likely to be taking multiple prescription medications.^{44, 121, 123}

III COSTS OF SEDATIVE USE

In 1993, approximately \$40 million Canadian dollars were expended on the five benzodiazepines that are used for sleep.⁵⁵

The sales of non-prescription sedative-hypnotic medications were estimated to increase from 5-15% in the years 1987-1994.⁹⁵ Walsh et al (1998) estimated that, in 1995, \$325.8 million US dollars were spent on non-prescription sleep medications.⁵²

The use of herbal products is expanding in the United States and Canada. A 1997 US survey projected that national expenditures for herbal medicine was 5.1 billion dollars, and there was a 380% increase in the use of herbal remedies between 1990 and 1997.¹²⁴ Sedative use has been associated with an increased frequency of falls and hip fractures in cognitively normal and disadvantaged individuals.¹²⁵ Brinsky et al (1997) determined that the increase in life-costs after sustaining a hip fracture is \$16,322 - \$18,727 US 1993 dollars per year.¹²⁶

IIK NON-SPECIFIC RISKS ASSOCIATED WITH ALL SEDATIVE-HYPNOTICS

All sedative-hypnotic medications can have adverse effects, regardless of their mode of action. Just as individuals are susceptible to fatigue from insomnia, they may also be susceptible to over-sedation induced pharmacologically. Use of long-acting and intermediate-acting benzodiazepines has been shown to increase risk for motor vehicle accidents, especially in older drivers.^{127, 128} Results from a case-control study found this increased risk of motor vehicle accidents to be significantly decreased with the use of short-acting benzodiazepines, such as triazolam.¹²⁷ Driving simulation tests have indicated that diphenhydramine impairs driving ability as much as alcohol, and that subjective measure of sedation did not accurately predict deficits in performance.⁵⁹ Compromised reaction time has been demonstrated with all sedative-hypnotics, including benzodiazepines and antihistamines.^{59, 60, 125, 129}

Sedative users, both acute and chronic, have demonstrated clinically relevant deficits in attention and neuromotor functioning, and unawareness of this diminished ability.^{59, 99,}
¹³⁰ Falls in elderly individuals are more likely to be injurious or fatal; the incidence of hip fracture as a result of falling increases exponentially over the age of 65 for both men and

women.¹²⁶ Ray et al (1987) showed that the use of psychotropic drugs, especially sedative-hypnotics with long half-lives, increases the risk of hip fracture.¹³¹ Patients taking short-acting sedative-hypnotic medications such as triazolam are also at higher risks, as these drugs are associated with severely incapacitating effects on motor function, particularly for the first few hours after dosing when patients experience debilitating ataxic effects.⁵⁰ Compromised self-care is also more common among elderly benzodiazepine users than non-users.^{125, 129}

III. POTENTIAL ADVERSE EFFECTS SPECIFIC TO BENZODIAZEPINE AND NON-BENZODIAZEPINE SEDATIVE USE

ACUTE ADVERSE EFFECTS

Acute adverse events associated with sedatives include over-sedation, unwanted residual sedation or morning hangover. Short-acting sedatives have been shown to elicit far less residual sedation and hangover because of their shorter half-lives.¹³² Ataxia and muscle relaxation are also side effects of sedative use, particularly benzodiazepines. Benzodiazepines have been associated with falls and hip fractures, especially in elderly individuals.^{33, 129, 131, 133}

All benzodiazepines have been shown to induce transient anterograde amnesia, or an acute memory loss that occurs after administration. This is likely due in part to the sedative nature of the drugs, but is also a feature of GABA_A receptor modulation.¹³⁴

Upon withdrawal of benzodiazepines, even after short-term use, rebound insomnia and anxiety may occur. With short-acting benzodiazepines, this is thought to be a more ominous occurrence, as it is thought to lead to dependence by encouraging patients to

continually re-administer to avoid rebound.^{128, 132} Daytime nervousness has been reported with therapeutic doses of triazolam.⁷⁸

Benzodiazepines may cause respiratory depression and are therefore contraindicated for sufferers of respiratory dysfunction and/or sleep apnea. Research indicates that respiratory depression is significantly decreased with the new non-BZ drugs.⁸⁰

Users of benzodiazepine sedative-hypnotic medications sometimes experience bizarre thoughts and emotions, such as paranoia, depersonalization, and derealization.[Balter, 1991 #33; ⁸¹

Benzodiazepine-induced sleep architecture has been shown to differ from natural sleep with respect to patterns of sleep stages. Sleep is generally lighter, with slow wave sleep and REM sleep both reduced in duration and frequency. The newer non-BZ drugs are less likely to induce these changes as both slow wave sleep and REM sleep are generally unaffected.^{76, 135}

ADVERSE EFFECTS WITH CHRONIC USE

Long term effects of BZ-receptor agonist use include tolerance and dependence. Tolerance to the pharmacodynamic effects of a drug occurs because of neuroadaptation. With respect to the GABA_A/BZ receptor system, preclinical evidence indicates that some subtypes of the GABA_A receptor are systematically down-regulated by chronic use with benzodiazepines. After chronic diazepam administration in mice, mRNA for the alpha-1 and gamma-2 subtypes seems to be less abundant. This is thought to be one possible explanation for the mechanism of neuroadaptation with chronic benzodiazepine use as both these subunits occur at a high frequency in the human CNS and are important determinants of receptor pharmacology.^{68, 71} Fujita et al (1999) employed single photon emission computed tomography (SPECT) technology to identify an initial down-regulation and

subsequent normalization of benzodiazepine receptors after 10 and 24 days of alprazolam treatment in healthy volunteers. This result prompted researchers to speculate that more than one mechanism may be involved in the development of neuroadaptation, and sequestration of receptors intracellularly may also occur.¹³⁶ Functionally, the body/CNS becomes adapted to the drug, and when therapy is stopped, a withdrawal reaction is precipitated. Furthermore, as the body becomes adapted to the drug, the pharmacological effect is decreased or diminished. The sedative properties of benzodiazepines have been shown to diminish after a prolonged period of use, prompting the recommendation that use does not exceed 2-4 weeks at a time.^{155,156}

Neuroadaptation, or “physiological dependence”, is marked by biochemical, physiological and/or behavioural changes that precipitate a withdrawal reaction after abrupt discontinuation or dose decrease following drug treatment, often for a prolonged period of time.¹³² Symptoms of benzodiazepine withdrawal frequently include rebound insomnia, anxiousness, restlessness, irritability, and tension. Symptoms often also include tachycardia, tremor or muscles twitching, paresthesia, GI disturbances such as nausea, blurred vision, hyperacusis, headache, and possibly seizures, hallucinations, paranoid delusions, delirium and/or confusion.^{79, 132} The severity of the withdrawal syndrome will depend on the dose, duration of use, and the benzodiazepine that is used/discontinued. For example, benzodiazepines that have a high affinity for their target receptor and a short half-life have a higher risk of generating neuroadaptation. However, not all patients develop tolerance, and some patients do not show signs of withdrawal upon discontinuation.¹³⁷ It has been hypothesized that there are characteristics of the users that interact with pharmacological determinants of dependence.¹³⁷⁻¹³⁹ Patient-related factors may include age, presence of chronic illness or personality traits, or concomitant substance abuse disorders.¹³⁹⁻¹⁴¹

Benzodiazepine-dependent patients have been shown to have learning and memory impairments,¹⁴² however, after detoxification, no permanent brain damage or abnormalities have been detected.¹⁴³

Neuroadaptation is not to be confused with abuse or “addiction”. Abuse has a strong psychological component, and is marked by recurrent use that interferes with a person’s life (i.e. failure to fulfill obligations at work, school and/or home; substance-related hazardous behaviour, substance-related social or interpersonal problems); or causes substance-related legal problems. The abuse potential of these drugs is very low.^{63, 137} Although neuroadaptation is not uncommon, there is little chance that abuse will occur. Behaviours associated with abuse, such as dose escalation, recreational use, multiple physician contacts, overwhelming need to use or impairment of functioning as a result of use – are rare in sole benzodiazepine users.¹³⁸⁻¹⁴⁰ Any misuse of benzodiazepines is generally associated with prolonged use. This is likely due to the neuroadaptation and to avoid withdrawal symptoms.¹⁴⁴ McInnes et al (1994) found that, in a sample of 640 inpatients in an Australian hospital, seven were found to have harmful benzodiazepine use, marked by use for over 2-4 weeks plus one of the following: drug seeking behaviour, withdrawal symptoms, or overdose as defined by DSM-III-R.¹⁴⁵ Romach et al found that, in a sample of 25 alprazolam users that presented to an outpatient treatment program to discontinue use, none of the patients exhibited behaviours associated with abuse or addiction.¹³⁸

Prolonged use may lead to accumulation of sedative-hypnotics. This is seen more often with long-acting sedatives, but has also been shown to occur with temazepam (see Section IIF, page 21).¹⁴⁶⁻¹⁴⁸ Reaction times in patients were shown to be significantly increased in patients after 7 days of continuous dosing, compared to single-dose effects.⁹

IIM INCREASED SENSITIVITY TO BZ-RECEPTOR AGONIST IN ELDERLY

Elderly individuals are more sensitive to psychotropic drugs due to changes in kinetics and also possibly dynamics. Altered pharmacokinetics is associated with aging, affecting drug absorption, distribution, metabolism and elimination. Some studies have shown that physiological changes occur in the aging brain, and consequentially the elderly may be more or less sensitive to the pharmacodynamic effects of drugs that act centrally. ¹⁴⁹

PHARMACOKINETIC CHANGES WITH AGE

As most people age, the percent of body water and lean muscle mass decreases and percentage of body fat increases. Benzodiazepines are fat-soluble drugs, and therefore the volume of distribution will be increased when this is the case. This subsequently leads to a prolonged half-life of the drug.

The degree of protein binding in the bloodstream decreases with age because of decreased plasma albumin concentrations.⁴⁰ Therefore, in older individuals there is more free drug circulating in the bloodstream at any given time that can act at its target, which may lead to enhanced effects. ⁸⁴

Liver and kidney function is another factor in old age. The liver's ability to metabolize drugs decreases over time and this leads to more drug entering the body at first pass and a more intense drug-induced effect. This is further enhanced if the drug is protein-bound, due to the aforementioned decrease in plasma albumin concentrations. Furthermore, declines in both liver and kidney function slow down the elimination process. This can result in a 2-3 fold increase in the half life of a drug.⁴⁰ It is not uncommon for kidney function to decrease by 40-50% in elderly individuals, even in the absence of kidney disease.⁴⁰ Longer half-lives may allow drugs to accumulate in elderly, whereas in younger

individuals this is less of a risk. Accumulation of drug effects contributes to daytime fatigue, memory impairment and ataxia.^{9, 83}

PHARMACODYNAMIC CHANGES WITH AGE

In addition to pharmacokinetic changes, aging may contribute to changes at the level of the GABA receptor in vivo. Although this has not been shown experimentally, several clinical studies have demonstrated differing sensitivities in older benzodiazepine users compared with younger controls.^{51 150, 151} For example, Castelden et al (1977) demonstrated that, at identical plasma levels, elderly individuals had more psychomotor impairment after 10-mg nitrazepam than younger controls.¹⁵⁰ Divoll et al (1981) demonstrated a decrease in plasma protein binding with temazepam in elderly individuals that may be responsible for increased sedative effects.⁸⁴ However, results of studies with diazepam suggest that the increase in free drug levels do not explain the 2-3 fold increase in the level of sedation seen between the young (i.e. young adults) and the aged (i.e. octogenarian) individual.¹⁵² Furthermore, clinical studies with midazolam given intravenously suggest that elderly subjects required less drug to achieve sedative and amnestic effects.^{149 153-154}

Mechanisms have been proposed, such as alterations in receptor densities with age or changes in subunit composition in GABA_A receptors, but are difficult to test and therefore exist only as theories presently.^{149,155} For example, Banay-Swartz (1993) showed in post-mortem studies different distributions of GABA in brains of adult (35-55 y.o.) vs. elderly (71-81 y.o.) individuals.¹⁵⁶ However, it is not established if amino acid levels are affected by death, and pre-existing disease states were not known. Rat models exist and have been used to test the hypothesis that changes in receptor binding occur and are in part responsible for the increased sensitivity of the elderly. However, no changes at the receptor level have

been conclusively found.^{157,158} This may not be representative of the human situation, or it may be that alterations are due to changes in GABA binding or inhibition. Some studies have reported an alteration in the subunit composition of GABA_A receptors in rats as well.^{159,160} The functional consequences of these findings are unclear.

