

A SURVEY ASSESSING CURRENT BENZODIAZEPINE PRESCRIBING PATTERNS  
AND FACTORS INFLUENCING BENZODIAZEPINE PRESCRIBING BY  
NEWFOUNDLAND AND LABRADOR PHYSICIANS

by

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## Abstract

The Health Transition Fund report (Kennedy & Goyer, 2002) indicated that prescribing practices for benzodiazepines (BZDs) are frequently inappropriate, but more difficult to influence than others. The inappropriate benzodiazepine (BZD) prescriptions and the inability to influence prescription behavior through educational means provides justification for further study to understand the underlying factors associated with prescriptions. A survey of physicians can help objectify the variable(s) that play role(s) in the prescription of BZDs. For this thesis, a self-administered cross-sectional survey was conducted among the physicians in Newfoundland and Labrador in 2007 to assess the prescribing patterns of BZDs and variables influencing them. Response rate was 30.68% (n= 297) of which 78.48% (n = 233) prescribed BZDs. The BZD prescribing patterns and factors affecting them were significantly influenced by demographic variables of the respondents; these findings may be used to develop physician education tools that may help to optimize the BZD prescribing patterns.

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## List of abbreviations

APA	American Psychiatric Association
BBB	Blood brain barrier
BZD	Benzodiazepine
BZDs	Benzodiazepines
CME	Continuing medical education
CNS	Central nervous system
CPA	Canadian Pharmacists Association
CPG	Clinical practice guidelines
DCH-MUN	Division of Community Health, Memorial University of Newfoundland
DoHCS	Pharmaceutical Services Division, Department of Health and Community Services
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders –IV-Text Revision

GABA	Gamma-aminobutyric acid
HIC	Human Investigation Committee
INCB	International Narcotics Control Board
NLCAHR	Newfoundland and Labrador Centre for Applied Health Research
NLCHI	Newfoundland and Labrador Centre for Health Information
NLPDP	Newfoundland and Labrador Prescription Drug Program
NPA	Newfoundland Pharmaceutical Association
PDCS	Professional Development and Conferencing Services
SOP-MUN	School of Pharmacy, Memorial University of Newfoundland
S-DDD	Defined daily doses for statistical purposes
W H O	World Health Organisation

## **Chapter 1: Background:**

The increase in the prevalence of benzodiazepine (BZD) usage coincided with the decline of barbiturate use in the 1960s. Since then, there has been a steady increase in the prevalence of BZD prescriptions (Lader, 1991). This was perhaps as clinicians considered (and still consider) benzodiazepines (BZDs) to be the clinically safe alternative to barbiturates, which were until then the choice of sedative-hypnotic agents for sleep disorders.

BZDs have a wide range of actions (anxiolytic, hypnotic, anticonvulsant, amnesic, and myorelaxant) which correspond to their clinical uses. As is the case with many drugs, they have adverse effects (tolerance, dependence, etc.) which occur from their acute and chronic use.

The World Health Organization (WHO) (1996) in its “Programme on Substance Abuse-Rational Use of BZDs” specified the following concerns regarding BZDs: their higher prevalence of use in women and the elderly, their role in poly-pharmacy (in conjunction with other medication), and their being prescribed outside the accepted guidelines. These initial concerns are further augmented by the findings of a recent cross-sectional European study among the general population, which reported that female gender, lower education, and higher age predicted the increased use of BZDs (Demyttenaere et al.,

2008). The risk/benefit ratio of BZDs become less favorable or even adverse as the treatment becomes prolonged, in which case the: efficacy wanes and risks accumulate (Lader, 1999). Long term use may also give rise to therapeutic tolerance which is manifested by the loss of efficacy or by dose escalation to maintain the effects/benefits of the drug (American Psychiatric Association or APA, 1990).

The Health Transition Fund was created by the Canadian government to implement pilot or evaluation studies focused upon health care issues. These studies were carried out between 1997 and 2002. The purpose of these studies was to create evidence-based information for decision-making as well as policy-implementing bodies. The Health Transition Fund report on the pharmaceutical issues (Kennedy & Goyer, 2002) stated that BZD prescribing practices are more difficult to influence than others. Additionally, the report indicated that current practices of prescribing BZDs are not amenable to change by “educational” intervention and in the event that change is desired, more direct methods are needed, such as regulation or financial incentives. A database study conducted by the School of Pharmacy, Memorial University of Newfoundland (SOP-MUN), Newfoundland and Labrador Centre for Health Information (NLCHI), Division of Community Health, Memorial University of Newfoundland (DCH-MUN), Pharmaceutical Services Division, Department of Health and Community Services (DoHCS) and the Newfoundland Pharmaceutical Association (NPA) in 1999 found that

two or more BZDs were inappropriately prescribed to 15.7% (Newfoundland and Labrador Prescription Drug Program or NLPDP) and 17.6% (non-NLPDP) of seniors. Diazepam (a long-acting BZD) was one of the most commonly prescribed inappropriate drugs (Newfoundland and Labrador Centre for Applied Health Research or NLCAHR, 2003).

The existence of inappropriate prescription behaviour and the inability to control these issues through educational means provides justification for the study of the underlying factors which influence the BZD prescribing habits of physicians. This thesis investigates a broad range of factors associated with the prescribing of BZDs. This was achieved by means of a survey of physicians practising in Newfoundland and Labrador to delineate the influences of physician characteristics on their prescribing practices. Exploring the influence of demographic characteristics such as age, gender, physician specialties, years of experience, etc. on BZD prescribing patterns may fill the knowledge gap in relation to the mental health issues faced by patients. It may also be instrumental in the development of effective strategies that help clinicians provide better health care to their patients.

## **Chapter 2: Literature Review:**

In the following section, I will provide an overview of literature pertaining to BZDs; specifically, topics such as epidemiology, pharmacology, and the medical/clinical use of BZDs with focus on physician characteristics will be discussed. I will also present the recommendations of recognised national and international guidelines on the clinical use of BZDs. This section (especially section 2.11) will lay out the scientific reasoning behind the inclusion of each parameter in the survey questionnaire presented in this thesis. Furthermore, the literature in this section will aide in interpretation of the results of the survey and its subsequent discussion (Chapter 4 and 5, respectively).

### 2.1 Literature search for overview on BZDs

The Embase, PubMed, and Cochrane databases were searched for peer reviewed articles and reports using the following keyword(s) either in combination or individually: BZD, BZDs, physicians, prevalence, survey, (ab)use, consumption, epidemiology, prescrib\*, prescription, behaviour, attitudes, perception, variables, factors, mechanism of action, pharmacokinetics, pharmacodynamics, clinical uses, adverse effects, side effects, seniors, elderly, guideline(s). The literature search was limited to articles pertaining to studies on human beings. Articles were only included if they were published in the English language. Additionally, in Embase, articles were included if any of the search term(s)

were the major focus of the publication. Furthermore, books, reference lists at the end of each article, Canadian government websites, and websites focused upon the BZD class of drugs or its indications were parsed to identify relevant information.

## 2.2 Epidemiology of BZD

Global epidemiology explained in the context of manufacture, consumption or via sales data provides information on the prevalence patterns of BZDs but not on the perceptions held by either the prescribers or the consumers of BZDs. Data on the epidemiology of BZDs across regions is presented below to help understand variations observed in its prevalence (especially in the elderly and in developed nations) in global settings.

The WHO (1996) in its “Programme on Substance Abuse-Rational Use of BZDs” reported that: 1. the sales data of BZDs especially in relation to short-acting drugs demonstrated an increase, 2. less than half the number of patients received it for a recognized indication, 3. even fewer patients received it for the advised duration, 4. the prevalence of BZD usage is higher in women and highest in older populations, and 5. older patients filled a higher percentage of BZD prescriptions than younger ones. The report also mentions that the countries with the highest volumes of pharmacy sales in 1989 were, in descending order: the United States, France, Japan, Italy, the United Kingdom, the former German Democratic Republic, Spain, Brazil and Canada. As this

report was not a meta-analysis of the studies but a review article, it was difficult to ascertain the accuracy and limitations of the data. There are wide variations in the definitions of BZD use and the observation period. Its prevalence rate can vary from 2.2% to 17.6%. A Dutch study of a prescription database in a study population of 18-75 year olds demonstrated prevalence rates from 0.2% (short-term users; period of observation:  $\leq 30$  days) to 8.9% (short- and long-term users; period of observation: 1 year). The ratio of female: male (2:1) users remained constant irrespective of the prevalence rate. In the short-term users, 51.1% were older than 45 years; while in the long-term users, 81.7% were 45+. The proportion of 45+ was fairly constant in the long-term users. In contrast, data concerning short-term users demonstrated that the longer the observation period, the lower the proportion of users over 45-years in age (Zandstra et al., 2002). Furthermore, a recently published retrospective database study on pharmacy dispensing habits concluded that 9.1 % of adult Swiss nationals (15 years and older) had used BZDs (period of observation: 6 months) in 2002 (Petitjean, Ladewig, Meier, Amrein, & Wiesbeck, 2007) and 56% of these patients had prescriptions lasting longer than 90 days (defined as long-term use). Long-term BZD prescriptions by physicians (more than 30 days) for any indication contradicts the recommendations of the guidelines developed in various regions (APA, 1990; WHO, 1996; Cooperstock & Hill, 1982).

An Australian study observed that a small but clinically significant number of patients

who usually do not take BZDs received them at the time of discharge from a teaching hospital. Practices like these may put them at risk of becoming long-term users (Howes, Ryan, Fairbrother, O'Neill, & Howes, 1996). Long-term usage of BZDs is observed in developed as well as developing nations. According to a 2007 Norwegian study, 11% of the patient population (seen by general practitioners) suffered from sleep disorders and about one-third of them were prescribed BZDs for more than 6 months (Sivertsen, Nordhus, Bjorvatn, & Pallesen, 2010). The average period of consumption of diazepam was found to be 10 years among chronic users in Brazil in 2001 (Ribeiro, Azevedo, Silva, & Botega, 2007). Additionally, it was revealed to be the most dispensed psychotropic agent in Latvia for 18-89 year olds patients between 2004 and 2007 (Vrublevska, Rukmane, Burmistrs, Sipols, & Muceniece, 2008). The prevalence of BZDs for periods longer than recommended has been documented from consumption (prescription) records and physician perspectives but the rationale behind these actions are not well understood.