It is well documented that elderly individuals require smaller doses to elicit pharmacological effect, however, it is not clear how much of this phenomenon is a result of altered pharmacokinetics or whether alterations in cerebral physiology are responsible. It has been shown undisputedly that there are alterations in kinetic characteristics of older individuals, and logically this would lead to greater sensitivity in these individuals.^{83, 84, 152} It has only been postulated that there are changes in cerebral physiology that contribute to this increased sensitivity as well.^{149, 150, 152, 154, 155} Experimentally, it is very difficult to separate pharmacodynamic effect from kinetics.¹⁶¹ Plasma concentrations of drug can be monitored and compared to sedative effect, however, it is difficult to relate plasma concentrations to receptor densities, and to GABA concentration centrally. Although the mechanisms of increased sensitivity in older people have not been elucidated, guidelines recommend lower doses of sedative-hypnotic medications be used in elderly patients.^{21,87,162}

II. N POTENTIAL ADVERSE EFFECTS SPECIFIC TO ANTIHISTAMINE USE

ACUTE EFFECTS

Morning hangover, residual sedation are common side effects with diphenhydramine.¹¹¹ Because of the potential for prolonged half-life of diphenhydramine in elderly individuals this may pose a greater risk for them.¹⁶³

Antihistamines bind at muscarinic cholinergic receptors and therefore anticholinergic side effects such as dry mouth and dry throat may occur. In overdose, atropine-like anticholinergic effects may occur, such as drying of the mucosa, fever, confusion, urinary retention, mydriasis, blurred vision, hallucinations, mental status changes, hypertension and tachycardia.^{106,164}

Antihistamine use in some individuals may cause paradoxical CNS excitation. Sufferers exhibit symptoms such as restlessness and insomnia.^{81, 111-164}

Other side effects that have been reported are: disturbed coordination, fatigue, nervousness, tremor, irritability, euphoria, paresthesia, diplopia, acute labyrinthitis, vertigo, tinnitus, dizziness, and neuritis.¹⁶⁴ Use of diphenhydramine may unmask or exacerbate motor disturbances such as tardive dyskinesia.¹⁶⁵

The elderly may theoretically be more sensitive to the effects of H1 antagonists. Yanai et al (1992) reports a decreased concentration of H1 receptors in elderly individuals as compared to younger.¹⁶⁶ Anticholinergic medications are not generally recommended for elderly individuals, particularly if they experience confusion in the night, because of their potential to negatively affect cognitive ability. Product monographs for products containing diphenhydramine in Canada stipulate that antihistamines are more likely to cause hypotension, sedation and dizziness in individuals over the age of sixty.⁸¹

Diphenhydramine is available over the counter and is sometimes used in suicide attempts.¹⁰¹ Overdose symptoms include seizures and hallucinations, as well as those symptoms previously mentioned. There have been some cases reported of rhabdomyolysis, a nonspecific syndrome in which contents of skeletal muscle cells leak into plasma and urine, resulting in skeletal muscle injury, and acute renal failure in diphenhydramine overdose.¹⁶⁴

CHRONIC EFFECTS

Neuroadaptation to the effects of antihistamines have not been reported, and drug-induced sedation is generally persistent, although reports are slightly ambiguous. Some studies indicate that tolerance to some of the sedative properties has been observed with subjects taking diphenhydramine for several days,¹⁶⁷ whereas others report no such changes over time, even after 12 weeks of treatment.¹⁶⁸ Some research indicates that individuals may be able to compensate for the sedative effects to some degree on tasks that demand attention.⁹⁹

Weight gain is a side effect of chronic use of antihistamines, including diphenhydramine.¹⁶⁸

Antihistamines are not generally recommended for use for more than a few days at a time for sleep.⁸¹ There is very little clinical research that has examined the long-term use of antihistamines for sleep.

IIo HERBAL PRODUCTS USED AS SLEEP AIDS

Herbal and 'natural health products' are gaining popularity in western culture. Some products that are used to promote sleep are listed in Table 3 (page 16). These products work by very different mechanisms and are derived from different sources. They have some characteristics in common, however- there is no regulations surrounding their use, they have been shown to be very safe with little or no side effects, and there is little evidence that they are efficacious.¹⁶⁹

Several clinical studies have been done to evaluate the efficacy of melatonin as a sleep aid. Results indicate that, although it may be useful for disturbances in circadian rhythm, there is little evidence that it is useful for insomnia due to other factors.¹⁷⁰

Kava has been shown in clinical studies to have some beneficial anxiolytic activity and has been listed by the German monograph for “*states of nervous anxiety, tension and agitation*”.¹⁷¹ Sedative properties are likely linked to the anxiolytic effects of the plant.

Tryptophan is an amino acid precursor of 5-HT that is obtained dietetically. There have been some studies to evaluate its efficacy as an antidepressant,¹⁷² and as an adjunct to antidepressant therapy,¹⁷³ but there is little evidence of efficacy as a sedative-hypnotic in non-depressed individuals.¹⁷⁴

HIP VALERIAN

Valerian is a common, odiferous plant that grows in North America and in Europe. There have been some clinical studies performed to assess the utility of valerian as a sedative-hypnotic, however they are difficult to interpret because of small sample sizes, unknown composition of valerian, unconventional and qualitatively poor assessments, and failure to account for possible confounding factors in study design. Despite the lack of conclusive evidence and the need for larger and controlled clinical studies, results indicate that valerian may be efficacious as a mild sedative.[Pharmacopeia, 1998 #219] German health authorities have approved its use as a sleep aid when used at recommended doses (400 – 900 mg per day).¹⁷⁵ No side effects have been associated with valerian at recommended doses. Sedation caused by valerian does not seem to be linked with alleviation of symptoms of anxiety or depression, and has been reported in otherwise healthy individuals.¹⁷⁶

Studies on the composition and pharmacology of valerian have been published and the active ingredients in valerian, which are found in the root, seem to be three-fold: sesquiterpenes, the valepotriates, and a small number of alkaloids.¹⁷⁷⁻¹⁷⁸ The composition

of these volatile oils varies substantially between species and cultivars, and several different ecotypes and races of the plant are known to exist.¹⁷⁹[Products, 1991 #61]¹⁷⁸ None of these compounds alone have been found to account for the sedative activity of valerian, thus it has been postulated that the combination of components of the plant may have an additive effect.¹⁸⁰ The mechanism of action of the compounds has not been fully elucidated. Preclinical evidence from rat cerebral cortex synaptosomal preparations indicate that valerian may act via GABA_A receptor modulation, similarly to the benzodiazepines.¹⁸¹⁻¹⁸² Some clinical studies have found that, compared to placebo, 400 – 450 mg valerian significantly decreased sleep latency,¹⁸³⁻¹⁸⁴ reduced number of night awakenings,¹⁸⁴⁻¹⁸⁵ or showed a significant positive effect on poor sleep.¹⁸⁵ However, between studies the results vary. One study reported that sleep latency is most effectively reduced in older individuals as compared to young,¹⁸³ whereas another reported that sleep was improved more in habitually poor sleepers as compared to good sleepers.¹⁷⁷⁻¹⁸³ Still others have found no difference in self-rated sleep quality in elderly subjects that took valerian.¹⁸⁶ The methods employed to study sedation in these studies were various and in most cases subjective data was not collected with a validated instrument.^{176, 177, 184, 185} Furthermore, in most studies, the effects of valerian on subjective sleep are not quantified in the published data (e.g. by number of minutes or number of awakenings).^{177, 185} Data from EEG studies,^{176, 177} and polysomnography¹⁸⁶ indicate either no significant differences compared with placebo,¹⁷⁶ or that the percentage of slow wave sleep (SWS) is increased in subjects, although this was not associated with any change in subjective sleep parameters and time asleep as compared with placebo.^{177, 186} One study by Leathwood & Chauffard (1984) in which subjects wore activity measures on their wrists indicated that sleep latency, but not total sleep time, was affected in poor sleepers. The US

pharmacopoeia has deemed the evidence for valerian's efficacy as a sedative-hypnotic inconclusive, and has called for larger and better-controlled studies.[Pharmacopeia, 1998 #219]

IIQ PATTERNS OF VALERIAN USE

Herbal drugs are sold over the counter in pharmacies, health food stores, and even grocery stores. Many different manufacturers produce different variations of herbal preparations, and therefore it is difficult to estimate how many people are using herbal medications at any given time. Estimates are generally made from surveys of community samples. For example, van Rijswijk et al (2000) surveyed an adult sample in the Netherlands and found that 1.7% of 1813 respondents had used an herbal preparation containing *Valeriana Officinalis* touted to improve sleep at least once in the 4 weeks prior to being questioned.¹²² Eisenberg et al (1997) surveyed adults in the US regarding their use of alternative therapies and found that 42.1% had used some sort of alternative therapy in the past year, and 26% had used an alternative therapy for sleep.¹²⁴

IIR ADVERSE EFFECTS OF VALERIAN USE

There are no reports of specific toxic effects associated with valerian use. However, some product monographs and reviews state that overdose of valerian may cause giddiness, stupor, confusion, and seizures.¹⁷⁴ Use of valerian is not recommended concomitantly with alcohol or sedative-hypnotic medications. Labels of products containing valerian are required to state "for occasional use only", and to warn against driving a car or operating heavy machinery.[Canada, 1998 #218] In a suicide attempt, a young adult reportedly consumed 18-24 g of valerian and complained of fatigue, abdominal cramps, tightness in the

chest, tremor, and lightheadedness. All symptoms were resolved within 24 hours after treatment with activated charcoal.¹⁸⁷

CHRONIC USE

Data on adverse effects due to chronic use of valerian are case reports only. There have been reports of hepatotoxicity with use of valerian in combination with skullcap.¹⁸⁸ In these reported cases, doses did not exceed those recommended, and therapy was not prolonged (range 3 days – 2 months).

A possible benzodiazepine-like withdrawal reaction has been documented in a man after entering the hospital to undergo surgery that purportedly consumed 500 – 2000 mg of valerian five times per day for several years.¹⁸⁹ The patient developed tachycardia, oliguria, tremor, signs of delirium, and high output cardiac failure. These symptoms improved when midazolam therapy was initiated.

Although clinical studies do not indicate any acute side effects associated with use of valerian, there is little known about the long-term use of these preparations. There is speculation that valepotriates and their degradation product, the baldrinals, may be mutagenic and/or carcinogenic.^{185, 190}

IIc CLINICAL STUDIES IN THE ELDERLY

Although individuals over the age of 60 receive a disproportionately large number of prescriptions for hypnotic medications and account for a large proportion of over the counter and herbal remedy use, they are often excluded from clinical studies of sedative medications.¹²⁰ It is important to study medications in elderly individuals because as the body ages, pharmacokinetics of medications may be altered – particularly those stored in fatty tissues such as several types of sedatives.¹⁹¹

Because of these differences it is difficult to predict how elderly individuals will be effected by sedatives with extrapolated data obtained from younger adults. Therefore, clinical studies should be conducted in a controlled and safe environment in the elderly before conclusions are drawn about medications' effect in this population.

II T SUMMARY

In summary, insomnia is a problem for the elderly in particular. Older individuals use a disproportionately large number of sedative-hypnotic medications. This usage and problems associated with it, such as motor vehicle accidents and falls are associated with a large cost burden to society. It is critical that information is available on the effects of sedative-hypnotics in the elderly in order to evaluate the relative benefits and risks of these treatments in the elderly.

This study systematically compared a benzodiazepine, an antihistamine, and an herbal product (Valerian) and their somnolescent properties in a randomized, placebo-controlled clinical trial with elderly volunteers. A pharmacokinetic component was not included since the active moiety or metabolites of valerian are unknown.

II U RATIONAL FOR DRUGS AND DOSES USED IN THIS STUDY

TEMAZEPAM

Temazepam 15 and 30 mg were selected as the positive control for this study. The sedative and psychomotor effects of temazepam have been well documented, particularly in the elderly. Temazepam is available in North America as 15 mg capsules, and 15 and 30 mg doses have been demonstrated as effective in several clinical studies.^{11, 78, 192, 193 194}

DIPHENHYDRAMINE

Most OTC preparations of diphenhydramine are available in 25 mg tablets or capsules. In this study 50 mg and 75 mg were chosen because of the reported lack of efficacy of 25 mg doses in elderly individuals by some researchers,^{112, 113, 195} and because no data was available on equivalent doses of diphenhydramine with temazepam.

VALERIAN

Most preparations of valerian are sold as 400 mg capsules. Clinical studies have employed doses of valerian between 400 and 900 mg per day.^{176, 177, 183-185} Therefore 400 and 800 mg valerian was chosen to be examined in this study.

SECTION III - METHODS

IIIA DESIGN

The study was a randomized, double-blind, crossover, placebo-controlled study in healthy adults aged 65 years and older who did not suffer from sleep disturbances and did not use hypnotics regularly. Each subject was administered single oral doses of temazepam (15 mg and 30 mg), diphenhydramine (50 mg and 75 mg), valerian (400 mg and 800 mg), and placebo in random order. Study days were separated by a minimum of two non-study days (72 hours).

IIIB SUBJECTS

Volunteers were recruited by word of mouth, by placing advertisements in volunteer centres at hospitals, elderly homes, public libraries, family practice offices and supermarkets, and on electronic bulletin boards on seniors web sites. A copy of the advertisement can be seen in Appendix 1 (page 108).

INCLUSION CRITERIA

1. Aged 65 years or older, either gender
2. Not regular users of prescription, OTC, or herbal hypnotics (i.e., use less often than once a week)
3. Willing to go to bed on the night prior to scheduled appointments at the same time each week
4. Willing and capable of giving written informed consent
5. Willing and capable of understanding and complying with study protocol
6. Have a fixed, non-institutional address
7. Willing to attend study sessions at the Centre for Addiction and Mental Health, ARF site
8. Willing to abstain from alcohol, caffeine, or any other psychotropic medications, and antihistamines, during study days and for at least 24 hours (antihistamines & alcohol) or 12 hours (caffeine) prior to testing.

EXCLUSION CRITERIA

1. Any medical or psychiatric condition requiring investigation or treatment
2. Use of hypnotic medication (other than study medication) taken during the course of the study.
3. Current use of any other psychoactive medications as confirmed by drug screening for benzodiazepines, barbiturates, amphetamines, or opiates
4. Current intake of more than 2 alcoholic drinks per day
5. Non-compliance or unreliability (e.g. urine screen positive for unreported drugs)
6. Subjects who have received an investigational drug within 30 days prior to the study
7. Known sensitivity or allergy to benzodiazepines, antihistamines or any herbal products
8. Use of alcohol (24 hours), chocolate, or caffeine-containing beverages 12 hours prior to visit
9. Subjects with clinically unacceptable values from physical examination, vital signs or clinical laboratory parameters as determined by study physician

IIIC DROP-OUTS

Exclusion from the study would result if subjects were non-compliance with the study protocol; developed a medical condition requiring treatment; an unreported prohibited medication or metabolites was detected in the urine screen; occurrence of any adverse effects from drug treatment; or if the subject were wished to withdraw from the study for any reason. In such an event, the subject would be compensated for the sessions that they had completed.

IIID SUBJECT'S CONSENT

The investigator or her designee was responsible for ensuring that the subject fully understood the nature and purpose of the study, and that their participation was voluntary. Consent forms were designed according to the International Conference of Harmonization (ICH) guidelines for good clinical practice and were in accordance with the Declaration of Helsinki, to assure the protection of the subject's rights. A copy of this consent form is located as appendix 2, page 109.