In 2000, the International Narcotics Control Board (INCB) released its annual report covering the topic of the over-consumption of internationally controlled drugs. It mentioned that ever since the second half of the 1980s, when governments started to report to the Board on BZDs, the average per capita consumption of BZDs has been much higher in Europe than in any other region. On average, consumption in European countries was three times higher than in the United States. The report also mentions that

the prevalence of anxiety and insomnia and the consumption of sedative hypnotics were growing in the developed countries, with the elderly being the main group of consumers. Another indication of growth in consumption of BZDs by developed nations was observed in 2011, with the United States along with Japan and Spain being the largest importers of BZDs (International Narcotics Control Board or INCB, 2012).

As per the United Nations (2004), the proportion of population in the developed nations is ageing at faster rate than in other regions of the globe. The Beers Criteria was updated to aid practicing clinicians in prescribing drugs which would ensure better outcomes among elderly patients (The American Geriatrics Society 2012, Beers Criteria Update Expert Panel, 2012). Long-acting BZDs are not recommended to be prescribed to the elderly according to the Beers Criteria. Inappropriate prescribing of long-acting BZDs in the elderly population was analyzed to be 5% in Ireland (study population:  $\geq 70$  years) (Cahir et al., 2010) and Sweden (study population:  $\geq 75$  years) (Johnell, Fastbom, Rosén, & Leimanis, 2007); 11.4 % in Japan, (study population:  $\geq 65$  years) (Akazawa, Imai, Igarashi, & Tsutani, 2010) and 21.3% in Taiwan (study of population:  $\geq 65$  years) (Lai et al., 2009). Studies conducted to analyze BZD use among the elderly showed distinct prevalence rates between developed nations such as the United States (13.7%; study population:  $\geq 65$  years) (Yang, Simoni-Wastila, Zuckerman, & Stuart, 2008), Austria (13.8%; study population:  $\geq 75$  years) (Assem-Hilger et al., 2009), and Australia (16%;

study population:  $\geq 65$  years) (Windle, Elliot, Duszynski, & Moore, 2007) and developing countries such as Brazil (21.7%; study population:  $\geq 60$  years) (Alvarenga, Loyola Filho, Firmo, Lima-Costa, & Uchoa, 2008). This distinction may be due to the extent of coverage for BZDs, access to health care resources, self-medication by patients, and the existence and implementation of regulations governing BZD prescriptions in these countries.

With respect to the consumption of zopiclone, it was found that state and privately insured Germans consumed about 2.7 DID in 2008 (Hoffmann, Hies, & Glaeske, 2010). DID is expressed as the defined daily doses per 1,000 inhabitants per day. Zopiclone is preferred over BZDs for the management of insomnia in elderly patients (Siriwardena, Qureshi, Gibson, Collier, & Latham, 2006). Note that zopiclone along with zaleplon and zolpidem are known as ‘z’ drugs or non-BZDs.

In 2012, the INCB published a report in regards to psychotropic substances based on statistical data received from various countries for the year 2011. Following are comments of the INCB (2012) with respect to the BZD class of drugs:

In 1984, Thirty-three BZDs were included in Schedule IV of the scheduling criteria adopted by the World Health Organization Expert Committee on Drug Dependence (1971 convention). This schedule includes substances with liability to abuse but which

pose a smaller, but still significant, risk to public health than substances included in Schedule III. Midazolam was added to Schedule IV in 1990 and brotizolam was added to it in 1995. The document uses ‘defined daily doses for statistical purposes’ (S-DDD) to analyse and report statistical data. This is proposed to be an approximate figure with a ‘certain degree of arbitrariness’ and is not the same as recommended dose in clinical practice. S-DDD for levels of consumption is calculated per thousand inhabitants per day. Some examples of S-DDD are : lorazepam: 2.5mg, diazepam: 10.0mg, clonazepam: 8.0mg, and midazolam: 20.0mg (INCB, 2012).

Twenty-two, twelve, and one BZD were generally classified as anxiolytics, sedatives-hypnotics, and anti-epileptics respectively. Data on the global manufacture and the approximate calculated consumption of anxiolytics did not match: global consumption level (18.5 billion S-DDD) was below the manufacture levels (19 billion S-DDD) of BZD. The level of approximate global consumption (7.7 billion S-DDD) was calculated to be more than the global output (manufacture) level (7 billion S-DDD) for sedatives-hypnotics type of BZDs. One possible explanation for this discrepancy could be an underreporting of manufacturing data. In 2011, global manufacture and approximate calculated consumption of the anti-epileptic clonazepam was calculated to be 975 million S-DDD and 1.01 billion S-DDD respectively. In 2011, Italy was the main manufacturer of all types of BZDs, including anxiolytics, sedatives-hypnotics and anti-epileptics. Lack

of data on BZD manufacture from countries like India and Brazil, which were also its major producers in 2010, may present an incomplete picture on the overall output of BZDs across the world.

Within the anxiolytics segment, alprazolam accounted for 36% of the total manufacture in 2011, followed by diazepam (27%) and lorazepam (19%). Lormetazepam (23%), brotizolam (21%), and triazolam (14%) accounted for more than 50% of the manufacturing in the segment of BZD sedatives-hypnotics. The United States was the largest consumer of anxiolytics such as alprazolam, diazepam and lorazepam, and antiepileptics such as clonazepam. Japan was the largest importer of sedatives-hypnotics such as, brotizolam and triazolam, and Spain was the largest consumer of lormetazepam. The accuracy of this report relies on voluntary submission of statistical data from the governing bodies in each participating state. One hundred and eighty-three out of 196 states are members of the INCB but not every member is compliant with the data submission process. For example: Canada did not report data on the consumption of drugs in schedules III and IV (which include BZDs) for analysis in 2011. Note that 'z' drugs such zopiclone and zaleplon are omitted in this report.

Regional variation in approximate BZD consumption was also observed, with anxiolytics being most consumed in Oceania and sedatives-hypnotics in Europe. Such variation may

be due to the impact of a multiplicity of factors such as health status of the population (US Burden of Disease Collaborators, 2013), age- based demographic differences, country specific regulatory or legislative laws on drug promotion (Mintzes et al., 2013), use of BZDs for different clinical indications and doses, and different prescribing practices as per the local clinical practice guidelines (CPG) among other reasons (Smith et al., 2008).

### 2.3 Epidemiology of BZD use in Canada

Between 1978-83, Canada had the second-lowest total BZD use among several Western countries. Analysis of BZD sales between 1978-87 in Canada, expressed as the defined daily dose (DDD) per 1000 inhabitants per day, showed that the use of these drugs was stable during the first half of the decade at 33 DDD/1000 inhabitants per day. From 1983 to 1987, this number steadily increased reaching 48 DDD/1000 inhabitants per day in 1987. The total use of slowly eliminated BZD declined, whereas the overall use of rapidly eliminated BZD increased ( Busto, Lanctôt, Isaac, & Adrian, 1989). Sales of a prescription drug does not automatically translate into its consumption (Mehuys et al., 2012), but it does provide a snapshot of the prescribing patterns of physicians.

Along with the steady increase in sales of BZDs, the prevalence of long-term use also rose in Canada. In 1989, BZDs were commonly used on a long-term basis, with 66% of the study population receiving at least one prescription. Females received substantially

more prescriptions than males. In the senior population, 80.8% received at least one prescription with triazolam being the most frequently dispensed central nervous system (CNS) drug (74 prescriptions per 1000 people) (Quinn, Baker, & Evans, 1992). A decade and a half later, women and seniors (aged 65 years and over) featured prominently in BZD usage patterns. Also, older age (65 years and over) was associated with long-term (more than or equal to 100 days) use of BZDs (Cunningham, Hanley, & Morgan, 2010).

Therapeutic Letters is a forum targeting therapeutic issues and was developed by the Therapeutic Initiative, a British Columbia Ministry of Health funded program. Their examination claimed BZD use in British Columbia grew between 1996 and 2002 by 11%; with 9.7% of the population receiving at least one prescription for a BZD in 2002 (Therapeutics Initiative, 2004). Given that the study could not be appraised critically due to the omission of details such as study methodology, it was difficult to ascertain the validity of their findings. However, a peer-reviewed article (comprising of a prescription database study) concluded that the BZD prevalence among British Columbians increased to 8.4% in 2006 from 7.8% in 1996 (Cunningham et al., 2010).

Therapeutics Letter further claimed that the seven most used BZDs were lorazepam (Ativan<sup>®</sup>), clonazepam (Clonapam<sup>®</sup>), zopiclone (Imovane<sup>®</sup>), oxazepam (Oxpam<sup>®</sup>), alprazolam (Xanax<sup>®</sup>), diazepam (Valium<sup>®</sup>) and temazepam (Restoril<sup>®</sup>). Five out of these seven have half-lives >10 hours (Therapeutics Initiative, 2004). A 2003 claims database

analyses reported different statistics: 8 different types of BZDs accounted for 90% of the prescribed BZDs for seniors (aged 65 years and older) in Nova Scotia with 19% of the prescribed BZDs having a long half-life (Smith et al., 2008). A lower percentage of males versus females (7.1% and 12.2%, respectively) received a BZD prescription in British Columbia (Therapeutics Initiative, 2004). This claim was validated by findings in a study by Cunningham et al. (2010) which concluded that more women received BZD prescription for long (more than or equal to 100 days) and short (less than 100 days) term periods in British Columbia in 2006. 25.4% of the population aged 65 and over in Quebec reported using BZDs in 2005-2006 and approximately 9.5 % of them were identified as having substance abuse issues (as per DSM-IV-TR criteria) (Voyer , Prévile, Cohen, Berbiche, & Béland, 2010). While Cunningham et al. (2010) noticed a decrease in BZD prevalence in the elderly (aged 70 years and older), they did observe an increase in BZD use in the middle aged (45 to 64 years) cohort. Comparative data showed that elderly Nova Scotians (aged 65 years and over) used BZDs twice as much as the elderly population in Australia from 2000 through 2003 (Smith et al., 2008). Though the explanation for regional variations in BZD prescribing patterns has not been studied, it may be due to factors such as patient demographics, disease epidemiology, access to health care etc. Note that the BZD-like drugs, which include zopiclone and zaleplon, were included in the data analyses of the following studies: Therapeutics Initiative, 2004; Smith et al., 2008; Cunningham et al., 2010.

Sales and prescription data demonstrate the prevalence or incidence of a drug in given populations. However, they neither elicit physicians' perspective on medication use nor do they examine the factors that influence the prescriber's decision making process to prescribe a drug to patients. In this case, a self reported survey among prescribers is critical to elicit such thoughts and perceptions.

#### 2.4 Epidemiology of BZDs in Newfoundland and Labrador and the barriers faced by prescribers

The prescription of BZDs in the elderly necessitates a cautious and careful approach as they are more sensitive to the potential side effects of these drugs on account of the altered pharmacokinetics and pharmacodynamics. In an effort to elucidate the prevalence of potentially inappropriate medication use in seniors of this province, analyses conducted by SOP-MUN, NLCHI, DCH-MUN, DoHCS & NPA reported that 15.7% and 17.6% of NLPDP and non-NLPDP seniors, respectively, were taking two or more BZDs (NLCAHR, 2003). BZDs bind on the same receptor. Hence it is necessary to avoid prescribing more than one BZD to the same patients on account of their different affinities to these receptors.

The Health Transition Fund report (Kennedy & Goyer, 2002) reported findings from their studies indicating that BZD prescribing practices are more difficult to influence than others, while also illustrating that current BZD prescribing practices are not amenable to

change by “educational” interventions. This report did not describe the study parameters utilized, hence it was difficult to gain insight into its sample population and methodology of the interventions used to influence BZD prescribing habits. The report further mentioned that if change is desired, other more direct methods are needed, such as regulation or financial incentives. This conclusion is contrary to the study findings by Hayward, Guyatt, Moore, McKibbin, & Carter, (1997) who found that peer consultation was the most cited source of information to make clinical decisions. On the other hand, (provincial) insurance plans were the least accessed tool to influence these clinical decisions. Additional statements in the Health Transition Fund report (Kennedy & Goyer, 2002) were that the measured impact on prescribing for BZD in the Elderly project (NA221) was disappointing as no changes were seen in Newfoundland, which was also confirmed by the findings of the Sleep and Anxiety Management Project (BC201-01). More physicians increased rather than decreased their BZD prescribing patterns, in relation to number of patients, volume of BZDs, and number of prescriptions (Kennedy & Goyer, 2002). An equivocal response was observed in the study by MacCarthy, Kallstrom, Kadlec, & Hollander (2012). Though the study by Hayward et al. (1997) postulated peer consultation as a factor which influences the practice patterns of prescribers, general practitioners reported a decrease (41%) or an increase (20.8%) respectively in prescribing medications after attending the peer to peer program addressing adult mental health topics (MacCarthy et al., 2012). Implementation of

evidence-based medicine gained traction in Canada around the 1990s, but lack of prevalence of optimal prescribing habits suggests that such evidence though disseminated are not fully embraced by prescribers (Evidence-Based Medicine Working Group, 1992; Pimlott et al., 2003). Lack of time and inadequate training acted as impediments to Canadian resident surgeons practicing evidence-based medicine (Bhandari et al., 2003).

Though the practice characteristics of resident surgeons differ from general practitioners' and other specialties including psychiatry, their concern about time constraints was identified as a barrier towards the adoption of guidelines by Canadian physicians as well (Hayward et al., 1997). Administrative measures such as electronic monitoring via drug alerts and integrated prescription systems providing real time access to prescription records of patients can reduce inappropriate prescribing to elderly patients aged 65 years and older (Dormuth, Miller, Huang, Mamdani, & Juurlink, 2012; Tamblyn et al., 2012). Though administrative measures to reduce inappropriate prescriptions are effective, modulating prescriber habits remains critical to better overall quality of care for patients. Administrative strictures on drug use are overridden when the prescriber decides that the benefits outweighs the risks associated with the therapy (Tamblyn et al., 2012); thus gaps in prescriber education should be addressed to reduce dissonance between clinical evidence and prescribing practice among the elderly. Eliciting views from stakeholders in the Canadian health care system may help to gain insights into their perceived barriers,

variables of importance, and suggested facilitators to providing optimized patient care. Subsequent implementation of multiple interventions targeting health care stakeholders may hold the key to the conundrum of resistance to the uptake of evidence-based medicine.

Inappropriate prescriptions and the inability to influence prescription behavior through educational means justify a study to understand the underlying factors associated with these actions. This type of survey will help to objectify the variable(s) which plays a role(s) in the prescription of BZDs.

### 2.5 Mechanism of action of BZDs

BZDs potentiate the effects of gamma-aminobutyric acid (GABA) by binding to the gamma subunit of GABA-A (protein complex) receptors. In contrast to BZDs, GABA binds to the alpha subunit of GABA-A receptors. GABA is an inhibitory neurotransmitter which is produced in brain. In general GABA influences a calming effect on the brain as approximately 40% of the millions of neurons all over the brain respond to GABA. This natural action of GABA is augmented by the BZDs which act to enhance the inhibitory influence on neurons. GABA binds with its receptors to produce an allosteric or structural change. These GABA bound neurons allow a greater than normal amount of chloride ions to pass to the inside of neuron. This leads to a decrease in the excitability of the said

neurons by other neurotransmitters. The reduction in response by GABA bound neurons to the other neurotransmitters causes the 'quietening effect' of GABA. BZDs binds at its receptors, situated in the protein complex on the outside of the neuron. This complex also contains the GABA receptor. It is pertinent to note that BZDs act by binding to a different subunit of the receptor i.e. it does not replace GABA at the neuronal receptor as the receptor has different binding sites for GABA and BZD, respectively. The combination of a BZD at this site potentiates the actions of GABA, allowing more chloride ions to enter the neuron and further increasing its unresponsiveness to other neurotransmitters. Various subtypes of BZD receptors have slightly different actions. One subtype (alpha 1) is responsible for sedative effects, while another (alpha 2) for anti-anxiety effects. Moreover, both alpha 1 and alpha 2 subtypes, as well as alpha 5, elicit anticonvulsant effects. The receptors in specific neuroanatomic areas seem to mediate specific clinical effects. Hence, it is likely that receptors in the cerebellum mediate ataxic effects, receptors in the brain stem or cortex mediate sedative effects, receptors in the hypothalamus mediate neuroendocrine effects (e.g., decreases in adrenocorticotrophic hormone, increases in growth hormone etc), receptors in the forebrain and hippocampus mediate amnesic effects, and receptors in the amygdala, hippocampus and other limbic brain areas mediate anti-conflict and anti-anxiety effects. Different proportions of the receptors must be occupied to produce different clinical effects ( Roy-Byrne & Cowley, 1991; Woods, Katz, & Winger, 2000).

An indirect effect of both GABA and BZDs is a reduction in the brain's output of excitatory neurotransmitters such as norepinephrine (noradrenaline), serotonin, acetylcholine and dopamine. These excitatory neurotransmitters ensure optimal functioning of a human body. Furthermore, they are necessary to meet the social, biological and physical challenges faced by humans in their daily life. Some of vital functions which are affected by the excitatory neurotransmitters include: normal alertness, memory, muscle tone and coordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control. Furthermore, there are non-GABA receptors present in the kidney, colon, blood cells and adrenal cortex which could be influenced by certain BZDs. The adverse effects of BZDs is linked to its dosage and actions on a range of receptors (Ashton, 2002).

## 2.6 Pharmacokinetics of BZDs

The clinical effects of BZDs are determined by pharmacokinetic and pharmacodynamic factors. The pharmacokinetic profile is an important consideration when prescribing multiple doses. It should be noted that it takes five half-lives to attain a steady-state blood level and once attained, it takes five half-lives of the drugs to be more than 90% eliminated from the body after dosing has been discontinued.

The onset and duration of action of BZDs are related to the mode of administration, the dissolution of the formulation, absorption, uptake in CNS and binding to form the BZD

GABA receptor complex (Lader, 1987).

The absorption of BZDs are rapid and almost complete from gastrointestinal tract. Unlike GABA which cannot pass through the blood brain barrier (BBB), BZDs can cross the BBB by passive diffusion and reach equilibrium in the CNS. The amount of drug in the brain is directly proportional to the unbound concentration in plasma.

BZDs are divided into two groups with respect to hepatic metabolism:

1. one which undergoes biotransformation or the Phase I process including mainly oxidation and dealkylation, and
2. Phase II process of conjugation to form glucuronides, sulfates, and acetylated compounds.

BZDs can undergo both Phase I and Phase II metabolism (diazepam, chlordiazepoxide, and flurazepam) or Phase II alone (lorazepam, oxazepam, and temazepam). Drugs metabolized via Phase II processes alone are better tolerated than Phase I/Phase II drugs by patients with liver impairments, such as alcoholics. Also, Phase I metabolism slows with age. Elderly patients taking BZDs which are metabolized via Phase I as well as Phase II processes are more likely to experience more adverse effects of these drugs due to diminished hepatic biotransformation/elimination.

Biotransformation produces a number of active metabolites. Each metabolite possess its

own kinetic properties with individual clinical profiles (therapeutic and toxic effects). For example, chlordiazepoxide has the following clinically active metabolites: desmethyl chlordiazepoxide, demoxepam, desmethyl diazepam and oxazepam; other examples of BZDs with active metabolites include diazepam (active metabolites: desmethyl diazepam, temazepam, oxazepam), halazepam, clorazepate, and prazepam. Lorazepam, oxazepam and temazepam do not undergo Phase I biotransformation and hence do not produce active metabolites.

BZDs which are rapidly cleared from the body are short-acting agents while the long-acting agents are the ones which remain in the body for a longer duration.

The elimination half-life is the time taken by the drugs to fall to 50% of the original concentration. The active metabolites of these drugs have their own elimination half-life, usually  $\geq 30$  to 50% longer than the parent compound. It is pertinent to note the relation between half-life and dependence, which is one of the adverse effects of BZDs. High potency BZDs with short half-life (alprazolam, lorazepam and triazolam) increase the risk of dependence (Nelson & Chouinard, 1999). The elimination half-lives of the BZDs vary greatly. Lorazepam, oxazepam, temazepam and lormetazepam have half-lives of about 6-24 hrs. As most of each dose is eliminated within a relatively short span of time, these compounds are suitable for acute, short-lived anxieties and insomnia. Triazolam has a half-life of less than four hours which makes it the shortest acting drug in the arsenal of

the BZD class of medications. Although flurazepam itself has a short half-life, it has a long-acting active metabolite which makes it unsuitable for the management of short lived anxiety or insomnia (APA, 1990).