The investigator/designee informed all subjects of the aims, methods, anticipated benefits, and potential hazards of the study including any discomfort that it may entail. All subjects received comprehensive verbal and written information. The principal investigator/designee provided verbal explanations to the subjects, and covered all potential risks, benefits and rights of the subjects, and other elements specified in the written information provided in the consent form. Subjects were given every opportunity to solicit information he or she did not understand were encouraged to ask for more information, if necessary. All subjects were clearly informed that they were at liberty to withdraw their consent to participate at any time without penalty or loss of benefits to which they would otherwise be entitled. Informed consent was documented and a copy of the signed consent form was provided to all subjects for future reference. The original signed consent forms are stored in the investigator's study file. The investigator or her delegate and the subject signed and dated the written consent form to indicate that consent has been obtained.

III E CONFIDENTIALITY

Confidentiality of the subjects is maintained by providing each individual with a subject number. Files are kept locked and all data will be presented as group data, or without a label.

III F BENEFITS TO SUBJECTS

There were no direct benefits to the subjects that participated in the study. However, the findings of his study may help patients using sleeping medications, or patients that may use sleeping medications in the future. Subjects were compensated for their time \$100 per study day of the study + \$100 for completing the medical assessment and to cover incidental fees (for a maximum of \$800 upon completion of the study).

IIIg PROCEDURES TO MINIMIZE RISKS TO SUBJECTS

In order to ensure safety of the subjects, doses of the drugs that were used in this study were all within the recommended range for elderly individuals.^{81, 196}

Subjects were asked to leave the room only when necessary (e.g. to use the washroom), and to notify a study staff member in this case. They were supervised and monitored by study staff throughout the study days, and asked to complete a side effects checklist so that reported effects could be monitored. Subjects were asked to rest if they felt fatigued, and a bed was available for that purpose. At the end of the study day, a taxi was provided for transportation home and study staff ensured that no subjects attempted to drive.

IIIh DRUGS

In this study, the effects of single doses of temazepam (15 mg and 30 mg), diphenhydramine (50 mg and 75 mg), valerian (400 mg and 800 mg) and placebo were compared in an experimental paradigm in healthy elderly volunteers.

The drugs that were used in this study included temazepam (Pharmascience generic) 15 and 30 mg, diphenhydramine (Pharmascience generic) 50 and 75 mg, and Valerian (Jamieson *Valeriana officianalis* capsules) 400 and 800 mg. Valerian capsules contained 100 mg of powdered root in a 1:4 ratio, which was considered to be equal to 400 mg of the plant product. The label claimed that product was “*quality assured*”. The lot # 6907 was used for all subjects in this study (expiry date: 11/01).

Staff at the pharmacy at the Centre for Addiction and Mental Health, Addiction Research Foundation site prepared 2 capsules that were identical in size, colour, and taste for each subject per session. A double dummy design was employed, as the high dose of valerian (800 mg, 2 capsules) did not fit into the largest capsule size, so for all sessions 2 capsules were provided.

III PROCEDURE

Potential subjects (e.g. individuals that responded to ads) had the study explained and were initially screened over the telephone with a pre-prepared information sheet and screening form (JG). If they passed the telephone screen they were then asked to visit the Centre for Addiction and Mental Health (CAMH) for further information and consenting. During this time potential subjects were given a tour of the lab facilities and practiced the computer assessments. Blood and urine samples were taken in the medical clinic by nursing staff and participants completed a baseline visit consisting of a standard medical assessment, performed by a physician in the Addictions Medicine Clinic. If they were deemed eligible at this point, they were enrolled into the study.

Enrolled subjects each presented for 7 study days, each separated by at least 3 days. Study sessions were scheduled to fit into the participants' schedules whenever possible.

Before the first session, the subjects practiced the computerized assessments at least twice on each of two occasions (total of four practice assessments). On the mornings before each session he/she performed another practice cycle, prior to completing the baseline assessment. The purpose of practicing was to reduce potentially confounding effects of learning over a study day and/or over the course of the seven sessions that might mask or exacerbate effects due to treatment.

Each visit began between 8:00 and 9:00 AM and lasted until 4:30 to 5:30 PM. After the practice session in the mornings, assessments were done at baseline, 0.5, 1, 2, 3, 4, 6, and 8 hours after drug administration. A urine sample was taken at baseline from each subject to screen for prohibited medications (e.g., benzodiazepines, barbiturates, or antihistamines, and other psychoactive medications). Participants were asked not to eat in

the mornings before study sessions; breakfast was provided after drug administration for all subjects. A standard lunch was also provided at midday. No caffeine or chocolate was allowed during study days.

The testing facilities consisted of a comfortable main room with a TV-VCR and movies, magazines and books, and a table and chairs where the subject could relax. A small hospital bed was located in an adjacent room where subjects could nap if they felt sleepy or sedated. They were asked not to leave the building or leave the vicinity of the testing room during study days. There were no windows in any of the rooms, and lighting and temperature were kept constant as much as possible.

Subjects were asked to come to sessions well rested and to keep a record of the approximate number of hours of sleep they received each night for the duration of the study. If they had slept poorly, had taken a medication that might interact with the study medications, or were not feeling well, the sessions were re-scheduled.

IIIJ ASSESSMENTS

OBJECTIVE MEASURES:

- **Manual Tracking Test** This is a computerized test that measures psychomotor ability, motor performance and perceptual speed. It was designed and adapted for Windows/mouse use after the DOS/SMS System joystick version. The original version is described by Kaplan (1985).¹⁹⁷ Instead of a joystick, the Windows version uses a mouse to control the lateral motion of the airplane figure to keep it centered as it scrolls down a winding sigmoid-shaped roadway of variable width. The scroll down speed could be adjusted to suit subjects' performance capabilities. Each measurement was the average of three consecutive 50-second trials. Results are scored as the percentage of the time that the airplane is kept over

the road. This assessment has been used previously in similar studies with younger adults.¹⁹⁸ It was concluded using data obtained from pilot elderly individuals (n=2) in this study that this assessment would provide reliable data in this population with sedative-hypnotic medications(Appendix 3).

- **Digit Symbol Substitution Test (DSST)** This is a computerized test adapted from the Weschsler adult intelligence test,¹⁹⁹ in which subjects make as many correct symbols-for-digit substitutions as possible within 90 seconds. The patterns matched to each digit are randomly assigned and change for each cycle. The subjects are required to use a mouse to maneuver the cursor for this assessment. The DSST is used by many investigators as a sensitive measure of psychomotor performance, reflected in speed of motor response, recognition of sensory information (i.e. pattern) and visuo-motor coordination (Appendix 4).²⁰⁰

SUBJECTIVE MEASURES:

- **Sedation Visual Analogue Scales (Drug Effects and Sedation VAS)** These scales were used to assess drug effects and momentary changes in affect. All tests were performed on a computer, and the subject makes a mark on a horizontal bar using a mouse. Scales consisted of a selection of visual analog rating scales. The sedation score was comprised of twelve synonyms for tired (e.g. sleepy, sedated, weary, bushed, etc. – see Appendix 5) and the subjects are asked to rate on the bar how much they agreed with the statement or feeling, (e.g. I feel tired a little....a lot, where 0 denotes they do not agree and 100 denotes they are maximally sedated) . Previous studies have indicated that these scales are reliable and very sensitive in measuring changes in sedation (Appendix 5).^{198, 201, 202 203}
- **Tufts University Benzodiazepine Scale (TUBS)** This was a computerized questionnaire with a self-rating scale for sedation and mood. This scale is often used in

studies to measure the effects of hypnotics and anxiolytics.^{11, 200} It consists of horizontal bars anchored at either end by opposing adjectives, similar to the VAS. To evaluate how the subjects are feeling along that dimension, a mark is made anywhere along the line. Three components of this scale (i.e., sedation, mood and autonomic) were completed (15 questions -Appendix 5).

- **Observer Rating Scale: DEBI** This is an observer-rating instrument, called the Drug-Elicited-Behaviour-Index (DEBI). This assessment was introduced after an amendment to the protocol so only data from 7 of 14 subjects are available. The observer (JG) rated the subjects' behaviour on a scale of 1-7, with anchors on the ends and in the middle, related to the effects of CNS depressants and stimulants. The scale included the following items: Talkativeness, Satisfaction with drug effect, Motor Activity, Friendliness, Giddiness, Mood Change, Response to External Stimuli, Speech impairment, Ataxia, Sedation, and Relaxation. This instrument has been used and validated in previous studies (Appendix 6).^{144, 204}

OTHER ASSESSMENT MEASURES

- **Side Effects Symptom Checklist** This is a 49-item checklist that has commonly been used in our laboratory to determine side effects of medications.^{10, 144} Subjects were asked to complete the checklist throughout the day, and were also asked to report side effects, if they occurred, to study personnel (Appendix 7).
- **Blinding Check** This form was presented to the subjects at the end of each study day asking which drug they thought they had received that day, listing all seven treatments. They were also asked why they believed this was the drug that they received. The purpose of this instrument was to ensure that blinding was effective in this study and it was not obvious to the subjects which treatments they were receiving and were responding with bias.

This measurement was implemented after an amendment of the protocol, and was therefore only completed by 7 of the 14 subjects (Appendix 8).

III.K SAMPLE SIZE

Sample size was calculated to ensure sufficient power to detect sedation effects of 50 mg diphenhydramine when compared to placebo. In a previous study, 50 mg of diphenhydramine administered to healthy adults elicited a score mean of 23.74 ± 20.79 on the sedation visual analogue scale compared to a placebo score of 0.40 ± 17.12 .¹⁶⁷ In order to detect a within-subject difference in treatment conditions, having a similar magnitude of standard error, with a power of 80%, and an alpha error of 0.05, we estimated that we would have needed a minimum of 8 completed subjects. However, since the sample size is based on only one study with one of the drugs that we tested, and on one subjective scale, we recruited 14 healthy elderly volunteers to ensure that the data had enough power to detect differences between treatments if they existed.

III.L DATA ANALYSES

Repeated measures analyses of variance (ANOVAs) that were performed to analyze the seven different treatments over the eight different times in each session did not have sufficient power to detect any significant difference between treatments ($7 \times 8 = 56$ different treatment data points for each subject). Therefore, area under the effect curve calculations were made for MTT and DSST scores (number of completed and number of correct trials), subjective sedation and composite mood scores (VAS scores) for each treatment and repeated measures ANOVAs were calculated with the seven different treatments as the repeated measure. Peak minus baseline scores were calculated for the same variables (i.e.,

MTT, DSST scores, subjective sedation and mood VAS scores), and the analyses were replicated. When results were found to be significant (i.e. $p < 0.05$), paired t-tests were conducted to determine which conditions were significantly different. Peak effects were also used in a two-factor ANOVA with drug (temazepam, diphenhydramine, valerian) and dose (low, high) as factors. Gender and weight were included as between subject factors in separate analyses.

Analyses of covariance (ANCOVA) were performed for all variables with age as a covariate. When an interaction was detected by this method and age by (variable) relationship was found to vary dependent on the treatment, individual linear regression analyses were performed to isolate where the age by (variable) interaction existed. If none of these individual regression analyses detected any significant effect of age, the discrepancy between the significant interaction in the ANCOVA and the lack of significant effects of age at each treatment was reflecting the decline in degrees of freedom associated with each individual analysis vs. the overall analysis. Therefore, to retain the degrees of freedom from the ANCOVA while examining the single effects of age on (variable), the mean square error term was used from the ANCOVA to determine the F value for each treatment.²⁰⁵ Degrees of freedom were from the linear regression (1), and the error term (72).

For peak minus baseline scores, placebo scores were taken at time = 1 hour (time when peak placebo effects were expected to occur). Analyses were also done with the placebo scores from the matched peak time of drug effect (i.e. if drug effect peaked at 2 hours, this was compared to placebo scores at 2 hours). No differences in levels of significance were found using either method, therefore results are presented comparing drug effects to placebo effects at 1 hour, for simplicity.

All statistical analyses were conducted using SPSS for windows version 10.0. Table 4 shows the levels of significance achieved (represented as alpha error values where $p < 0.05$ is significant) and observed power (where $1 - \beta > 0.80$ is sufficient) with repeated measures ANOVAs.

Table 4. Significance of Repeated Measures ANOVA results for Variables

VARIABLE	SIGNIFICANCE/ OBSERVED POWER Area under the effect curve	SIGNIFICANCE/ OBSERVED POWER Peak-baseline scores
Sedation summary score (VAS)	$p < 0.001$ / $1 - \beta = 0.987$	$p = 0.001$ / $1 - \beta = 0.979$
MTT	$p = 0.001$ / $1 - \beta = 0.965$	$p < 0.001$ / $1 - \beta = 1.000$
DSST (completed)	$p = 0.013$ / $1 - \beta = 0.872$	$p < 0.001$ / $1 - \beta = 0.988$
DSST(correct)	$p = 0.039$ / $1 - \beta = 0.779$	$p < 0.001$ / $1 - \beta = 0.984$
Fatigued-spacey (VAS)	$p = 0.009$ / $1 - \beta = 0.894$	$p = 0.005$ / $1 - \beta = 0.923$
Anxious-excited (VAS)	$p = 0.063$ / $1 - \beta = 0.721$ [NS]	$p = 0.097$ / $1 - \beta = 0.661$ [NS]

NS = not significant

$1 - \beta$ = observed power for the ANOVA

p = observed alpha error or significance level

Sedation scores were analyzed as the sum of responses to the VAS sedation component as recommended by several researchers because of the inter-subject variation that is inherent in subjective ratings.^{113, 195, 200} Subjects were asked to rate their levels of sedation on twelve different adjectives which were all synonymous (Appendix 5). The sum of these scores represents the 'sedation summary score'.

To analyze changes in mood, the scale was broken down into component parts. Sedation comprised the following two measures: normal-spacey energetic-fatigued. Greenblatt et al (1991)^{11, 200} found that these items were affected by benzodiazepines, including temazepam. Scale reliability analyses were performed using 30-mg temazepam

scores because this was the highest dose of our positive control. Chronbach's alpha for energetic-fatigued and normal-spacey was 0.844, where $\alpha > 0.80$ is considered significant.²⁰⁵ The following components: calm-anxious and relaxed-excited, comprised the measurement of anxiety. Scale reliability analysis had a Chronbach's alpha of 0.96 as computed using temazepam 30 mg scores.

Subjective ratings of sedation to observer ratings were measured using different scales. Therefore, scores were calculated as percentages (where 100% was the highest sedation score and 0 was maximally alert). Percentages were compared using Pearson correlation coefficient.