### 2.7 Pharmacodynamics of BZDs

BZDs achieve inhibitory effects by enhancing the effects of GABA. They bind to a gamma subunit of the neuronal receptor located in the CNS causing more influx of chloride ions into the neuron thereby making it hyperpolarized and less sensitive to excitatory neurotransmitters. Much as the pharmacokinetic properties differ among individuals, the pharmacodynamics may display large interindividual differences which are reflected by variations in BZDs sensitivities and the rate of development of tolerance and dependence. The receptor characteristics may be affected by prior use of BZDs, by other drugs and by patients' clinical state (Roy-Byrne & Cowley, 1991).

### 2.8 Adverse effects of BZDs

The population of seniors (aged 65 years and over) in Newfoundland and Labrador is set to reach nearly 20 % of the total provincial population by 2016 (Government of Newfoundland and Labrador, 2006). Monitoring the health care of seniors is necessary as they are at an increased risk of drug-drug interaction(s) on account of being prescribed medications from different therapeutic classes (The American Geriatrics Society 2012

Beers Criteria Update Expert Panel, 2012). The survey population (prescribers) described in this thesis is expected to continue providing health care to the changing demographics of Newfoundland and Labrador. Understanding the risks and adverse effects associated with BZDs will help to better understand the context of this study: elicitation of variables associated with BZD prescribing. The following sections elucidate the risk(s) faced by the (younger) adult population and seniors who consume BZDs.

### 2.8.1 Tolerance, dependence and withdrawal

The known adverse effects of BZDs, which are physiologic dependence and tolerance, are clinical conditions which are related to the pharmacodynamics of these drugs.

There are two types of dependence: physiologic and psychological. Physiologic dependence is generally subsequent to prolonged drug exposure; the exposure time required to produce physiologic dependence may vary with different BZDs. This is demonstrated by ‘objective’ physiologic alterations when BZDs are stopped.

Psychological dependence denotes ‘subjective’ experiences of ‘craving for drug’ and an ‘unpleasant sensation’ when the drug is discontinued. Both, physiologic and psychological dependence may coexist (Greenblatt & Shader, 1978).

A variety of parameters are responsible for influencing the modification of the CNS functions. Some of the important factors are: drug dose and duration, pharmacological

differences in the derivatives, and predisposition of different users. This adjustment to the CNS is manifested via dependence. BZDs are classified according to their potency. Since high potency BZDs have a greater affinity to receptors, they produce a similar effect at a lower dose. High potency BZDs (with short half-life) such as alprazolam, lorazepam and triazolam tend to increase risk of dependence (Nelson & Chouinard, 1999).

Tolerance is manifested by diminished response to drug administration after multiple doses and necessary dose escalation in order to achieve the effect of the previous dose. Tolerance can be of two types: receptor site tolerance/adaptation, characterised by changes in drug-receptor interactions due to prolonged exposure of the drug (at any concentration) to the CNS receptor. The other type of tolerance is metabolic or pharmacokinetic tolerance denoting 'the effect of prolonged drug exposure on its own kinetic properties' (Greenblatt & Shader, 1978).

Pharmacokinetic variables of BZDs such as rate of absorption, lipophilicity and receptor affinity and patient variables influence the rate, extent and time for the onset of tolerance. Since long length exposure of the receptor to BZDs facilitates the onset of tolerance, prescribing BZDs at a low dose and for short periods of time may help to avoid it (Nelson & Chouinard, 1999).

Withdrawal of a BZD leads to discontinuation symptoms: recurrence, rebound, and

withdrawal. Recurrence symptoms are the same as the original symptoms for which a BZD was prescribed. They are observed after the BZD is terminated. Rebound symptoms are similar to recurrence symptoms, except that they are more intense. Withdrawal symptoms are novel symptoms dissimilar from the original ones and are experienced after abrupt discontinuation of a BZD (Nelson & Chouinard, 1999).

Short-acting BZDs are preferred for managing transient insomnia and short-term anxiety amongst others clinical conditions. However, abrupt discontinuation of short and intermediate acting BZDs can lead to the emergence of rebound symptoms. Endogenous neurobiological compensatory mechanisms are activated to manage the effects of the BZD receptor complex. Abrupt withdrawal of any drug produces withdrawal and rebound effects on account of the unrelenting compensatory mechanism which readjusts itself to the new drug-free situation after a certain time interval. However, when the amount of BZD is decreased in a deliberate systematic method, the aforementioned mechanism readjusts itself accordingly before finally returning to baseline. Thus, in order to eliminate the risks of developing withdrawal or rebound symptoms, guidelines recommend against the instant withdrawal of BZDs. Slow tapering off of a BZD after switching the patient to a long-acting BZD is the preferred protocol of discontinuation of BZDs (Nelson & Chouinard, 1999).

### 2.8.2 Cognitive effects and psychomotor effects

Acute BZD administration causes sedation, drowsiness, psychomotor slowing, anterograde amnesia and difficulties in learning new material while chronic use leads to tolerance, impaired visuospatial and visuomotor abilities, decreased intelligence quotient, motor coordination, psychomotor speed, speed of information processing, verbal learning and concentration. Most of these effects show improvement after discontinuation of the therapy, but the improvement never rises to that of non-users of the drug. Hence, patients should be advised of the possible cognitive effects before initiating treatment. Verbal learning and remembering information gathered after the initiation of BZDs was also found to be impaired; though memory of information stored prior to BZD administration was not affected (Lader, 1999; Stewart, 2005).

The ability of BZDs to impair cognition and psychomotor function is important not only for the patient's health but also for the safety of co-workers. Hence, careful prescribing should be practiced by taking into account individual personality traits, psychiatric illness and lifestyle of the patient, or in workers performing complex psychomotor functions such as driving, handling machinery, etc. (Roy-Byrne & Cowley, 1990).

BZDs may impair memory in two distinct ways: by causing acute amnesia (anterograde

amnesia) for a brief period of time following high dose parenteral administration and by impairment of recall that occurs during chronic BZD administration.

Memory impairment also depends upon the dose and route of administration as a higher dose and intravenous administration may cause increased impairment. The differences in BZD users is also a factor in affecting memory since elderly patients and those with a history of sedative hypnotic drug use are more likely to report impairments. Alcohol can potentiate the actions of BZDs through direct effect on the chloride ion channels associated with the BZD receptor. At higher doses, alcohol and BZD use fail to produce any effect on account of maximum stimulation of chloride channels but at low doses they mainly have an additive effect (Roy-Byrne & Cowley, 1991).

BZDs may impair psychomotor functioning and consequently lead to impaired automobile driving when taken in acute as well as high doses. However, automobile driving is neither predictably nor consistently impaired by repeated therapeutic doses of BZDs and its also likely that therapeutic doses alone do not play a large role in accidents. Alcohol and advanced age increase the psychomotor toxicity of BZDs when taken on an acute or long-term basis (APA, 1990).

The short half-life of BZDs in chronic use is found to increase the risk of cognitive impairment because notwithstanding the development of tolerance to psychomotor

impairment, cognitive impairment is observed subsequently after the use of these drugs (Roy-Byrne & Cowley, 1990).

### 2.8.3 Falls/Hip fractures in seniors

The diminished capacity of the Phase I process in the elderly leads to accumulation of BZDs in the body. Accumulation of BZDs in the body may expose the patient to serious adverse effects. In the community dwelling elders, the odds ratio for BZD associated falls is 1.48 (Leipzig, Cumming, & Tinetti, 1999). The number of medications taken by the elderly is directly proportional to the risk of falls (Cumming, 1998). Also, psychotropic medications have a strong causal relationship with falls in the elderly (Cumming, 1998). Epidemiological evidence shows that while approximately 10% of hip fractures could be due to BZDs, the use of BZDs significantly increases the risk of hip fracture by at least 50% in the elderly. In addition, the health care system and patients bear the high burden of mortality and morbidity caused by falls. Hence, it would be prudent to prescribe cautiously to older patients with their prescriptions meriting continuous supervision (Cumming & Le Couteur, 2003).

## 2.9 Substance abuse

BZD abuse can be defined by identifying two patterns: deliberate abuse to achieve euphoric effects and unintended misuse by patients who use the prescribed BZDs for

long-term inappropriately or at a higher dose than required (O'Brien, 2005).

Deliberate abuse of BZDs usually starts with the misuse of prescriptions (which are either obtained from licensed medical practitioners or forged or bought) and 'is usually a recreational and thrill seeking behavior'. Recreational abuse of BZDs alone is uncommon and is usually part of polydrug abuse (especially to augment methadone) in drug abuse and alcohol abuse populations. People who use BZDs for euphoric effects also use them for treating the withdrawal symptoms/adverse effects of alcohol or substance abuse (O'Brien, 2005).

The prescription of BZDs in persons with a history of substance drug abuse should be ideally avoided. But if deemed necessary, the use of BZDs in any person with actual or hypothetical predisposition to chemical dependence should be accompanied by constant and close monitoring for any signs of abuse or dependence such as tolerance, which includes escalation of dose and insistence on concomitant use of alcohol (Roy-Byrne & Cowley, 1990).

#### 2.10 Guidelines for prescribing BZDs

As this study is part of a larger study which includes American physicians, the recommendations outlined in this section include those made by the WHO (1996), the Ministry of National Health and Welfare, Canada (Cooperstock & Hill, 1982), and the

American Psychiatric Association (APA, 1990).

The prescription of BZDs is a complex process where a variety of factors should be taken into consideration before initiation of the prescription so that the patient can obtain maximum benefit from the therapy while experiencing no (ideally) or minimal harm.

The guidelines, in general, recommend the following:

1. Before prescribing, the physician should evaluate the patient using screening instruments, clinical interviews, general medical evaluation, physical examination, and laboratory procedures (to rule out liver/kidney dysfunctions) (WHO, 1996; Cooperstock & Hill, 1982).
2. The patients should be presented with alternate therapies for their clinical condition(s) (WHO, 1996).
3. The choice of BZDs should be made on the basis of elimination half-life, rate of absorption, metabolism of drug, and the adverse events expected to be experienced by the patient after ingestion (APA, 1990; WHO, 1996).
4. The lowest dose to achieve the desired outcome for the shortest duration necessary should be prescribed (APA, 1990).

5. Long-term treatment should be practiced when benefits outweighs the risk (WHO, 1996; APA, 1990).
6. Treatment should be regularly reviewed for long-term users (APA, 1990).
7. As sensitivity to BZDs increase with age, the elderly should be prescribed these drugs carefully (APA, 1990; Cooperstock & Hill, 1982). Long-acting BZDs with active metabolites should usually be avoided in the elderly (e.g. diazepam, chlordiazepoxide, flurazepam, nitrazepam). When BZDs are prescribed in older people, short-acting BZDs are preferred (Cooperstock & Hill, 1982).
8. BZDs should be avoided in pregnant and lactating women (Cooperstock & Hill, 1982). According to the Centre for Addiction and Mental Health (2009), the non-BZD hypnotic zopiclone may be used during breastfeeding and, for short-term use, during pregnancy.
9. Children can be given a BZD for a brief period if deemed necessary for seizures and in anaesthetic procedures (WHO, 1996; Cooperstock & Hill, 1982).
10. Before prescribing, the physician should ascertain any drug abuse tendencies in the patient (APA, 1990).
11. The guidelines recommend that BZDs be prescribed for one to two weeks for short-term anxiety as it decreases the chances of dependence and provides the physician with

the chance to monitor individual dose-response (Cooperstock & Hill, 1982).

12. For transient insomnia caused by disruption of circadian rhythms (such as in overnight travel, rapid transit over time zones, alteration of shift work or temporary admission to hospital), a hypnotic drug with a short duration of action and few residual effects would be appropriate to use on one or two occasions (WHO, 1996). For short-term insomnia resulting from temporary environmental stress, hypnotics may occasionally be indicated, but should be prescribed in low dosages for one or two weeks only, or intermittently. As with their recommendations for anxiety and, (severe) insomnia too, BZDs may be prescribed for one to two weeks (Cooperstock & Hill, 1982).

13. The Canadian guidelines (Cooperstock & Hill, 1982) further recommend the use of BZDs in the treatment of some types of continuous seizures, and for a variety of neuromuscular disorders such as cerebral palsy and tetanus.

14. BZDs are safe and effective drugs to use in alcohol withdrawal. However, the side effects of memory impairment, drowsiness, and lethargy as well as the potential for dependence means that they may interfere with other therapeutic approaches dealing with stress management, coping behavior or drinking behavior modification. Therefore, BZDs used for this purpose should be in reduced dosages over a relatively short period of time, usually for no more than two weeks (WHO, 1996; Cooperstock & Hill, 1982).

15. Anaesthesia: Diazepam can be used as an intravenous anaesthetic during minor surgery, and in a variety of diagnostic tests generally administered in hospitals (Cooperstock & Hill, 1982).

### 2.11 Rationale behind the inclusion of variables in the questionnaire for the survey examining BZD prescribing patterns of physicians in Newfoundland and Labrador

The survey questionnaire is an adapted version of the questionnaire developed by the Maine Benzodiazepine Group. The respondents were measured on individual and practice characteristics, (factors influencing) prescribing patterns, guidelines awareness and uptake, and self –medicating behaviour. The data collection on the aforementioned parameters was to help me compare the individual and practice characteristics of physicians with other parameters and discover any significant patterns in BZD prescribing by physicians in Newfoundland and Labrador.

In the following sections, I will be discussing the relevance of each parameter (Q1-17) in the questionnaire in context of the Canadian health care landscape only. I have accessed and critically appraised observational (quantitative and qualitative) and interventional studies published in peer reviewed journals only. The key words used to search databases (mentioned in section 2.1) for the aforementioned literature search were: the parameter

under study (for example: gender), region under study (Canada), and focus of survey : ‘benzodiazepines’ , and ‘physicians’. Additionally, I used the following key words: ‘mental’ or ‘psychiatric’ or ‘neurolog\*’. I have also gathered information from data published on government and professional bodies’ websites.

### 2.11.1 Gender of physicians

Gender of Canadian physicians was identified as one of the contributors to differing medical practice patterns (Garfinkel et al., 2004; Weizblit, Noble, & Baerlocher, 2009). Though neither survey directly addressed BZD prescribing habits of prescribers, it focused on questions concerning the quality of care provided to patients with mental health ailments. Gender-based variation in patients seen by clinicians and the different prescribing patterns of the clinicians may have implication(s) on the treatment outcomes among Canadians with mental health issues; for example: Garfinkel et al. (2004) reported that, among psychiatrists, women see more patients with anxiety disorders than men and men prescribe more pharmacotherapy to patients than women. Furthermore, in 1990, a prescription database study revealed that male physicians (average of 65.2 BZD prescriptions) prescribed more BZDs to elderly patients (aged 65 years and older) than their female counterparts (average of 32.3 BZD prescriptions) (Thomson & Smith, 1995).

With more women entering the physician workforce in Canada, especially in the field of general/family practice (Canadian Institute for Health Information (CIHI), 2012), it becomes pertinent to explore the differences or similarities in BZD prescribing patterns of male and female physicians (Q1) in Newfoundland and Labrador.

### 2.11.2 Practice setting of physicians

A survey reported that general practitioners cited multidisciplinary settings as a facilitator to management of mental health concerns (Fleury, Farand, Aubé, & Imboua, 2012). Similarly, in a qualitative study, general practitioners reported multidisciplinary settings to be an enabling factor and lack of group practice settings to be a barrier to management of mental health disorders (Fleury, Imboua, Aubé, Farand, & Lambert, 2012). Evolving general practice is leading to almost half (40%) of physicians' time being spent on adults with mental health issues (Collins, Wolfe, Fisman, DePace, & Steele, 2006). Depression, anxiety, and insomnia amongst others are considered mental health issues. Use of BZDs in such conditions is prevalent among Canadian patients (Bartlett, Abrahamowicz, Grad, Sylvestre, & Tamblyn, 2009; Cunningham et al., 2010; Hogan, Maxwell, Fung, & Ebly, 2003). This prevalence brings forth the relevance of studying the effect of practice settings (Q6 and Q7) of the prescribers on their BZD prescribing habits.

### 2.11.3 Experience of physicians

Prescriber characteristics such as year of graduation (Q3), which reflects the standards of basic training received, and years of practice (Q4), which reflects the experience in patient interaction and prescribing of medications, are parameters which contribute towards the selection of treatment modality(ies) for disease management (Sketris, Langille Ingram, & Lummis, 2007). A 1994 published study found that there was no significant association between prescribing for elderly patients with physician characteristics such as length of practice (in years), age, and practice size (Davidson, Molloy, Somers, & Bedard, 1994). However, a recent study (Egualé et al., 2012) reported differing prescribing patterns with respect to graduation year of physicians: medical graduates of recent years (1980-1989 and 1990-2004) (odds ratio: 1.08 and 1.08 respectively) in comparison to earlier years (1960-1979) were significantly more likely to prescribe off-label medications. The same study found that more than 90% of the off-label prescriptions for clonazepam and oxazepam have been associated with its off-label use without any supporting scientific evidence. Furthermore, 43.6% of the patients with insomnia and 46.5% of the patients with generalized anxiety disorders were analyzed to be prescribed off-label drugs including BZDs. Though this study focused upon off-label use of medications, the statistically significant associations between insomnia and clonazepam along with generalized anxiety disorders and oxazepam merits the inclusion

of parameters which study the effect of length of practice (and time since completion of medical studies) of the prescribers.

2.11.4 Cohort (specialty) of physicians, types of BZDs prescribed, and indications for the use of BZDs

In Canada, more than half of the physician workforce is accounted for by general practitioners (CIHI, 2012). From 1997 to 2006, family physicians were increasingly prescribing more medications (including psychotropic medications) to older Canadians (Bajcar et al., 2010). More than half of the general practitioners in Quebec, Canada were found to be either monitoring the pharmacotherapy (61.1%) or providing ‘support therapy’ to patients (59.3%) with common mental health issues (Fleury, Farand, et al., 2012). BZDs are mainly labeled for mental health indications and as anti-convulsant medication (Canadian Pharmacists Association or CPA, 2008). In this survey (Q8), examining BZD prescribing trends with respect to prescribers’ specialties such as neurology, psychiatry, and family medicine (general practice) will help me compare the similarities and differences in the prescribing patterns of each cohort of physicians. It is pertinent to note that this survey was mailed to all physicians registered with Professional Development and Conferencing Services (PDCS), Faculty of Medicine, Memorial University of Newfoundland and Labrador, to examine the prescribing trends of BZDs

within all cohorts of physicians.

The list of BZDs (Q10) presented in this survey matches the approved list of drugs in Canada (Table 2.1) and includes BZDs (estazolam and quazepam) available in the United States. It has been noted that direct to consumer advertising in the United States has significant impact on the Canadian stakeholders' (patients) perceptions of drug therapy (Mintzes et al., 2003 ). Furthermore, different BZDs have varying levels of risks for fall related injuries in the elderly; for example, lorazepam was not only the highest prescribed BZD among new elderly users (n= 10,197) but also had the largest cohort of fall related injuries (n= 841) when compared to other BZDs (Sylvestre, Abrahamowicz, Capek, & Tamblyn, 2012). Given this context, understanding the extent of prescribing for each BZD (Q10) in Newfoundland and Labrador will help me understand the prevalence of available BZDs from the prescriber's point of view. The pharmacological actions of BZD (anxiolytic, hypnotic, anticonvulsant, amnestic, and myorelaxant) are generally in congruence with its approved indications (see Table 2.1). Indications (Q11) listed in the questionnaire reflect the approved indications of BZDs (see Table 2.1 ) and indications listed in the review article by Longo & Johnson, 2000. Also, off-label use of BZDs has been noted for depression, grief reaction, nausea (anti-vertigo), and severe agitation associated with mania (bipolar disorder) (Egualé et al., 2012; Rechinsky, 2011).

2.11.4.a Indications and clinical uses of BZDs: Though BZDs are mainly associated with symptom management of insomnia and anxiety, they are also used in other clinical conditions. As mentioned earlier on page 1, BZDs have five pharmacological actions. They are therefore clinically used in the treatment of conditions which are associated with these aforementioned pharmacological actions. Following are the clinical uses of BZDs (Longo & Johnson, 2000):

1. Anxiety disorders

- a. Acute anxiety
- b. Generalized anxiety disorder
- c. Panic disorder
- d. Phobias (social, simple)
- e. Post-traumatic stress disorder
- f. Obsessive-compulsive disorder
- g. Anxiety associated with medical illness: cardiovascular, gastrointestinal, somatoform disorder

2. Insomnia

3. Convulsive disorders

a. Acute status epilepticus

b. Neonatal seizures or febrile convulsions

c. Preeclampsia

d. Tetanus

e. Adjunct to other anticonvulsants

4. Amnestic (before surgery or procedure)

5. Spastic disorders and other types of acute muscle spasm: cerebral palsy, multiple sclerosis and paraplegia secondary to spinal trauma

a. Involuntary movement disorders

b. Restless leg syndrome

c. Akathisia associated with neuroleptic use

d. Choreiform disorders

e. Myoclonus

6. Detoxification from alcohol and other substances

7. Other adjunctive uses: Surgery, Dentistry

8. Diagnostic studies, such as computed tomography, magnetic resonance imaging, and endoscopy

9. Cardioversion and Chemotherapy

Table 2.1 (see below) is adapted from eCPS, which outlines the labeled indications for each type of BZD which is available in Canada (CPA, 2008).