For the purposes of this study, "practice effects" have been defined as the improvement with the psychomotor assessments in a study day because of practice. "Learning effects" have been defined as the improvement of ability with the computerized assessments over the course of the study, i.e. from one study day to the next. To assess practice effects, the mean placebo scores were analyzed with repeated measures ANOVA using time as the repeating factor (8 assessments in one day). To assess learning effects, mean baseline scores for each session were compared using repeated measures ANOVA, with session as the repeated factor (7 sessions).

SECTION IV – RESULTS

IV A – SUBJECT DEMOGRAPHICS

Fourteen healthy adults, 8 men and 6 women with a mean age 71.6 years (range 65-89 years) and mean weight of 76.8 kg (range 58.5 - 86.5 kg) were recruited to participate as volunteers (Figure II). Twelve subjects were caucasian, one oriental and one black.

Thirty-eight calls were received, 27 of these individuals were screened over the telephone, and 15 individuals underwent a physical assessment. Only one person failed the physical assessment because of unstable high blood pressure requiring treatment. Reasons for non-inclusion were not interested (7); lived too far away/inconvenient (2); not over 65 years old (2); taking contraindicated medication/s (4); somatic problems (e.g. uncontrolled diabetes – 4); already enough male subjects enrolled, looking for females (4).

Twelve of the 14 recruited subjects had stable or chronic health problems such as treated hypertension (3); controlled diabetes (1); previous orthopedic surgery (2); impaired hearing (2); arthritis (10); mild asthma (1); GI troubles (2); allergies (abstained from medications – 2), or were taking medications prophylactically such as atorvastatin for high cholesterol (3); or anastrozole (remission from breast cancer - 1).

Figure II. Recruitment Statistics. Of 38 calls received, 14 elderly individuals were enrolled. Of these 14, no subjects dropped out of the study or were terminated.

IVB OVERALL DIFFERENCES BETWEEN TREATMENTS

Using repeated measures ANOVAs with treatment as the single factor, significant differences were detected between the means of MTT (mean percent time over the road), DSST (number of completed trials), sedation summary score and the fatigue-spacey scales. No differences were found on measures of anxiety using either AUC data or peak effects ($p > 0.05$, both). Two-factor ANOVAs with drug (3) and dose (2) as the factors did not yield significant results for any of the variables tested.

Gender and weight were included as between subject factors in separate analyses, but no interactions were detected, except on the peak sedation score, when a significant interaction was detected in weight by treatment. One subject was found to have a large subjective response to placebo; when this anomalous subject was removed from the analysis, this interaction disappeared.

Analyses of covariance using age as the covariate detected significant treatment by age interactions on sedation, fatigued-spacey and MTT scores ($p < 0.01$, $p < 0.05$ and $p < 0.05$, respectively) but not DSST scores (neither number of completed nor number of

correct trials) using area under the curve data. When one subject (who was an outlier reporting a strong placebo effect) was removed from the analysis, there was still an age by treatment interaction on sedation and fatigued-spacey scores ($p < 0.05$, both analyses), but not on MTT scores ($p = 0.053$). Using peak data, age by treatment interactions were only seen on MTT scores ($p < 0.01$). Exclusion of the placebo-responder from the analysis did not affect the outcome, and therefore all subjects were included in the regression analyses.

When the oldest subject (age 89 years) was removed from the analysis, no treatment by age interactions were detected on any of the variables (sedation, MTT, DSST, or fatigued-spacey, for either AUC data or peak scores).

When a significant difference in the means of a repeated measures ANOVA was detected, paired t-tests were done to determine which of the means were significantly different. The results of these paired-t tests have been used to determine the individual statistical differences on the graphically represented data (Sections IIIc and IIIId). Regression analyses are also presented in these sections.

IVC - OBJECTIVE EFFECTS - PSYCHOMOTOR IMPAIRMENT

Figures III and IV (a-c) show the mean baseline-corrected treatment effects $\pm$ standard error for all treatments and doses on objective measures over the course of a session. Figure III represents the baseline-corrected MTT score, while Figure IV is the baseline-corrected number of completed trials with the DSST. The number of correctly completed trials with the DSST scores were very similar and is those data are therefore not shown.

A dose-dependent impairment in psychomotor ability was seen with 30 mg and 15 mg temazepam compared to placebo (Figure IIIa + IVa). Peak effects occurred at 1 hour for 30 mg and 30 min – 1 hour for 15-mg temazepam. Psychomotor ability returned to

baseline levels after 8 hours for both doses. Mean baseline-corrected peak MTT scores were -30.38 ± 16.52 and -4.38 ± 14.72 for 30 mg and 15 mg temazepam, respectively, compared to 3.73 ± 7.07 with placebo. Baseline-corrected DSST scores were -5.07 ± 6.07 and -1.71 ± 2.89 for 30 and 15 mg temazepam, respectively, compared to 0.00 ± 4.15 with placebo. Scores after 30 mg temazepam were statistically significant from placebo for both MTT and DSST ($p < 0.001$ and $p < 0.01$). MTT scores after 15 mg temazepam were significantly different from placebo ($p < 0.05$), but DSST scores were not ($p = 0.11$).

Significant impairment on the MTT was detected after diphenhydramine 75 mg compared to placebo (-4.06 ± 9.04 compared to 3.73 ± 7.07 for placebo, $p < 0.05$), but not on the DSST (-0.71 ± 2.37 for 75 mg diphenhydramine compared with to 0.00 ± 4.15 , $p = 0.055$). No impairments were detected with 50 mg diphenhydramine on either the MTT or the DSST (peak MTT score = -2.11 ± 10.85 and peak DSST score -1.43 ± 4.75) compared to placebo on either of the measures ($p = 0.13$ and $p = 0.19$, respectively). Peak impairment on psychomotor tasks occurred with 75 mg diphenhydramine at 1 - 2 hours and at 2 hours for diphenhydramine 50 mg. Levels approached baseline after 8 hours (MTT scores were -0.24 ± 6.58 for 75 mg and 3.15 ± 10.99 for 50 mg diphenhydramine, respectively, compared to 1.40 ± 8.42 for placebo). Temazepam had a quicker onset of action compared to diphenhydramine. Impairment is evident on the MTT and DSST at 30 minutes with 30 mg of temazepam, whereas no impairment was evident with diphenhydramine until 1 hour and then on the MTT only. The magnitude of response was much greater for temazepam than for diphenhydramine as well (Tables 6 and 7).

Figure II. Results from the Manual Tracking Test (MTT). Results are presented as baseline corrected mean percent time over the road $\pm$ standard error (SEM). Lower scores indicate greater magnitude of impairment. The star symbol denotes statistical significance at the $p < 0.05$ level.

Figure III. Digit Symbol Substitution Test. Results are presented as baseline corrected mean of the number of completed trials $\pm$ SEM. The star symbol denotes a statistically significant level of impairment at $p < 0.05$.

No drug effects were evident on either objective measure with valerian (Figures IIIc & IVc). Peak MTT scores occurred at 6 hours for 800-mg valerian (-0.37 ± 18.16) and 3 hours for 400 mg (-0.67 ± 8.52) and were not found to differ significantly compared to placebo ($p=0.42$ and $p=0.15$ for 800 mg and 400 mg, respectively).

Peak DSST scores occurred at 6 hours for 800-mg valerian (0.64 ± 3.67) and at 4 hours for 400-mg valerian (-0.3571 ± 2.50), and were not significantly different than placebo ($p=0.72$, both doses).

DSST scores after 800-mg valerian appeared to be slightly increased compared with placebo. To explore this result, the peak increase in psychomotor ability with 800-mg valerian, 1.79 ± 2.67 at 2 hours (in contrast to peak decrease or impairment, as above), was compared to placebo. The results did not achieve significance ($p=0.14$).

Using linear regression analyses and peak scores, age was found to be a predictor of impaired MTT performance after treatment with 30 mg temazepam ($r = -0.488$, $F_{(1,72)} = 6.75$, $p<0.025$), and with 15 mg temazepam ($r = -0.740$, $F_{(1,72)} = 12.34$, $p<0.01$). There were no age by treatment interactions found with any of the other active treatments or placebo ($p>0.05$, all). Figure V demonstrates graphically the correlation between increased age and baseline-corrected peak MTT scores for placebo and 15 mg temazepam. All subjects were included in the analysis and in the graph.

IVd - SUBJECTIVE MEASURES – SEDATION SCORE

Figures VI and VII show the mean baseline-corrected treatment effects $\pm$ standard error (SEM) of the different medications on subjective measures over the course of a session for all subjects. Figure VI represents the mean baseline-corrected VAS - sedation summary scores $\pm$ standard error. Figure VII shows mean baseline-corrected scores $\pm$ standard error of the “energetic-fatigued” and “normal-spacey” component of the TUBS. No other changes in any indices of mood were significantly affected by treatment and these data are not shown.

A dose-dependent increase in sedation was seen with 15-mg and 30-mg temazepam compared with placebo (Figure VIa). Peak sedation occurred at 2 hours with 30-mg temazepam, and was significantly different from placebo at the $p < 0.05$ level (mean $\pm$ SEM = 326.50 $\pm$ 75.61 compared to 51.14 $\pm$ 40.68 with placebo). Sedation with 15 mg temazepam also peaked at 2 hours (189.29 $\pm$ 63.65), but this was not significantly different from placebo ($p = 0.12$).

Both doses of diphenhydramine elicited significant levels of sedation ($p < 0.05$, both doses). The effects did not appear to be dose dependent; peak levels for each were comparable in magnitude (277.64 $\pm$ 337.60 for 75 mg compared to 299.50 $\pm$ 305.37 for 50 mg diphenhydramine). Time course of effect was different for the two doses, however. Peak sedation occurred earlier in the session with 75-mg diphenhydramine (2 hours) than for 50-mg diphenhydramine (4 hours).

Similarly to the pattern seen with objective assessments, temazepam shows a faster onset of action as detected by subjective sedation ratings. Sedative response is evident with 30-mg temazepam after 30 minutes, whereas with diphenhydramine there is no difference

Figure V. Interaction of age and baseline-corrected peak MTT score after placebo and 15 mg temazepam treatments. There is a positive correlation between age and placebo MTT score (Pearson correlation coefficient $r = 0.794$ when placebo responder is included), whereas there is a negative correlation between temazepam and age ($r = -0.740$). Age was found to be a predictor of impairment induced by 30 mg and 15 mg temazepam.

Figure VI. Subjective sedation summary scores. Changes in subjective sedation as measured by visual analogue scales. The star symbol denotes a statistically significant increase in sedation at the $p < 0.05$ level.

Mean $\pm$ SEM fatigue and spacey scores

Figure VII. Peak “energetic-fatigued” and normal-spacey scores (VAS) $\pm$ SEM. None of the scores were different from placebo at the $p < 0.05$ level.

from placebo until 1-2 hours. However, in contrast to psychomotor impairment, the magnitude of response at peak effects is comparable in 30-mg temazepam, 75-mg and 50-mg diphenhydramine (Table 8).

There was no significant change in sedation with either dose of valerian when compared with placebo ($p = 0.18$ and $p = 0.94$ for 800 mg and 400 mg, respectively). The peak sedation scores with valerian 800-mg occurred at 4 hours (113.00 ± 161.66) and 3 hours for valerian 400-mg (54.64 ± 111.51).

Time of peak effects on the items “energetic-fatigued” and “normal-spacey” matched the sedation scores in all cases. There were no differences in any of the treatments vs. placebo (peak placebo score taken at 1 hour = 24.9 ± 48.8). However, there were significant differences in the means determined by repeated measures ANOVA, and scores after treatment with 30 mg temazepam (peak = 61.2 ± 63.4 at 2 hours) were significantly different from all other active treatments (see Figure VII and Table 9 for values).

Significant age by treatment interactions were detected for sedation scores and fatigued-spacey scores using AUC data. Regression analyses found that age was a predictor for sedation by 30-mg temazepam ($r = 0.475$, $F_{(1,72)} = 9.69$, $p < 0.01$). This result was stable when the placebo responder was excluded ($r = 0.477$, $F_{(1,66)} = 10.20$, $p < 0.01$). This was not found to be the case for 15 mg temazepam ($F_{(1,72)} = 2.04$, $p > 0.05$), nor any of the other active treatments ($p > 0.05$, all).

Similarly, age was found to be a predictor for increased fatigued-spacey scores after treatment with 30 mg temazepam ($r = 0.437$, $F_{(1,72)} = 8.01$, $p < 0.01$), but not with 15 mg

temazepam ($r = 0.352$, $F_{(1,72)} = 2.24$, $p > 0.05$), nor with any other active treatment, ($p > 0.05$, all).

Age was furthermore found to be a predictor for increased placebo-induced sedation ($F_{(1,72)} = 7.97$, $p < 0.025$, when the placebo-responder subject was removed this interaction disappeared ($F_{(1,66)} = 0.47$, $p > 0.05$).

Significant weight by treatment interactions were found using subjects' weights in kilograms as a between subject factor. When one subject that was seen to have a marked placebo response on subjective sedation scores was removed from the analysis, there was no interaction between weight and treatment on any of the variables.

IVE – COMPARISONS BETWEEN TREATMENTS

The data presented so far have been the results of each treatment compared with placebo over the time course of the sessions. Table 5 summarizes the results of the seven treatments compared with placebo on each of the assessments. MTT scores are percent time over the road scores, DSST is number of completed trials. Sedation is the VAS summary sedation scores and mood represents the VAS scores on the composite mood scale “energetic-fatigued” and “normal-spacey”.

Table 5. Effects of medications on all assessments, compared with placebo. A “+” denotes an increase in effect, while “-” denotes a decrease, or impairment.

Assessment	Tem 30	Tem 15	Dph 75	Dph 50	Val 800	Val 400
MTT	-	-	-	no change	no change	no change
DSST	-	no change	no change	no change	no change	no change
VAS – Sedation	+	no change	+	+	no change	no change
VAS – fatigued + spacey	no change	no change	no change	no change	no change	no change

In order to obtain a fuller understanding of their comparative pharmacology, all possible combinations of the seven treatments compared with each other were analyzed with paired t-tests when a significant difference was detected in the means with repeated measures ANOVA, as with placebo. These data are presented in Tables 6-9.