Table 2.1 Labeled indications for BZDs available in Canada.

Drug	Anxiety Disorders	Insomnia	Perioperative Medication	Seizure Disorders <sup>a</sup>	Skeletal Muscle Spasticity	Alcohol Withdrawal
Alprazolam	Yes					
Bromazepam	Yes					
Chlordiazepoxide	Yes					
Clobazam				Yes		
Clonazepam				Yes		
Clorazepate	Yes			Yes		Yes
Diazepam	Yes		Yes	Yes	Yes	Yes
Flurazepam		Yes				
Lorazepam	Yes		Yes	Yes		
Midazolam			Yes			
Nitrazepam		Yes		Yes		

Drug	Anxiety Disorders	Insomnia	Perioperative Medication	Seizure Disorders <sup>a</sup>	Skeletal Muscle Spasticity	Alcohol Withdrawal
Oxazepam	Yes					Yes
Temazepam		Yes				
Triazolam		Yes				

Note: a: Used in adults and children.

The present survey also includes zopiclone, zolpidem and zaleplon (also known as “Z” drugs or BZD-like / non-BZD drugs). They are primarily used to manage insomnia.

Zopiclone and zolpidem along with BZDs are approved as sleep aid medications (Health Canada, 2009).

#### 2.11.5 Enquiry into reason(s) to continue prescribing BZDs beyond 90 days

A 5-year database (1990-1994) study examined the BZD prescription patterns in new users among the elderly Canadian population aged 65 years and older (Bartlett et al., 2004). Though this study excluded ‘geographically isolated’ patient groups in Quebec and hospitalized patients and did not examine actual BZD consumption, it did capture data pertaining to 89% of the elderly population. The following results were reported:

45% of the patients in this study had a single period of continuous BZD use for more than 30 days. The mean number of distinct periods for uninterrupted BZD use was 3.2 (standard deviation 3.3). As the majority of patients had greater than 1 period of uninterrupted BZD use, assessing the reasons for prescribing BZDs beyond 90 days (average duration of single period of uninterrupted BZD use (minimum days) X average number of periods of continuous use: 30 X 3: 90 days) would elucidate the prescriber's viewpoint to continuously prescribe BZDs (Q12) for more than the recommended period of time (Cooperstock & Hill, 1982). Furthermore, long-term BZD use or inappropriate prescriptions have been defined as BZD use beyond 90 days (Preville et al., 2012).

#### 2.11.6 Prescribing more than one BZD to the same patient

As discussed in section 2.4, inappropriate prescriptions of two or more BZDs were found among Newfoundland and Labrador seniors (NLCAHR, 2003). Question 13 (a and b) of the survey is to elicit the prescriber's point of view regarding the use of more than one BZD in the same patient and the reasons behind these actions.

#### 2.11.7 Factors influencing BZD prescribing habits of physicians in Newfoundland and Labrador

Health Council Canada's background paper 'Optimal Prescribing and Medication Use in

Canada' acknowledges suboptimal prescribing in Canada and discusses interventions to improve it. As per the paper, the decision-making process for a prescription is influenced by variables associated with: 1. prescriber demographics and attitudes, 2. practice setting, 3. medication, 4. patient, and 5. external factors such as detailing by pharmaceutical representatives, regulations by government, etc. (Sketris et al., 2007).

2.11.7.a Medication related factors: The influence of drug interactions needs to be taken into account prior to prescribing BZDs as there was a three fold increase in prescriptions among the elderly (aged 65 years and over) from 1997 to 2006 (Bajcar et al., 2010). Among community dwelling elderly populations, about 23% of BZD users were exposed to a risk of drug- drug interactions due to simultaneous prescriptions for BZDs and other drugs (Preville et al., 2012). Medication related factors (Q14) such as side effects, indication, and effectiveness of drug are parameters influencing the decision-making process of clinicians in prescribing a drug. For example, while temazepam was effective in alleviating insomnia in a 2-week randomized clinical trial in subjects aged 70 years and older, its relative effectiveness (with respect to diphenhydramine) in the management of insomnia needs to be weighed against the risk of falls when considering its prescription (Glass, Sproule, Herrmann, & Busto, 2008). This adverse effect of BZDs was validated via database study by Sylvestre et al., 2012, who concluded that current and past exposure to BZDs increases the risk of fall-related injuries in seniors. The importance of the risk of BZD abuse is elucidated in section 2.9.

2.11.7.b Peer group: As part of a quality improvement initiative, the implementation of a practice support program (peer to peer training) for general practitioners and their staff in British Columbia was evaluated (via survey) for its perceived impact on clinical practice and patients. In this survey, 41% and 20.8% of general practitioners reported a decrease and increase respectively in prescribing medications after attending the Adult Mental Health Module. While this is an equivocal response to peer facilitated intervention, the long-term impact assessment for the same program revealed that general practitioners had sustained their confidence in prescribing medications for mental health conditions (MacCarthy et al., 2012). Though selection bias and difficulty in verifying the actual sample size are limiting factors for this study, consultation with peers can be concluded as one of the factors affecting quality of care by clinicians (Q14).

2.11.7.c Insurance coverage, cost of medication, and drug availability: Provincial formulary listing of any drug is the result of clinical and pharmacoeconomic evaluation of the drug by the Canadian Drug Expert Committee, which is an advisory body to the Canadian Agency for Drug and Technologies in Health (a government agency providing evidence based recommendations on health care to all decision makers) (Canadian Agency for Drugs and Technologies in Health, 2013). With respect to seniors in Newfoundland and Labrador, the cost of selective medications is reimbursed through the 65Plus plan (Government of Newfoundland and Labrador, 2013 ). Canadian physicians

refer to the formulary as an important tool in their decision making process to prescribe medications to seniors aged 65 years and older but mention that inequity in access to medications and time lost in filling paperwork for the reimbursement process are constraints to using the formulary effectively (Suggs et al., 2009). The impact of factors such as insurance and cost of medications (Q14) can lead to a better understanding of barriers and facilitators in optimal BZD prescribing among Newfoundland and Labrador physicians.

2.11.7.d Pharmaceutical industry and physicians' relations : The Canadian public does not have negative views on industry-physician interactions wherein information on the medication is shared (Holbrook et al., 2013). Similar perceptions are held by Canadian residents who actively sought drug-related data from the pharmaceutical industry (McCormick, Tomlinson, Brill-Edwards, & Detsky, 2001). Given that the majority of such interactions (64%) result in a prescription (Mintzes et al., 2013), it is pertinent to understand the impact of the pharmaceutical industry on clinicians' prescribing patterns (Q14).

2.11.7.e Availability and affordability of counselling: It was noted that family physicians in Ontario have a decreased belief in psychotherapy as an effective treatment modality for older patients with mental health issues (Mackenzie, Gekoski, & Knox, 1999). A

shift in that perspective was observed; a recent study showed that general practitioners noted collaboration with a psychiatrist or access to specialized mental health services as facilitators to providing quality of care to mental health patients (Fleury, Imboua, et al., 2012). Non-pharmacological therapy such as cognitive behavioural therapy is postulated to be cost effective in the international arena, though this finding is yet to be ascertained in a Canadian context (Myhr & Payne, 2006). Examining the influence of such non pharmacological variables (Q14 & Q16) on BZD prescribing patterns of physicians in Newfoundland and Labrador is important as BZDs are prescribed for indications which may be managed by non-pharmacological therapy (Jensen & Regier, 2010).

2.11.7.f Patients' requests: A pan-Canadian survey among the English speaking members of the College of Family Physicians of Canada noted an increase (82.7%) (95% CI 75.3% to 88.3%) in the prescribing of antibiotics for lower respiratory tract infections by family physicians when faced with pressure from patients compared with 46.5% (95% CI 39.3% to 53.8%) when no pressure was felt (McIsaac & To, 2004). Though this study is on a different class of drugs and may incur responder's bias due its nature of methodology, it does report a statistically significant relationship between prescribing and the patient's demand for a prescription. Studying the effect of this parameter (Q14) on BZD prescribers (physicians) can bring forth the contribution of patients in the clinical decision-making process.

2.11.7.g Clinical practice guidelines: For adult (18 to 64 years) patients, receiving pharmacological treatment in accordance with mental health guidelines demonstrated a reduced need for hospitalization although it did increase the number of clinical meetings with the prescriber (Sewitch, Blais, Rahme, Bexton, & Galarneau, 2007). A 2006 database study (Cunningham et al., 2010) concluded that 3.5% of residents (all age groups) of British Columbia were using BZDs for more than 100 days and the elderly population accounted for nearly half of the long term users. This study reported a decrease of BZD use in patients over 70 years and an increase of BZD use among the middle aged patients from 1996 to 2006. Furthermore, it surmised that disseminated literature (including guidelines) had little effect on the patterns of BZD use. One of the limitations of this dataset study is that it assumed prescriber awareness of BZD related literature and further assumed the prescriber's agreement with the findings and recommendations in such literature. Another approach to study the effects of guidelines is in conjunction with other tools (such as continuing medical education or CME) which may help improve the uptake of recommendations/policy statements. One such study (Rahme et al., 2005) reported that CME along with the provision of guidelines (in comparison with no intervention) can optimize the prescribing patterns of general practitioners for elderly patients with osteoarthritis. The findings of this study are relevant to my thesis because it focused on prescribers' prescribing to a population similar to one served by the sample in my survey. Though guidelines have not shown to

reduce the incidence of BZD prescriptions as per the Health Transition Fund Report (Kennedy & Goyer, 2002), Canadian family physicians have expressed positive views on evidence based medicine (guidelines) (Hayward et al., 1997). The questions pertaining to the degree of adoption of guidelines (Q14), source and disagreements with the guidelines (Q15) and guidelines as a useful tool to optimize prescribing habits (Q16) can be helpful in the development of BZD CPG.

#### 2.11.8 Continuing medical education by an expert

Self-reported CME needs were assessed among newly licensed Canadian family physicians in 2001. Rural family physicians were significantly more likely to cite the need for CME for mental health concerns than their urban counterparts (47.4% v. 30.8%;  $p=0.043$ ) (Curran et al., 2007). As the survey population in the study by Curran et al., (2007) included a lower proportion of members practicing in the field of geriatrics and psychotherapy than other certified members of the College of Family Physicians, the aforementioned values may be an underestimation of the actual needs of the specific cohort of family physicians. CME can take different forms and approaches. One effective approach is an in-person lecture by a peer physician who is considered a subject matter expert across multiple points of care (Wright et al., 2008). This clinical trial by Wright et al. (2008) was conducted among surgeons and pathobiologists, which limits its resonance to certain a cohort of physicians. Its findings regarding the effectiveness of CME

by experts was similar to a study focusing on the effects of online education provided by an expert on opioid and BZD prescribing skills to family physicians (Midmer, Kahan, & Marlow, 2006). The respondents in the study by Midmer et al. (2006) reported a significant increase in the counseling of patients on sleep hygiene after an email based discussion of cases with an addictions physician (expert) (before-after difference = 0.24;  $p= 0.03$ ). Though the physicians reported an increase in counseling for sleep hygiene, the online discussion with the expert neither resulted in improved management of patients with BZD dependence nor was it successful in improving their belief in better outcomes for patients with BZD dependence, anxiety disorders or insomnia. In the present study, the question (Q16) on CME by an expert is pertinent to understanding the current educational needs of Newfoundland and Labrador physicians, especially for rural clinicians (Q5).

#### 2.11.9 Personal use of BZDs by physicians

Raza, Ilnyckyj, & Bernstein (2006) proposed that the age and practice region of Canadian specialists were significant correlates for their compliance with colorectal screening guidelines; younger specialists (50 to 65 years) were more likely to get screened for colorectal cancer than specialists aged 65 and older, and specialists in the Maritime provinces were less likely to get themselves screened than their counterparts in the rest of

Canada. This survey focused on personal choices of prescribers on undergoing preventive health measures (rather than therapeutic medication as is the case in the present survey). While the extrapolation of its conclusions to my present survey sample or central theme is limited as it excluded general practitioners, the survey does shed some light on the personal choices and behaviours of prescribers (specialists). One of the findings in the survey by Raza et al. (2006) indicated disagreement with current knowledge on disease management to be one of reasons cited by specialists who chose not to undergo screening for colorectal cancer. Since personal health choice(s) of physicians may play a role in the work place functioning of physicians and quality of care provided to patients, the question pertaining to personal use (Q17) is presented to explore the possibility (and/or extent) of self-medication with the drug (BZDs) among the respondents.

## **Chapter 3: Methodology:**

### 3.1 Study type/design

A cross-sectional postal survey was conducted among physicians throughout the province of Newfoundland and Labrador. The survey consisted of a cover letter (1 page) (Appendix A) and a self-administered questionnaire (2 pages) (Appendix B), which was mailed to the study population with a request to return the completed questionnaire in the pre-addressed business reply envelope within a month. The design of this survey protocol included two contacts with the study population in order to ensure better response rate. The first contact was to approach the physicians (respondents) to participate in the survey as well as screen out those who were no longer practising in Newfoundland and Labrador. The numeric code on the return envelope of the first mail out was only to know the identity of the non-respondents in order to send the replacement questionnaire to them. The second contact via the replacement questionnaire was made with non-respondents only. Similar to the first contact, the second contact cover letter (Appendix C) requested the respondents to return the completed questionnaire in the pre-addressed business reply envelope. The survey was anonymous and completely voluntary. The staff at PDCS, Faculty of Medicine, Memorial University separated the completed questionnaires from their envelopes so that none of the study team members could

identify the respondents with their answers. While the cover letters were individually signed to invoke a feeling of personalization, they were addressed as “Dear Doctor” to maintain anonymity in case they were returned with the completed questionnaires. The list of physicians was obtained from the offices of PDCS. The physicians were not given any compensation for their participation. The study documents were mailed via regular Canada Post.

Relevance of survey design: The study was designed as a postal survey to maintain anonymity, to give the respondents a choice to complete the questionnaire at his/her convenience and to conduct the study with limited finances.

Limitation of the design: Online resources were not explored to conduct the survey.

### 3.2 Target population

PDCS is ‘an academic and service unit of Faculty of Medicine (MUN)’ which provides a range of services including research related surveys in addition to its mission to support the fulfillment of the Faculty of Medicine’s continuing professional development mandate through educational research and development. Therefore, its database is constantly updated and can be viewed as a reflection of the physician population in Newfoundland and Labrador. All physicians ( $N = 984$ ) registered with PDCS were approached to take part in this survey. The study population included all specialities of

physicians. This was due to the fact that BZDs have a wide range of pharmacological actions and, can be prescribed by any physician.

### 3.3 Survey instrument development

The questionnaire was initially conceived and developed by the Maine Benzodiazepine Group in 2005 to conduct a survey among the physicians in Maine. For the present study, the questionnaire (Appendix B) was revised for the following reasons:

i. to better reflect the Newfoundland and Labrador drug utilization scenario.

For example: A recent study conducted by SOP-MUN, NLCHI, DCH-MUN, DoHCS and NPA showed that elderly patients in Newfoundland and Labrador are concurrently or subsequently prescribed more than one BZD (NLCAHR, 2003). The guideline by WHO (1996) explicitly states that only one BZD should be prescribed per patient hence question 13 was incorporated to enquire about concurrent prescribing of more than one BZD to the same patient and the reason(s) for this action.

ii. to present an exhaustive (wherever possible) list of choices to the respondents.

For example:

a. the list of medications in question 10 which asked the respondents about the currently

prescribed medications included all the BZDs available in Canada as well as the United States along with the “Z” drugs zolpidem, zaleplon and zopiclone. b. all the basic pharmacological actions of BZDs along with the top five answers (received in the Maine survey) and the original choices were listed in question 11 which enquired about the reasons to prescribe BZDs.

Furthermore, the modifications to the questionnaire were based upon the findings from the literature (Chapter 2, section 2.11) review and recommendations by 4 reviewers.

Survey instrument: The survey instrument consisted of a cover letter and copy of the questionnaire. The cover letter outlined the study objective, study design, and administrative details such as the deadline, etc. It also pointed out the confidentiality, anonymity and voluntary nature of the survey. The questionnaire consisted of two sections. Section 1 had questions pertaining to the demographic information of the respondents: age, gender, speciality, years of medical practice, year of completion of medical education, practice population, practice type (multidisciplinary/group/solo), practice setting (hospital/office etc.), and finally, whether the respondent currently prescribes BZDs.

Section 2 collected data regarding the prescribing patterns of physicians.

The section starts with questions on the types of BZDs ( in addition to the “Z” drugs and

Carisaprodol) prescribed and is followed by questions on the reasons for prescribing BZDs as well as reasons for prescribing these drugs beyond 90 days. Question 13 enquires about the concurrent prescribing of more than one BZD to the same patient. Question 14 deals with 14 factors affecting the prescribing of the medication. The rate of agreement on the influence of each factor on prescribing medications was marked on a 7-point Likert scale, in which “1” indicated total disagreement and “7” indicated total agreement. The next questions were to understand the opinion(s) regarding the guidelines used to prescribe BZDs and the most suitable method for disseminating information which can help improve the prescribing of medications by the physicians. The survey ended with the question regarding personal usage of BZDs by the respondents beyond 30/60/90 days. Each question was a multiple choice with the option of recording one’s own response under the ‘others’ category to gather a response(s) not included in the list.

#### 3.4 Validity and reliability of the cover letters and questionnaire

This questionnaire was developed to study the prescribing patterns of this particular study sample only and hence it was not tested for reliability. The external validity of the cover letters (Appendix A and Appendix C) and questionnaire (Appendix B) was judged by 4 reviewers: two physicians, one epidemiologist, and one pharmacist. Recommendations made by all 4 reviewers were incorporated into the survey instrument.

#### 3.5 Ethical considerations

This study was approved by the Human Investigation Committee (HIC) at Memorial University of Newfoundland; it was conducted as per the methodology stated in the ethics submission application and as per the policies outlined by HIC. The respondent's consent to participate was implied by the return of the completed questionnaire. The study design ensured anonymity of the respondents.

### 3.6 Steps for data analysis

The data was tabulated in MS ACCESS, graphs were prepared in MS EXCEL and statistical analysis was performed using SPSS version 16. The data was double checked to ensure zero percent error and accurate representation of the results. The data analysis included a descriptive analysis (measures of central tendency, standard deviation, frequencies, percentages, and range). Additionally, the chi square analysis and the Fisher's exact test were employed between the independent (Section 1) variables and the dependent (Section 2) variables ( $p$  was set at 0.05). The qualitative analysis was performed on the responses recorded under 'other' by grouping similar responses together.

## Chapter 4: Results

This chapter deals with the results taken from the data analysis. The details of data analysis are mentioned in methodology section. The descriptive analysis is presented in two sections as the questionnaire also is divided into two sections. The results of the inferential statistics are presented along with the relevant effect size (phi or Cramer's  $\nu$ ). The effect size is calculated to measure the strength of association between two variables. The effect sizes mentioned in this study are interpreted according to Cohen's standards (Valentine & Cooper, 2003).

### Sample size results:

297 prescribers (out of 984 approached) from Newfoundland and Labrador responded to this survey. 16 questionnaires were sent back with the "return to sender" mark on them and following reasons were cited: recipient moved away (15) or deceased (1). Response rate for the survey was therefore 30.68%. The average response rate for mailed surveys among health care professionals was concluded to be 57.5%; the low response rate to this survey may be due to the use of business reply return envelopes<sup>1</sup>, lack of pre-notification for this survey, physicians' policy to not participate in surveys, limitations in the PDCS database, and inclusion of question pertaining to BZD personal use by prescribers

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<sup>1</sup> Use of (first class) stamped return envelope increased the response rates to postal surveys amongst physicians and general population as well.

because it may have been deemed as a ‘sensitive’<sup>2</sup> question by respondents (Cook, Dickinson, & Eccles, 2009; Edwards et al., 2009; VanGeest, Johnson, & Welch, 2007; Wiebe, Kaczorowski, & Mackay, 2012).