On the MTT, impairment with 30-mg temazepam was significantly greater than with any of the other drugs or doses (Table 6). On the DSST, impairing effects are not as evident as with the MTT, but 30 mg of temazepam scores are still significantly different than both doses of valerian (Table 7).

On the DSST, there was no statistically significant difference between temazepam 30-mg and either the lower dose of temazepam (15-mg), or either dose of diphenhydramine. There is a difference between scores with 30-mg temazepam and placebo, and both doses of valerian (Table 7). After Bonferroni correction, only $p < 0.002$ is considered significant. Therefore, only 30 mg temazepam on the MTT is significantly different from placebo and all other treatments (Tables 6 & 7).

Table 6. Peak baseline-corrected MTT scores and significant differences (paired t-tests) in effect compared to placebo and to all drugs and doses. Times of peak effects were reported in Section IIIc. Values are mean peak scores +/- standard deviations (STDEV).

	PLACEBO 3.73 ± 7.07	TEM 30 -30.38 ± 16.52	TEM 15 -3.96 ± 7.36	DPH 75 -4.06 ± 9.04	DPH 50 2.11 ± 10.85	VAL 800- 0.37 ± 8.16	VAL 400 -0.67 ± 8.52
TEM 30	p<0.001		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
TEM 15	p<0.05	p<0.001		X	X	X	X
DPH 75	p<0.05	p<0.001	X		X	X	X
DPH 50	X	p<0.001	X	X		X	X
VAL 800	X	p<0.001	X	X	X		X
VAL 400	X	p<0.001	X	X	X	X	

X= not significant

Table 7. Peak baseline corrected DSST scores (# completed trials) and significant differences (paired t-tests) in effect compared to placebo and to all drugs and doses. Times of peak effects as reported in Section IIIC. Values are mean peak scores +/- STDEV.

	PLACEBO 0.3 ± 1.9	TEM 30 -4.2 ± 5.3	TEM 15 -1.7 ± 2.9	DPH 75 -1.3 ± 1.9	DPH 50 -1.6 ± 5.0	VAL 800 1.8 +/- 2.7	VAL 400 0.7 +/- 1.9
TEM 30	p<0.01		X	P=0.051	X	p<0.05	p<0.05
TEM 15	X	X		X	X	p=0.052	X
DPH 75	p=0.055	p=0.051	X		X	X	X
DPH 50	X	X	X	X		X	X
VAL 800	X	p<0.05	p=0.052	p<0.01	p<0.05		X
VAL 400	X	p<0.05	X	p<0.05	X	X	

X = not significant

Sedation scores on the VAS show similarities in magnitude of effect between 30-mg temazepam, and both doses of diphenhydramine, as well as between both doses of valerian and placebo. 15-mg of temazepam does not appear to be as sedating as 30 mg temazepam or either dose of diphenhydramine, but more sedating than placebo or valerian 400 mg or 800 mg (Table 8).

Reported feelings of “fatigue” and “spacey” were much higher for temazepam 30 mg than for any other treatments or placebo (Table 9).

None of the comparisons can be significant when p<0.002 is required for significance (i.e., after Bonferroni correction; Tables 8 & 9).

Table 8. Peak baseline-corrected Subjective Sedation Scores and significant differences (paired t-tests) in effect for all possible comparisons. Times of peak effects were reported in Section IIIC. Values are mean peak values +/- standard deviations.

	PLACEBO 51.14 ± 152.20	TEM 30 326.5 ± 282.9	TEM 15 189.3 ± 238.1	DPH 75 277.64 ± 337.6	DPH 50 299.5 ± 305.4	VAL 800 113.0 ± 161.7	VAL 400 54.6 ± 111.5
TEM 30	p<0.05		p=0.52	X	X	p<0.01	p<0.01
TEM 15	X	p=0.52		X	X	X	X
DPH 75	p<0.05	X	X		X	X	p<0.05
DPH 50	p<0.05	X	X	X		p<0.05	p<0.05
VAL 800	X	p<0.01	X	X	p<0.05		X
VAL 400	X	p<0.01	X	p<0.05	p<0.05	X	

X = not significant

Table 9. Areas under the effect curves for baseline-corrected energetic-fatigued and normal-spacey and significant differences (paired t-tests) for all possible comparisons. Times of peak effects were reported in Section IIIc. Values are mean peak values +/- standard deviations.

	PLACEBO 24.9 ± 48.8	TEM 30 61.2 ± 63.4	TEM 15 13.4 ± 48.1	DPH 75 29.5 ± 51.9	DPH 50 29.6 ± 34.3	VAL 800 22.0 ± 30.5	VAL 400 7.2 ± 24.6
TEM 30	X		p<0.01	p<0.05	p<0.05	p<0.05	p<0.05
TEM 15	X	p<0.01		X	X	X	X
DPH 75	X	p<0.05	X		X	X	X
DPH 50	X	p<0.05	X	X		X	X
VAL 800	X	p<0.05	X	X	X		X
VAL 400	X	p<0.05	X	X	X	X	

X= not significant

IVF - OBSERVER RATINGS - DEBI SCORES

Peak observer-rating scores using the DEBI were similar in magnitude and pattern to subjective ratings of sedation using the VAS. When the scores were normalized to a percentage and compared, the Pearson correlation coefficient $r = 0.947$ and this was statistically significant at the $p<0.001$ level.

Figure VIII. Comparison of observer and subjects' ratings of sedation. Trend line represents the correlation between subjective ratings of sedation (VAS) and observer ratings of sedation (DEBI) for 7 subjects. $R = 0.947$

III G - BLINDING CHECKS

Subjects were able to guess at which drug they received 34% of the time, and in 27% of cases they guessed the appropriate dose of the drug as well. In 60% of the cases with 30 mg of temazepam subjects were able to guess which medication they had received, compared to 30% for 15-mg temazepam, 20% for 75 mg of diphenhydramine and 10% for 50 mg of diphenhydramine.

Eighty percent of subjects with 30 mg of temazepam felt that they had received 'something', or guessed at another one of the active treatments. This occurred with all treatments at the following frequencies: 15 mg of temazepam (60% of subjects), 75 mg of diphenhydramine (80%) 50 mg of diphenhydramine (90%), 800 mg of valerian (50%) and 400 mg of valerian (40%) and placebo (50%).

In the case of valerian, individuals were more likely to guess 'placebo' than 'valerian'. Thirty-eight percent of cases with 800 mg and 44% of cases with 400 mg valerian guessed 'placebo' was the drug they had received compared to the 13% and 22% that guessed correctly.

In 19% of cases, subjects were unable to guess at any medication listed and wrote nothing in the space provided.

IVH - PRACTICE AND LEARNING EFFECTS

Figure IX. Mean MTT scores for placebo sessions. Data are presented as mean +/- SEM raw scores and have not been corrected for baseline scores. Results show no statistically significant increase in ability over the course of the day.

Effect of practice over each session day was measured by comparing scores over time throughout placebo days. No change in ability is apparent over session days and no statistically significant change could be found (Figure VI).

Figure X. Mean Baseline scores for each session for all treatments. The difference in mean ability at baseline from sessions 1 – session 7 is statistically significant ($p < 0.05$) and therefore there was an underlying learning effect with the psychomotor tasks, particularly the MTT.

Effect of learning over experimental sessions was measured by comparing baseline scores for all sessions. A significant learning effect was seen over the 7 experimental sessions (Figure VII, $p < 0.05$).

IV1 – SIDE EFFECTS

Side effects are reported in Table 11, page 72. “Drowsiness” and “fatigue” were the most frequently reported side effects - reported in 93% and 64% respectively with temazepam 30mg, compared to 36% and 21% with placebo. These were also the most frequently reported side effects with both doses of diphenhydramine; drowsiness was reported in 43% and 71% of subjects for 75 mg and 50 mg of diphenhydramine, respectively. Anticholinergic side effects were not more common with diphenhydramine than with temazepam (i.e. 28% and 21% reported dry mouth after 75 mg and 50 mg diphenhydramine, respectively, compared to 21% with 30 mg temazepam and 35% with 800 mg valerian).

Subjects reported the most side effects with the high dose of temazepam (30 mg), and the fewest with the low dose of valerian (400 mg). There were fewer side effects reported with valerian 400 mg than with placebo. No unusual or serious side effects were reported with any of the medications.

Table 10. Frequency of reported side effects by body system

Body System	Adverse Reaction	TEM 30 (%)	TEM 15 (%)	DPH 75 (%)	DPH 50 (%)	VAL 800 (%)	VAL 400 (%)	PLA (%)
CNS	drowsiness	92.9	57.1	42.9	71.4	50.0	28.6	35.7
	fatigue	64.3	50.0	14.3	28.6	7.1	7.1	21.4
	headache	14.3	14.3	28.6	0	0	14.3	21.4
	general weakness	28.6	14.3	7.1	35.7	0	0	28.6
	inability to concentrate	28.6	21.4	21.4	21.4	7.1	0	7.1
	lightheadedness	42.9	28.6	21.4	28.6	7.1	21.4	14.3
	dizziness	35.7	0	7.1	7.1	0	0	0
	clumsiness	42.9	7.1	7.1	14.3	0	0	0
	slurred speech	7.1	0	0	0	0	0	0
	memory loss	7.1	0	0	0	0	0	0
	loss of balance	50.0	28.6	21.4	14.3	0	0	0
	confusion/disoriented	7.1	0	7.1	7.1	0	0	0
	anxiety	7.1	0	0	0	0	0	0
	"drugged"	0	0	7.1	7.1	0	0	0
	sedated	0	0	0	0	7.1	0	0
	"spacey"/"weird"	0	7.1	7.1	0	0	0	7.1
Metabolic /Nutrition	loss of appetite	7.1	0	0	0	0	0	0
Special Senses	metallic taste in mouth	0	0	0	0	7.1	0	0
	double vision	7.1	0	0	0	0	0	0
	blurry vision	14.3	0	7.1	7.1	0	0	0
	burning mouth/thirst	0	0	14.3	14.3	0	0	0
Gastrointestinal	dry mouth	21.4	14.3	28.6	21.4	35.7	14.3	28.6
	dry throat	28.6	7.1	35.7	21.4	21.4	14.3	21.4
	nausea	7.1	0	7.1	0	0	0	0
	hungry/ increaed appetite	0	7.1	0	0	7.1	0	7.1
	loss of appetite	7.1	0	7.1	0	0	0	0
	heartburn	7.1	7.1	0	0	0	0	0
Musculoskeletal	muscular weakness	0	0	0	14.3	7.1	0	7.1
	difficulty walking	50.0	21.4	7.1	14.3	0	0	0
	numbness	14.3	7.1	7.1	7.1	0	0	0
	abdominal/back pain	14.3	0.0	14.3	0	0	0	0

SECTION V - DISCUSSION

The purpose of this study was to examine the comparative pharmacodynamics of temazepam, diphenhydramine and valerian vs. placebo. This study demonstrates a time and dose response to temazepam and diphenhydramine in elderly subjects compared to placebo and valerian. Results indicate that there was a differential effect of 30 mg temazepam, and possibly of 15 mg of temazepam and 75 mg diphenhydramine compared with placebo and valerian on psychomotor ability as determined by the MTT. This impairment was only evident for 30-mg temazepam on the DSST, and not after Bonferroni correction. Impairment on the objective assessments due to 30 mg temazepam was greatest, followed by temazepam 15-mg and 75-mg diphenhydramine (about the same magnitude of effect), then diphenhydramine 50-mg. Placebo and 400-mg valerian showed slightly less impairment than 800-mg valerian.

Increased subjective sedation (visual analogue scales) was noted with 30-mg of temazepam and both 50-mg and 75-mg diphenhydramine compared to placebo and valerian. These did not achieve statistical significance after Bonferroni correction. No differences between placebo and either dose of valerian on either objective or subjective measures were detected. There was a large variation in response seen with all of the medications and placebo on both subjective and objective assessments.

Temazepam 30-mg elicited an increase in reported fatigue and feeling “spacey” compared to all other treatments except placebo. None of the other measures of mood, i.e. autonomic, contentedness or anxiety, were different across treatments.

More side effects were reported with both doses of temazepam and diphenhydramine compared to placebo and valerian, and the most commonly reported effects were “drowsiness” and “fatigue”, followed by “dry mouth” and “dry throat”.

The comparison of all the treatment effects in Tables 6-9 included 21 different comparisons for each variable (i.e. MTT, DSST, sedation, etc). Therefore, because an alpha error of $p < 0.05$ is not conservative enough to exclude the possibility that one of these comparisons will occur by chance, Bonferroni correction factor was introduced, adjusting the acceptable alpha error to $p < 0.002$. This correction factor is considered very conservative and in studies like this one may be excluding real differences in treatment.²⁰⁶

Objective tests indicated that treatment with 30-mg temazepam had a significant negative effect on psychomotor abilities as determined by tracking and DSST, whereas 15-mg temazepam had a significantly impairing effect on tracking ability only. Temazepam at doses of 20-60 mg have been shown to affect reaction time, driving and tracking ability and visuo-motor abilities in healthy male and female volunteers,^{3,11,148, 207, 192-208} healthy elderly,²⁰⁹⁻²¹⁰ and elderly inpatients⁹ in single- dose studies such as this one. This effect on psychomotor ability is a common characteristic of all benzodiazepines.^{76, 87, 137} For temazepam, this response has been shown to be dose-dependent, with higher doses having more detrimental effects.^{3,148, 207-211,219}

The goal of psychomotor testing is to determine if the drugs in question affect the ability to perform routine, complex psychomotor tasks such as driving, or functioning in the workplace or home.²¹² Psychomotor tests should be chosen for their ability to

simulate real-life events. For example, impairment in driving ability due to sedation is thought to be reflected in breakdown of steering, positioning on the road, and reaction time skills, and any psychomotor ability assessment should aim to measure these skills.^{212, 213} In general, batteries of psychomotor indicators are used to determine the level of pharmacologically induced impairment so that several aspects of performance can be evaluated.

The literature surrounding sedative-hypnotic medications alludes to many different assessments of psychomotor function. The DSST has been employed in many studies, and has been shown to be a consistent measure of benzodiazepine-induced performance decrements.^{62, 112, 148, 200, 207, 211, 214-219} The principle determinant of ability on the DSST should be the recognition of visual information, along with motor ability (pointing and clicking), sustained attention and concentration.²²⁰ The DSST is commonly used to assess sustained attention and concentration, response speed and visuo-motor coordination in studies evaluating the effect of benzodiazepines.²¹² Tracking assessments are thought to be more useful for evaluating the immediate effects of benzodiazepines (i.e. the acute or peak effects), and to be useful for modeling aspects of driving.²¹²

This study demonstrated a statistically significant decrement in psychomotor ability with 15-mg temazepam and 75-mg diphenhydramine on the MTT, but not on the DSST. Some studies report a differential effect on different components of psychomotor ability. For example, in a study by Roth et al, there were no significant decrements in reaction time or visuo-motor response as determined by the DSST after treatment with 15 or 30 mg temazepam in healthy younger volunteers.¹⁴⁸ Kunsman et al (1992) found that 15 mg of temazepam had a negative effect on psychomotor ability as determined by a

tracking test similar to the MTT, but not by reaction time in healthy younger individuals.¹⁹² Studies by Greenblatt et al (1989) and Rush & Griffiths (1996) also found that 15 mg and 15 mg/70 kg doses of temazepam in healthy younger volunteers did not induce significant impairment on the DSST, even at peak sedation.^{11, 207}

With diphenhydramine, 1 mg/kg doses in healthy volunteers showed differential effects on alertness and attention, where alertness, but not attention, was negatively affected.⁹⁹ Lines et al.(1997) found no decrements in psychomotor or cognitive ability in healthy elderly volunteers, even after multiple dosing over 4 days. The DSST was employed in that study, but no tracking tests.¹⁹⁵

The results of the present study indicate that the MTT is a more sensitive measure of impairment on psychomotor tasks, in particular to the effects of the more subtle medications, such as 15-mg temazepam or 75 mg diphenhydramine. Another possible explanation is that the elderly subjects that were recruited for this study did not achieve a high baseline level on the DSST, and that treatment-induced changes were more difficult to identify. This may also explain why age may have been a predictor of temazepam-induced psychomotor impairment on the MTT but not the DSST.

No significant psychomotor impairment could be detected with 50-mg diphenhydramine on either the MTT or the DSST. Studies that have evaluated the effects of diphenhydramine-induced impairments in cognitive and psychomotor abilities have shown inconclusive results. For example, some studies that have employed 50-mg diphenhydramine and the DSST,²¹⁹ and/or some sort of tracking test to assess psychomotor ability show no significant impairment in healthy,^{109,221} or elderly volunteers.¹⁹⁵ In contrast, several studies have noted a significant detriment in psychomotor ability with 50-mg diphenhydramine in healthy younger adults, using

DSST,^{114,222} reaction time assessments,^{218,223} driving, tracking or simulated assembly line assessments,^{59-60,224,218,222,223,225,226} or EEG recordings.^{98, 219} Furthermore, in healthy elderly, impaired performance with 50 – 75 mg diphenhydramine on cognitive assessments and DSST,¹¹² DSST and reaction time have been demonstrated.^{113,114}

In summary, results from this study and the literature suggest that drug-induced impairment may affect differential aspects of psychomotor ability. A comprehensive battery of tests that is sensitive to different aspects of performance is useful in studies of sedative hypnotics. Future research may wish to include another aspect of psychomotor function, such as simple or choice reaction time assessments, that may increase the sensitivity of the battery of assessments, particularly in the elderly. Furthermore, because of the concern of cognitive impairment and the use of anticholinergic medications in the elderly, further research may also wish to examine the effects of these drugs on memory and cognitive functioning.

Results from this study indicate that, although 15-mg temazepam and 75-mg diphenhydramine cause significant psychomotor impairment, levels of impairment are still much less than that induced by 30-mg temazepam.

Some studies have compared benzodiazepines to antihistamines in an experimental setting. For example, Saletu et al (1987) have showed that 50-mg of diphenhydramine has less of an effect on subjective sedation than 2 mg lorazepam, but more than placebo in healthy younger adults.¹⁰⁹ Subjects that took 50-mg diphenhydramine were seen to improve on tests of concentration and reaction time compared to subjects that took either combination of lorazepam + diphenhydramine (1 mg + 25 mg) or lorazepam alone (2 mg). No psychomotor deficits on the critical flicker

fusion threshold (CFFT) assessment (psychomotor assessment) were noted for diphenhydramine compared with lorazepam or the combination drug.¹⁰⁹ Curran et al. (1998) also show no decrease in ability on the DSST or the CFFT with diphenhydramine 25 or 50 mg compared to lorazepam (2 mg).²²¹

In this study, subjects were allowed to nap whenever they felt sleepy during session days. Roehrs et al (1993) demonstrated that naps can reduce or eliminate sedative effects of diphenhydramine and triazolam.²²⁷ They also found that napping reduced diphenhydramine-induced psychomotor impairment, but not triazolam-induced impairment. It is possible that the lack of impairment seen with diphenhydramine in the current study may have been in part because of the restoring effects of naps between assessments.

Time-course of effect and pharmacodynamic profiles were shown to be different for temazepam compared to diphenhydramine, with temazepam having a quicker onset of action (about 30 minutes), and a dose-dependent effect on sedation. Subjective effects with both doses of temazepam and 75-mg diphenhydramine peaked at 2 hours, whereas peak sedative effect of 50-mg diphenhydramine was 4 hours. Diphenhydramine had a slower onset of action, about 1-2 hours.

This study's results with temazepam are consistent with the literature; it has been shown to have an onset of action of approximately 30 minutes with a peak effect after 2 or 3 hours at comparable doses of temazepam in younger individuals,^{3, 11, 207} and elderly individuals.^{7, 84} Time course of effects has not been found to differ between younger and elderly individuals in an experimental setting.^{7, 83, 84} Diphenhydramine has been shown to have an onset of action of 1 hour²²⁴⁻²¹⁸ and peak sedative effects at comparable doses

(i.e. 50 mg and 50 mg /70 kg) at 1.5 – 4 hours in younger,²¹⁸⁻²²³ and 2-4 hours in elderly individuals.^{112, 113} No time course of effect was evident with valerian compared to placebo in this study.

Increased age was found to be a possible predictor for increased sensitivity to temazepam on the MTT and subjective ratings of sedation. Results with neither diphenhydramine nor valerian were affected by increased age. Neither gender nor subjects' weights were found to have an interaction with treatment effects.

²¹¹As discussed in Section II.M, the elderly are thought to be more sensitive to benzodiazepines because of alterations in kinetics (e.g. liver and kidney function), and perhaps physiological characteristics (e.g. increased cognitive decline, and/or possibly increased BZ receptor densities). Researchers have shown that kinetic parameters of temazepam (i.e. peak plasma concentrations, volume of distribution, half-life or clearance) are not affected significantly by age,⁸⁴ or, are only affected by increased age in females.⁷ Greater free fraction and faster time to peak effects have been noted in older subjects compared to young, likely due to decreased blood albumin concentrations.⁸⁴⁻²²⁸ Gender has been shown to affect volume of distribution and half-life of temazepam.^{7, 84} In the current study, when the eldest subject was removed from the analysis age by treatment interactions disappeared. This subject also had the lowest body weight and was female, although no interactions were noted when weight or gender were included in any of the ANOVAs as between subjects factors. There has been much speculation in the literature that there are changes in BZ receptor densities in the brains of elderly individuals, and that this may be a normal physiological consequence of aging.¹⁵⁰⁻¹⁵²⁻¹⁵⁴⁻¹⁵⁵⁻²⁰⁹⁻²²⁹ Because no kinetic analyses were done in this study, it is

impossible to know if this apparent increased sensitivity is due to increased free fraction of drug, which is likely to cause a more intense effect, or if physiological characteristics played a role.

Interestingly, no increased sensitivity was noted with diphenhydramine, or valerian with increased age. Some studies have reported age-related changes in diphenhydramine clearance rates, half-life and volume of distribution,²³⁰ while others show no differences between kinetics of younger and elderly.¹⁰⁵ Also, volume of distribution of H1 (histamine) receptors in the CNS in elderly individuals has been shown to be decreased compared to young¹⁶⁶ and therefore, theoretically, the soporific effects of diphenhydramine would be expected to be more pronounced in older individuals. However, Scavone et al (1998) tested 25-mg diphenhydramine in younger and elderly individuals and found that, although plasma concentrations of diphenhydramine were similar in both cohorts, the pharmacodynamic effect (as measured with the same instruments that were used here) was greater in younger subjects. Berlinger et al (1982) report that, although elderly women were found to be slightly more susceptible to psychomotor-impairing effects of 50-mg diphenhydramine than younger, this was much less than the increase in sensitivity seen with benzodiazepines.¹¹³

No studies have compared the effects of valerian in younger and elderly individuals.

The sedative effect of 30-mg temazepam was reliable and similar to what is consistently reported in the literature with healthy younger volunteers,¹⁴⁸ young insomniacs^{4,229-194} older insomniacs,²²⁹ hospital in-patients,²³¹ and elderly insomniacs.²³² Studies also report a dose-dependent increase in subjective and objective (i.e. EEG recordings) measures of sedation with 15 – 30 mg temazepam.^{4, 233}

In this study, sedative effect of the lower dose of temazepam (15 mg) did not differ statistically from placebo, in contrast to other published reports with younger,^{11, 148} insomniac^{194, 233} and elderly subjects.⁷⁸ This is especially surprising in mostly benzodiazepine-naïve elderly subjects. Some studies have reported no subjective sedation after doses of 15-mg temazepam in young adults.¹⁹² Bixler et al (1978) showed no sedative effect of 30-mg temazepam in a sleep lab study with otherwise healthy insomniac patients.²³⁴ However, a post-marketing study performed by Fowler et al (1980) in the UK reported that, almost 93% of the mostly middle-aged and elderly individuals surveyed used 10 – 20 mg temazepam per day for sleep.⁸⁵ A 28-day clinical trial examined 15-mg temazepam in elderly insomniac patients and found that a significant proportion of patients reported improved sleep and longer sleep times.⁷⁸ A sleep lab study, where doses of temazepam ranging from 7.5 mg to 30 mg were given at night in a transient insomnia model indicated that 7.5 mg had some positive effects on sleep stimulation.⁴ This may indicate that, for poor sleepers that are using a sedative-hypnotic clinically, a lower dose is more efficacious than in a study with otherwise healthy individuals that employs an experimental design, such as this one.

Both doses of diphenhydramine elicited a significant degree of sedation, however this was not dose-dependent. The peak sedative effect was similar in magnitude for both doses, although the time to peak sedation was faster for the higher dose (2 hours for 75 mg diphenhydramine compared to 4 hours for the 50 mg dose). In both cases, a residual sedative effect was present at the end of the study days, although the data shows that these effects were abating. These results are consistent with published literature. Curran et al. (1998) showed a dose-dependent increase in subjective ratings of sedation with 25

and 50 mg diphenhydramine in healthy younger volunteers. Furthermore, they found that 50-mg, but not 25-mg diphenhydramine elicited a subjective rating of sedation that was significantly different than placebo.²²¹ In published clinical studies with diphenhydramine (50 mg), peak sedative and cognitive effects occurred at 2 – 4 hours.^{59-98,224-222-223-219}

The results of this study and other published studies indicate that doses over 50 mg diphenhydramine have no increased effect, and that this may be the ceiling dose for sedation. Studies have indicated that 50-mg diphenhydramine is an effective hypnotic dose, in young individuals,⁹⁸⁻²²⁴⁻²²²⁻²²³⁻²¹⁹ psychiatric patients²³⁵ and insomniac patients.^{108, 236 237} In one study, doses up to 150-mg showed no increase in soporific effect (flat dose-response curve),²³⁶ while in other studies, lower doses (i.e. 12.5, 25 and 50 mg) have showed a dose-response relationship.^{223, 235} Positron emission tomography (PET) technology has been used to examine binding of antihistamines in the frontal cortex while correlating sedative effect.¹⁰¹ Results indicate that soporific effects level off after occupancy of H1 receptors reaches 70-80%, and that increased doses have little additive effect on sedation. An abuse liability study that tested run-in doses of up to 600-mg diphenhydramine in past substance-abusing adults found that over doses of 100-mg, increased doses lead to increased side effects and feelings of drug effect, but not sedation.⁶²

In this study, the only reported changes in mood occurred with 30-mg of temazepam during peak effects, and only on the component measuring fatigue and “spacey” feelings. These results concur with other similar studies, for example Roth et al (1979) found no change in mood after 15 or 30 mg of temazepam in healthy younger

volunteers (1979).¹⁴⁸ Doses of 20 mg and 30 mg of temazepam have been found to lead to decreased self-rated feelings of anxiety and increased feelings of sedation and “drunkiness” in younger experimental subjects.²¹¹⁻²³⁸⁻²³⁹ Feelings of “spacey-ness” and/or confusion have been reported with doses as low as 15-mg temazepam,^{11, 238} although this was not the case in this study. No changes in these indices of mood were found with either dose of diphenhydramine or valerian. No overall differences could be detected in anxiety scores, or any of the other measures of autonomic or mood (e.g. contentedness). Diphenhydramine has been shown by some researchers to increase feelings of “fatigue” and “confusion”, and decrease feelings of “vigor”.^{99, 167, 219} “Jitteriness” and increased anxiety have also been reported with diphenhydramine use.²²³

Observer ratings of sedation showed strong correlation with subjective ratings, indicating that subjects were likely insightful about their conditions. This is in alliance with other studies employing self- and observer-rating scales with benzodiazepines^{240, 241} and antihistamines.⁹⁹ Observer ratings are often employed in clinical and experimental settings with psychoactive medications, either with or without adjunct self-rating scales. Observations by a clinical observer are thought to produce less variability than self-rating as inter-rater reliability is less problematic.²⁴⁰

Blinding checks indicated that subjects often knew when they had received a sedative medication. They were furthermore often able to identify when they had received the highest dose of temazepam. The subjects’ ability to guess the proper medication decreased as the strength of the treatment (i.e. drug-induced sedation) decreased. This result is common with sedative medications, even when subjects are

sedative-naïve.²¹⁶⁻²⁴² A blinding check was employed to ensure that the subjects were not aware of which medication they had received and were reacting in a biased manner. It is possible that sedation ratings were enhanced when subjects suspected that they had received an active treatment. This could possibly explain, in part, why objective and subjective assessments did not correlate as well as expected.

Subjective and objective measures of sedation show differential effects with respect to time to peak effect and magnitude of effect for diphenhydramine and temazepam, but not valerian (no discernable effects were seen with valerian on either measure). Results from MTT and DSST peaked slightly earlier than subjective measures. This may have been because objective measures were more sensitive to the initial sedative effects during sessions. As subjects became more aware of a drug effect, they may have compensated, i.e. increased attention to the task to counter impairment. This effect has been noted with attentional tasks previously.^{99, 224} It is contentious as to which of these measures has more clinical relevance, however.²³⁸⁻²⁴³⁻²⁴⁴ Because insomnia is not a fatal disease, the impact on quality of life and ability to work and function as determined by subjective assessment is often thought to be the most important outcome in evaluation of sedative-hypnotics.³¹⁻⁷⁸⁻²³¹⁻²³⁸⁻²⁴⁵ Morning-after effects on psychomotor function may be more important than acute effects clinically and have been studied extensively for temazepam.⁸⁻²¹⁰⁻²³¹⁻²³⁸⁻²⁴⁶⁻²⁴⁷ However, elderly patients are known to rise in the night often, particularly for toilet purposes or because of disruptions in sleep, which may be dangerous if a sedative-hypnotic medication has been consumed that has ataxic effects.^{50, 129} Therefore, it is important to study impairment caused by these drugs in a comparative manner.

The results of this study indicate no sedation, alteration in psychomotor ability, or any side effects as a result of treatment with either 400 or 800-mg *Valeriana Officinalis*.

Kuhlmann et al (1999) studied the effects of 600-mg valerian on reaction time, psychomotor ability and correlated this to sleep quality the morning after dosing in healthy volunteers.²⁴⁸ In that study, no effect was seen on any of the psychomotor indices or subjective sleep quality after a single dose, or after 14 consecutive treatment days.

The paucity of good clinical studies with valerian makes it difficult to compare results. Subjective ratings of sleep quality have been made on binary or trinary scales instead of 100-mm visual analogue scales, which are generally used in the assessment of sedative effect, although this limited the selection for research subjects.^{177,183,185} However, results of these studies indicate that there may be an improvement in the quality of sleep with valerian treatment. Schmitz et al (1998) have reported an improved quality of life as well as improved sleep with valerian in insomniacs.²⁴⁹ Wheatley (2001) found that 600-mg of valerian before bed for 6 weeks improved stress-induced sleep deficit in adult insomniacs.²⁵⁰ In contrast, other studies report no improvement of subjective sleep quality.^{176 186 248}

Objective measures of sleep (i.e. EEG and activity recordings) show no effect on total sleep time or number of awakenings after valerian treatment in young volunteers^{176, 184} or elderly poor sleepers¹⁸⁶, despite reported increases in slow wave sleep and decreased activity in the last third of an 8-hour period.²⁵¹ It could be that valerian is having some effect in these studies, but the doses are too low to identify any clinically relevant improvement in sleep. It is also possible that valerian is not an effective sedative

compound, but does affect sleep parameters in such a way as to improve sleep in individuals that suffer from insomnia (e.g. by increasing the amount of slow wave sleep, or deep sleep). This is addressed by Schultz et al (1998), who speculates that *“valerian is not a suitable agent for the acute treatment of insomnia. Its essential value may lie in its ability to promote natural sleep after several weeks of use..”*¹⁷¹

Doses of valerian were chosen on the basis of precedence – all other published clinical reports have used 400– 900 mg in assessing valerian’s effects on sedation and psychomotor function.¹⁷⁶⁻¹⁷⁷⁻¹⁸³⁻¹⁸⁵ However, in most of these studies, the extraction was performed as part of the research, by the lab.^{176, 177, 183, 184} Because of differences in extraction, and perhaps time lapse between extraction and use of the product, it is possible that the doses that were used in this study were not sufficient, and that larger doses may have elicited a pharmacodynamic response.

The valerian that was used in this study was purchased from a pharmacy, and although the label claimed “quality assurance”, it is not known whether the sample of valerian used in this study contained the purported active ingredients. It has been demonstrated that label claim on herbal medications does not guarantee that the active ingredients are present.^{252, 253} The alkaloids that are thought to partially confer sedative properties of valerian are unstable. Beliveau states that *“it is unlikely that a medicinal tea or pharmaceutical preparation containing valerian could be a useful sedative unless care has been taken in the drying, conservation and formulation processes.”*²⁵² The results of this study therefore, can be attributed either to a lack of sedative effect by valerian, or an inactive sample, or sub-clinical doses of valerian tested, or a combination of these factors. Valerian can be tested for its active compounds by high performance liquid chromatography (HPLC) and/or gas chromatography (GC) techniques.^{254, 255} Essential

oils are first isolated from the roots and/or rhizomes of the plants, then the content of valepotriates and essential oils such as valerenic acid can be examined and quantified. This technique has been established in labs previously and will be performed with the lot used for this study as well. The ingredients that will be measured are valerenic acid, acetoxyvalerenic acid, hydroxyvalerenic acid, and/or valeranal and valepotriates (e.g. valtrate, isovaltrate).²⁵⁵

The present study used a single-dose, experimental paradigm to examine the comparative pharmacology of temazepam, diphenhydramine and valerian vs. placebo in healthy elderly individuals. This was an introductory study to examine acute effects of the drugs, and therefore it is difficult to generalize these results to elderly poor sleepers that might be taking the medications clinically. This study examines the potential efficacy of the drugs, but does not address their effectiveness. Efficacy *per se* has not been addressed as in a clinical trial, however, since subjects were volunteers and did not suffer from sleep disturbances. The next logical step in this research would therefore be to examine the comparative efficacy of these medications in an appropriate population of elderly insomniacs.

Insomnia is often comorbid with poor physical and/or psychological health status. Therefore, insomniacs may not be as healthy as the subjects in this study were, and/or may be more likely to be taking more concomitant medications.

Sleep aids are generally taken at night before bed, whereas treatment in this study was administered in the morning before breakfast after a good night's sleep. This would have affected the pharmacokinetics of the drug, and most likely the pharmacodynamic profile as well.

One of the ubiquitous drawbacks to studies that rely on psychomotor assessments and subjective reports is the degree of variability seen. This is evident in this study in all the assessments, as demonstrated by the large standard deviations around the means of all scores in all assessments (see RESULTS, Sections IVC and IVD). Psychomotor ability in the elderly is variable *a priori*, more so than in younger adults, possibly due to differential rates of aging and decline,²⁵⁶⁻²⁰⁹ and therefore psychomotor assessments are inevitably associated with variation in ability that compounds with differential drug effects. In this study, a computer and a mouse were used for all the assessments. Several subjects had not used a computer before and required training, however a few of the subjects were quite familiar with computers and “pointing and clicking” technique. Ten of the 14 subjects had arthritis to some degree in their hands and therefore experienced difficulty with assessments. All of the subjects wore corrective eyewear – the strength of which varied. Other sources of variation may have been differences in health status, liver and kidney function, and/or concomitant drug use. Any or all of these parameters would have affected the kinetics of the drugs.^{20, 40, 155, 209} Drugs were not administered by weight, but rather as in a clinical setting, by dose. Although weight was not found to interact with treatment response, this factor may still have contributed to variation. It may have been more appropriate to measure body fat, rather than weight, since benzodiazepines distribute in the fatty tissue and this may affect kinetics.

Kinetics of diphenhydramine has been shown to differ in caucasians and oriental individuals.¹⁰⁶ Two of the 14 subjects in this study were non-caucasian (1 oriental and 1 black), which may have furthermore contributed to differential response.

Although subjects reported that they were “good sleepers”, this was a purely subjective report (i.e. no sleep diaries or polysomnography were done to ensure absence

of sleep disorders). Past drug and alcohol use were screened for, but again this was a subjective report. Past usage of hypnotics and/or alcohol have been shown to alter responses to benzodiazepines in other research.^{136, 257} [van Steveninck, 1997 #329] Subjects may have answered according to what they thought inclusion criteria were to be included in the study, as financial compensation was provided.

Personality traits,¹⁴¹ and sub-clinical levels of cognitive dysfunction¹¹² have been seen to significantly affect response to sedative-hypnotic medications in previous studies. Elderly are susceptible to cognitive decline and this may affect both subjective ratings and the objective tests.^{9, 112, 258} In this study, subjects were not screened for cognitive decline. This may contribute to the differential responses seen between-subjects in some cases.

It was demonstrated that a significant learning effect occurred with the psychomotor tasks over the course of the seven sessions, despite attempts to control for this. It may also be that carry-over treatment effects occurred and this construed results to some degree. To avoid this possible confounder, this study would have recruited seven different arms, each comparable in age, health status, and other demographic characteristics. In order for this study to have enough power to detect differences in pharmacodynamic effect, we would have needed to recruit hundreds of subjects. Unfortunately, limitations on time, finances and resources made this impossible. The crossover design that was employed here has been used in similar studies and has proven effective, as well as pragmatic.^{113, 114, 144, 192, 195, 208, 216, 259, 260} The results presented in Section IV indicate that we obtained sufficient power to analyze the data and detect differences between treatments.

SECTION VI – CONCLUSIONS AND FURTHER RESEARCH

Subjective sedation and ratings of “fatigue” and “spacey” indicate that the strongest sedative was 30-mg temazepam, followed by 50-mg and 75-mg diphenhydramine (equal sedative effects), and then by 15-mg temazepam, which was not significantly different from placebo, but showed a trend towards enhanced sedation. Neither dose of valerian showed any difference from placebo on subjective sedation or mood.

Psychomotor impairment scores (MTT) indicate that the most drug-induced impairment occurred after 30-mg temazepam, followed by 15-mg temazepam and 75-mg diphenhydramine (comparable impairment), and then by 50-mg diphenhydramine. Neither dose of valerian showed any difference from placebo on either the MTT or the DSST.

A useful hypnotic medication would logically be one that induced sedation, but did not affect psychomotor function appreciably, or cause side effects.^{76, 248} In this respect, judging from the results of the present study, diphenhydramine 50 mg appears to be an acceptable alternative to benzodiazepine therapy in elderly individuals for the treatment of acute sleeplessness. Significant effects were seen on subjective sedation, but no significant psychomotor impairment or side effects were noted. Furthermore, more advanced age seemed to be a predictor for increased sensitivity to temazepam – this was not the case with diphenhydramine.

In order to evaluate the efficacy of these medications they must be tested in a less experimental and more clinical setting. The Canadian Institutes for Health Research

(CIHR), who funded this research, have also provided funding for another related experiment where temazepam, placebo and one of diphenhydramine or valerian will be tested in a home-based, 3-way crossover study in elderly insomniac patients (DSM-IV criteria). The subjects will take each of the test medications for 2 weeks at home before bed and sleep diaries will be used as the primary endpoint. Psychomotor testing will be done in the mornings at baseline and after 1-week (when subjects have reached steady state). The study is limited to placebo and two other treatments, due to restrictions on time, money and to reduce order effects. Because of the lack of effect with both doses of valerian, and the potential for 50-mg diphenhydramine as an acceptable pharmacotherapy for sleep, this author proposes that the next phase of the study compare 15-mg temazepam, 50-mg diphenhydramine vs. placebo in the two-week study. Doses of 15-mg temazepam had an effect on sedation although it did not reach statistical significance in this study. When taken at home and at night it has been found to be efficacious in the literature. Moreover, 30-mg temazepam had an intense effect on psychomotor impairment that may compromise safety if taken outside of an experimental situation in some patients.

To attempt to reduce some of the variation in response, it is suggested that cognitive assessment(s) be performed as part of the inclusion criteria for the study. Also, analysis of plasma levels would give further insight into some of the issues around the increased sensitivity that we have noted here with benzodiazepines vs. no increased sensitivity to diphenhydramine.

Because of the reported negative effects on memory caused by benzodiazepines, and the increased prevalence of dementia in older persons, it is also suggested that a memory assessment be added. Also, because of the incongruent results with the MTT

and the DSST, perhaps another aspect of psychomotor impairment could be tested, such as simple or choice reaction time. Because insomnia is mainly a subjective complaint that has a negative impact on quality of life, this may be another interesting assessment to include, particularly when the drugs will be used clinically for longer periods of time. An instrument such as the SF-36 (short-form-36), is a well-validated quality of life instrument that has been used in several clinical studies, and may be useful as an adjunct assessment in this upcoming study as well.

Another interesting component of this research and research involving benzodiazepine compounds and the elderly is the increased sensitivity with age. Several researchers have reported that, at similar plasma levels, the sedative effect of benzodiazepines is greater in elderly.^{9,150,152-155,209,258} The mechanisms of this increase in sensitivity are not known and are very difficult to test experimentally.^{149,155-156,258} However, with emerging imaging technology, perhaps some of these questions can be addressed in living humans. For example, PET (positron emission tomography) allows one to measure receptor occupancy in vivo, and is minimally invasive.^{261-262, 263} Flumazenil, a benzodiazepine receptor antagonist, has been labeled with C¹¹ to explore benzodiazepine receptor densities in CNS previously.^{264-262, 263} Thus, it may be feasible to compare the pharmacokinetic, pharmacodynamic properties of temazepam and contrast this to in vivo receptor densities as determined by PET.

Valerian had no effects on subjective sedation, or psychomotor impairment, and caused no side effects. In this study, one lot of valerian was used and part of that sample

has been retained for chemical analysis. Because of the variability in herbal products, the presence or absence of active constituents should be elucidated, for completeness.

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Appendix 1

Acute Pharmacological Effects of Temazepam, Diphenhydramine, and Valerian in Healthy Older Adults

➤ **Advertisement**

~~ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED~~

For a study about the effects of sleeping medication (prescription, non-prescription, and herbal) in **older adults that are NOT CURRENTLY TAKING sleeping pills.**

**Sunnybrook & Women's College Health Science
Centre, Sunnybrook site and the Centre for Addiction
and Mental Health, Addiction Research Foundation
needs healthy males and females, 65 years and older to
participate.**

Must be available weekdays during working hours for 7 separate days, and be willing to answer a variety of questionnaires after administration of a medication.

**If interested, please call Jennifer
at 416-535-8501, ext. 4437**

Confidentiality ensured

Financial Compensation will be provided!

[illegible]

Appendix 2

Consent form

Centre for
Addiction and Mental Health

Toronto, Ontario
Canada M5S 2S1
Tel: 416 595 6888

Centre de toxicomanie
et de santé mentale
33, rue Russell
Toronto (Ontario)
Canada M5S 2S1
Tel: 416 595 6888

CONSENT FORM

I _____ hereby consent to participate in the research study entitled "The acute pharmacological effects of temazepam, diphenhydramine and valerian in healthy older adults" that is taking place at the Centre for Addiction and Mental Health, Addiction Research Foundation (ARF) Division, 33 Russell Street, Toronto, Ontario M5S 2S1 under the supervision of Dr. U. Busto (ARF), Dr. B. Sproule and Dr. N. Herrmann (Sunnybrook and Women's College Health Sciences Centre). I have been asked to participate in this study because I am over 65 years of age and in good health. The purpose of this research, the procedures that will be followed, and the possible risks have been explained to me by _____.

In consenting to participate, I understand that:

1) DESCRIPTION AND PURPOSE OF THE STUDY

The purpose of this study is to determine and compare the effects of a prescription, non-prescription and herbal remedy in older adults. In recent years, the use of non-prescription and herbal medications for sleep has increased, though their effects in older adults have not been shown consistently. This study will determine the effects of two doses of a prescription medication called temazepam (e.g. Restoril®), a non-prescription medication called diphenhydramine (e.g. Nytol®), and an herbal medication called valerian and placebo (an inactive substance) over the next few weeks.

2) STUDY DETAILS

Before the study begins, I will receive a medical assessment to determine my state of health. As part of this assessment, a urine sample and blood sample of about 60 ml (2 oz) will be taken from a vein in my arm. Also, I will receive an information sheet that will outline any special instructions that I need to follow to participate in the study (e.g. avoiding certain medications). I understand that there will be a total of 12 participants in this study.

Better understanding, prevention and care
Mieux comprendre - prévenir - soigner

Addiction Research Foundation
Fondation de la toxicomanie
et de la santé mentale
Centre Institute
of Psychiatry
Centre psychiatrique
The Dowry Institute
Institut Dowry
33, rue Russell
Centre
Centre de santé mentale
33, rue Russell
Associated with the
University of Toronto
Affilié à l'Université
de Toronto

I will come to the Clinical Experimental Lab at the Addiction Research Foundation (ARF) for 7 study days, each separated by at least 3 days. The procedure for each of the study sessions is as follows: At the beginning of each session, I will be requested to provide a urine sample for the screening of drugs. In each of the seven sessions I will receive one of the following (orally) at 9:00 a.m.: 15 or 30mg temazepam, 50 or 75mg diphenhydramine, 400 or 800mg valerian, or placebo in random order. By the end of the study I will have received each of the medications and doses listed above, and none will be given to me more than once. The capsules will look identical, and neither myself nor the person testing me will be aware of which I am receiving. I will be asked to rate the effects of the medication in a variety of questionnaires and perform some simple tests (e.g. a test simulating driving), and report any side effects I may be experiencing at the time of testing. The questionnaires and tests should take approximately 20 minutes to complete, and will be repeated 8 times over 8 hours at regular intervals.

During the study day, I will relax in a comfortable patient lounge with reading material, a VCR and a television in between the testing procedures. In the morning of each study day I am required to arrive by 8 a.m. I will be provided with a light breakfast 1 hour after taking the medication, and at 1 p.m. I will be provided with a light lunch. I will be taken to my residence by a taxi at the end of the study day. Also, throughout the duration of the study, I will be required to keep a record of the number of hours of sleep that I get daily.

3) RISKS AND DISCOMFORTS

I can expect little risk associated with the blood sampling done during the medical assessment, although I may experience slight bruising or inflammation. The doses of the medications used in this study are well within the doses used in common medical practice for healthy older adults.

Temazepam is a prescription medication that has been used clinically to treat insomnia for many years. This medication is one of a group of drugs known as benzodiazepines. Benzodiazepines are very well tolerated. At the doses that I will receive, the most

common reported side effects may include sedation, drowsiness and poor coordination. However, many individuals do not experience any side effects.

Diphenhydramine is a non-prescription medication that has been used as a sleeping medication and as an antihistamine (for allergies) for many years. The most common side effects of this drug at the doses I will receive are drowsiness, dizziness, dry mouth, nausea and nervousness. Again, many subjects do not experience any side effects.

Valerian is an herbal product that is used to help induce sleep. This product is generally considered safe, especially when used for short periods of time. Europeans have used valerian for centuries, and German health authorities have approved its use as a sleep aid having no adverse effects when used at recommended doses.

4) BENEFITS

I will not benefit directly from participating in this study, but the findings of this study may help other patients who use sleeping medications. In consideration of my time and incidental expenses, I will receive \$100 per completed session (\$800 if I complete the medical assessment and 7 study days). My payment will be made by cheque and requires 1 to 2 weeks to be processed. If I withdraw early, I will receive compensation on a pro-rated basis according to the number of days I have completed.

5) PARTICIPATION

I understand that my participation in this study is voluntary and I can withdraw from the study at any time and for any reason. If I do decide to withdraw from the study, this will not in any way affect my future medical care or any benefits to which I may be entitled. The investigators may terminate my involvement in the study at any time, for example, due to medical reasons or for not following the study procedures.

6) CONFIDENTIALITY

I understand that by participating in a study at the ARF, certain information will be maintained on the ARF's file database and I will also have an official health record. I understand that all subjects participating in research at ARF must have these files and that

they are protected by law as all hospital files are. I understand that information contained on either file may be available to ARF staff.

My identity and the information obtained in this study will be kept strictly confidential and secure, available only to the researchers in the study. The data will be identified by my initials and date of birth only, and not by my name. Published reports and presentations at scientific meetings will refer to grouped data and no individual will be identifiable.

MY CONSENT

The acute pharmacological effects of temazepam, diphenhydramine and valerian in healthy older adults

The purpose of this research, the procedure to be followed, and the possible risks associated with the study have been fully explained to me. I have had the opportunity to ask questions and my questions have been answered satisfactorily. I understand that I will be free to withdraw from the study at any time and this will not affect the care I receive or the benefits to which I am entitled. I voluntarily consent to participate in this study.

I have been given a copy of this consent form to take home with me and I understand that I may contact Dr. U. Busto at (416) 535-8501, ext. 6812, or Jennifer Glass at (416) 535-8501, ext. 4437 to ask any further questions I may have concerning the study.

_____
Name of subject (print)

_____
Signature of subject

_____
Date

_____
Signature of investigator

_____
Date

_____
Signature of witness

_____
Date

Appendix 3

Manual Tracking Test (example)

Appendix 4

Digit Symbol Substitution Test (DSST) (example)

9

Appendix 5

Sedation Visual Analogue Scales (Drug Effects and Sedation)

Please indicate how you are feeling right now by clicking on the gray bar...

Drowsy

A little

70

A lot

Number: 1

Total: 27

L. Anchor

SEDATION scale...

R. Anchor

1	A Little...	<i>Drowsy</i>	A Lot...
2	A Little...	<i>Slowed down</i>	A Lot...
3	A Little...	<i>Sleepy</i>	A Lot...
4	A Little...	<i>Sedated</i>	A Lot...
5	A Little...	<i>Tired</i>	A Lot...
6	A Little...	<i>Worn out</i>	A Lot...
7	A Little...	<i>Listless</i>	A Lot...
8	A Little...	<i>Fatigued</i>	A Lot...
9	A Little...	<i>Exhausted</i>	A Lot...
10	A Little...	<i>Sluggish</i>	A Lot...
11	A Little...	<i>Wearry</i>	A Lot...
12	A Little...	<i>Bushed</i>	A Lot...

MOOD scale...

13	<i>Calm</i>	I feel...	<i>Anxious</i>
14	<i>Normal</i>	I feel...	<i>Bloated</i>
15	<i>Normal</i>	I feel...	<i>Sad</i>
16	<i>Energetic</i>	I feel...	<i>Fatigued</i>
17	<i>Thinking slowed down</i>	I feel...	<i>Thinking speeded up</i>
18	<i>Peaceful</i>	I feel...	<i>Tense</i>
19	<i>Normal</i>	I feel...	<i>Spacey</i>
20	<i>Friendly</i>	I feel...	<i>Seclusive</i>
21	<i>Normal</i>	I feel...	<i>Elated</i>
22	<i>Unhungry</i>	I feel...	<i>Hungry</i>
23	<i>Unpleasant</i>	I feel...	<i>Pleasant</i>
24	<i>At ease</i>	I feel...	<i>Nervous</i>
25	<i>Relaxed</i>	I feel...	<i>Excited</i>
26	<i>Normal</i>	I feel...	<i>Easily irritated</i>
27	<i>Discontented</i>	I feel...	<i>Contented</i>

Appendix 6

Observer rating scale (DEBI)

Hypnotics in the Elderly Study

Date: _____

Subject #: _____

Session #: _____

Observer Rated Drug-Elicited Behaviour Inventory (DEBI)

(Ratings to be based on the previous 15 minutes)

- A. **TALKATIVENESS**
1. Silent
  2. .
  3. .
  4. talking at least half the time with observer or other subjects
  5. .
  6. .
  7. .
- B. **EASE AND CONFIDENCE IN EXPERIMENTAL SITUATION**
1. hesitant, uncertain, withdrawn, shy
  2. .
  3. .
  4. . *Fits in well, comfortable*
  5. .
  6. .
  7. Extreme bravado, boasting, acts as if he is running the experiment
- C. **EXPERIENCING SATISFACTION WITH DRUG EFFECT**
1. clear statement, subject does not like drug effect
  2. .
  3. .
  4. Neutral or no response
  5. .
  6. .
  7. Clear statement, subject likes effect
- D. **MOTOR ACTIVITY**
1. very obvious decrease
  2. .
  3. .
  4. Normal
  5. .
  6. .
  7. Non-stop agitation, restlessness

Hypnotics in the Elderly Study

Date: _____

Subject #: _____

Session #: _____

E. GIDDINESS

1. None
2. .
3. .
4. high, cheery giggle
5. .
6. .
7. unstoppable giggles, laughing

F. MOOD CHANGE

1. no change
2. .
3. .
4. Moderate change
5. .
6. .
7. Extreme as compared with baseline

G. RESPONSE TO EXTERNAL STIMULI

1. non-responsive
2. .
3. .
4. Focused on some external stimuli
5. .
6. .
7. notices and comments on virtually everything in the environment

H. SPEECH

1. markedly slurred
2. .
3. .
4. Normal
5. .
6. .
7. Markedly articulate

I. MOTOR ACTIVITY

1. None
2. .
3. .
4. Moderate
5. .
6. .
7. Extreme

Hypnotics in the Elderly Study

Date: _____

Subject #: _____

Session #: _____

J. MENTAL ACTIVITY

1. high sedation
2. .
3. .
4. None
5. .
6. .
7. high stimulation

K AGITATION

1. Normal
2. .
3. .
4. Mildly agitated, moves
5. .
6. .
7. Paces non-stop

Appendix 7

Side effects symptoms checklist

SIDE EFFECTS SYMPTOM CHECKLIST

Symptoms	Present?	
1 Anxiety	Yes	No
2 Fatigue	Yes	No
3 Dry Throat	Yes	No
4 Confusion	Yes	No
5 Hallucinations	Yes	No
6 General weakness	Yes	No
7 Sore tongue	Yes	No
8 Chest pain	Yes	No
9 Excessive sweating	Yes	No
10 Vomiting	Yes	No
11 Numbness/tightness	Yes	No
12 Difficulty breathing	Yes	No
13 Gas or bloating	Yes	No
14 Nausea	Yes	No
15 Trouble swallowing	Yes	No
16 Wheezing	Yes	No
17 Diarrhea	Yes	No
18 Memory loss	Yes	No
19 Palpitations (heart pounding)	Yes	No
20 Muscle weakness	Yes	No
21 Skin rash	Yes	No
22 Joint stiffness	Yes	No
23 Blurred vision	Yes	No
24 Loss of feeling in any body part	Yes	No
25 Increased salivation	Yes	No
26 Drowsiness	Yes	No
27 Joint pain	Yes	No
28 Abdominal pain	Yes	No
29 Unusually hot	Yes	No
30 Sore throat	Yes	No
31 Clumsiness	Yes	No
32 Nasal congestion (stuffy nose)	Yes	No
33 Tremor (shakes)	Yes	No
34 Headaches	Yes	No
35 Dry mouth	Yes	No
36 Back pain	Yes	No
37 Dizziness or fainting	Yes	No
38 Difficulty walking	Yes	No
39 Loss of balance	Yes	No
40 Agitation or excitement	Yes	No
41 Shortness of breath	Yes	No
42 Chills	Yes	No
43 Loss of appetite	Yes	No
44 Heartburn	Yes	No
45 Muscle pain	Yes	No
46 Facial warmth	Yes	No
47 Choking sensation	Yes	No
48 Inability to concentrate	Yes	No
49 Lightheadedness	Yes	No

Appendix 8

Blinding check

*Acute pharmacological effects of temazepam, diphenhydramine,
and valerian in healthy older adults.*

U. E. Busto, Pharm. D.

On each of the seven days here, you will receive either a medication, or a placebo. After today's session, which of the following seven alternative treatments do you think you had? (please check one of the following):

- ☐ 30 mg temazepam (prescription medication)
- ☐ 15 mg temazepam
- ☐ 75 mg diphenhydramine (over-the-counter medication)
- ☐ 50 mg diphenhydramine
- ☐ 800 mg valerian (herbal medication)
- ☐ 400 mg valerian
- ☐ placebo (blank or sugar pill)

Why do you think this is the medication that you have received?

How did you feel today in general?

Any other comments?