The questionnaire collected data with respect to the demographic (section 1) and prescribing patterns and the factors affecting them (section 2).

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<sup>2</sup> Amongst all sections of population, inclusion of ‘sensitive’ questions reduced the rate of response to postal surveys.

## **Section 1**

### **Analyses of all respondents to the survey (Sample size $N = 297$ )**

The majority, 183 (64%) of the respondents were male. Furthermore the majority of respondents were : between the age of 45 to 54 years [99 (37.9%)], had practiced for 20 to 29 years [89 (31.6%)], completed their studies between 1975 to 1984, [94 (33.5%)], practiced in population of 100,000 or more [152 (53.9%)]. Most of respondents practiced in an office setting [123 (48%)], in a group [143 (56.1%)], were general practitioners [129 (49.4%)] and finally, did prescribe BZD to their patients [233 (78.5%)].

### **Analyses of the respondents who prescribe BZDs (Sample size $N = 233$ )**

Table 4.1 and Figures 4.1 through 4.5 display the results of the descriptive analyses of the demographic information of the respondents who prescribe BZDs. As seen in the data of the overall respondents, the majority of the respondents are: male, in the age group of 45 to 54 years, general practitioners, practiced in a group setting, and have had 20 to 29 years of practice. The respondents are concentrated in urban areas. Note that there is no significant difference between BZD prescribers and non-prescribers among the respondents in this survey.

Figure 4.1 below displays gender characteristics of respondents who prescribe BZDs. As shown clearly below, more number of male respondents prescribe BZDs in their practice.

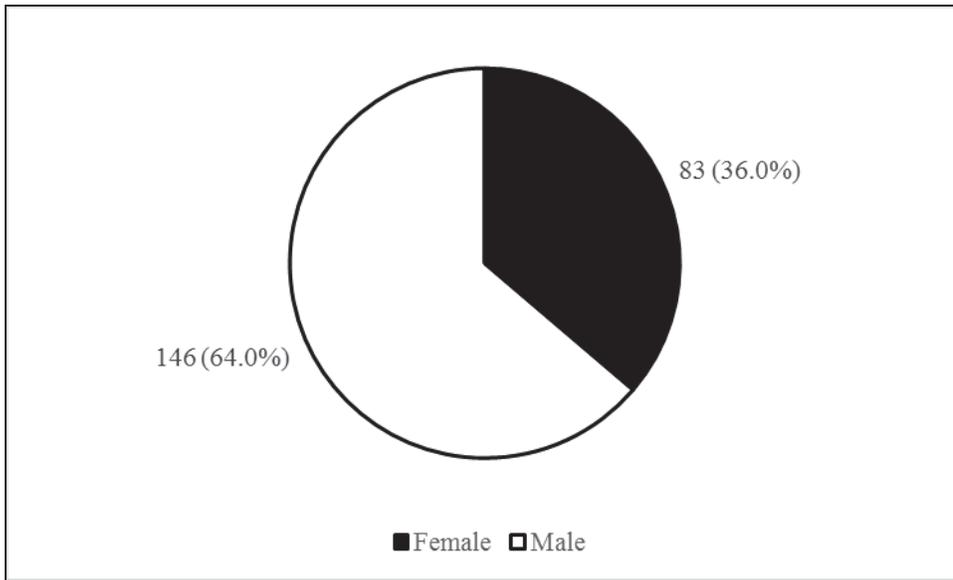


Figure 4.1 Gender of respondents prescribing BZDs (Actual  $N = 229$ ; Missing = 4)

With respect to age of the respondents who prescribe BZDs (Figure 4.2), majority of respondents ( 36.5%) belong in 45 to 54 years category, followed by 35 to 44 years old respondents ( 26.0%), then 55 to 64 years (19.2%) , 25 to 34 years (14.4%), and finally, 65 to 74 years old respondents (3.8%).

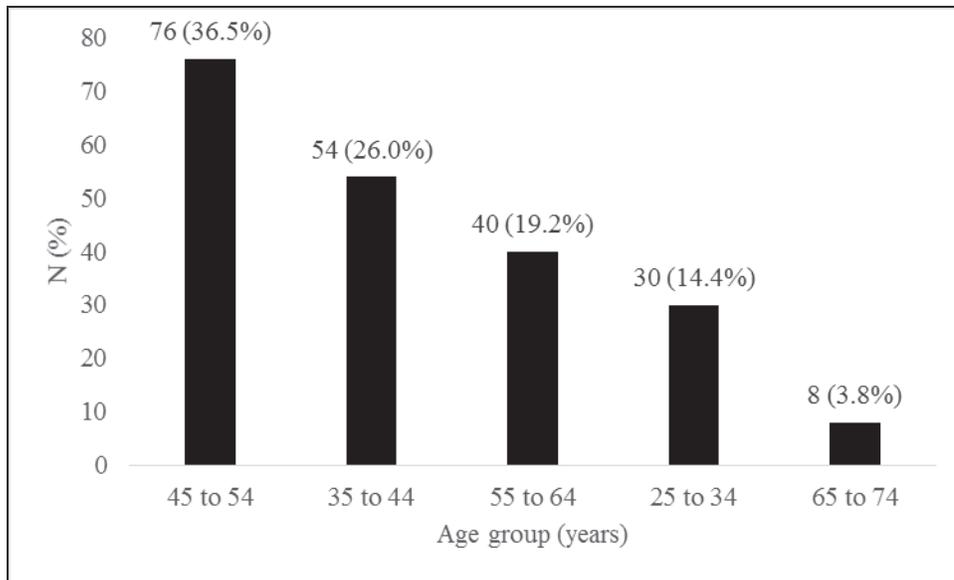


Figure 4.2 Age of the respondents prescribing BZDs ( Actual  $N = 208$ ; Missing = 25)

Figure 4.3 below shows that the majority of respondents (32.7%) have practiced for 20 to 29 years and least number of respondents (2.7%) have 40 to 49 years of experience. 24.3%, 23.0%, and 17.3% respondents have practiced for 0 to 9 years, 10 to 19 years, and 30 to 39 years respectively.

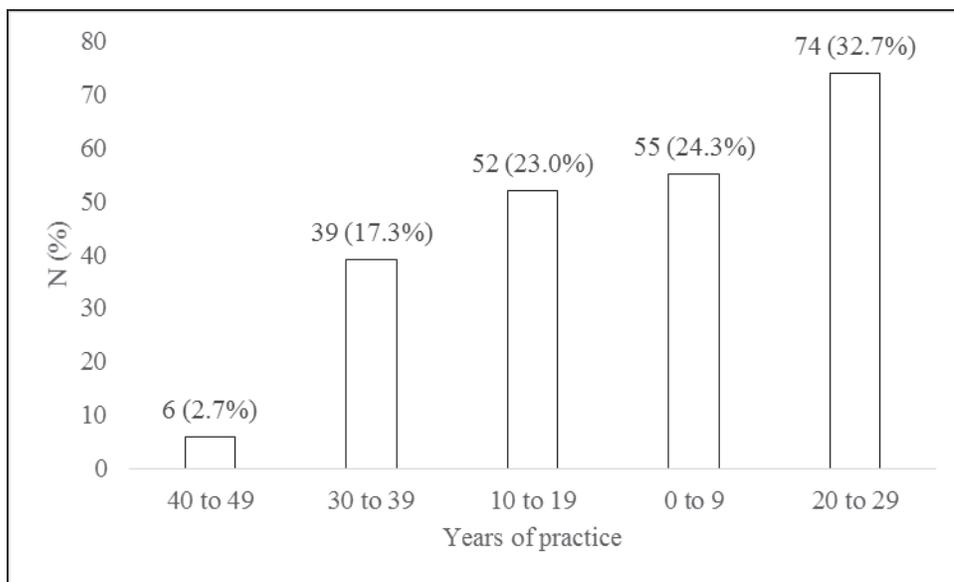


Figure 4.3 Years of practice of respondents prescribing BZDs (Actual  $N = 226$ ; Missing = 7)

Respondents mainly practiced (Figure 4.4) in areas with population density of 100,000 or more (48.0%), followed by :10,000 to 24,999 (17.2%), 5000 to 9,999 (13.7%), 2000 to 4,999 (8.8%), 25,000 to 49,999 (5.7%), less than 2000 people (3.5%) and finally, in area with population between 50,000 and 99,999 (3.1%).

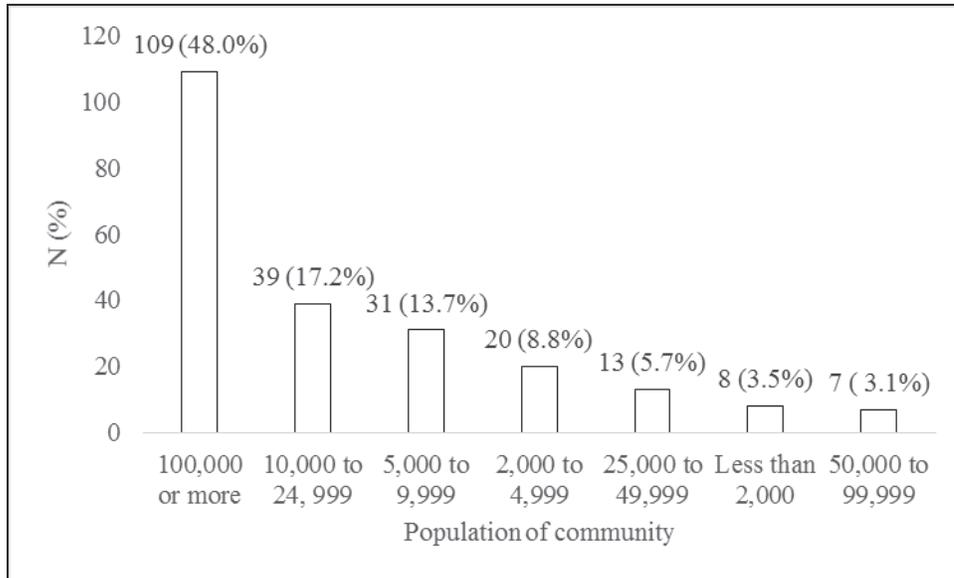


Figure 4.4 Population of community in which respondents prescribing BZDs practice  
(Actual  $N = 227$ ; Missing = 6)

As seen below in Figure 4.5, respondents who prescribe BZDs mainly practiced in group setting (57.4%) and least number of respondents (1.5%) have marked both, alone as well as multidisciplinary setting as their practice setting.

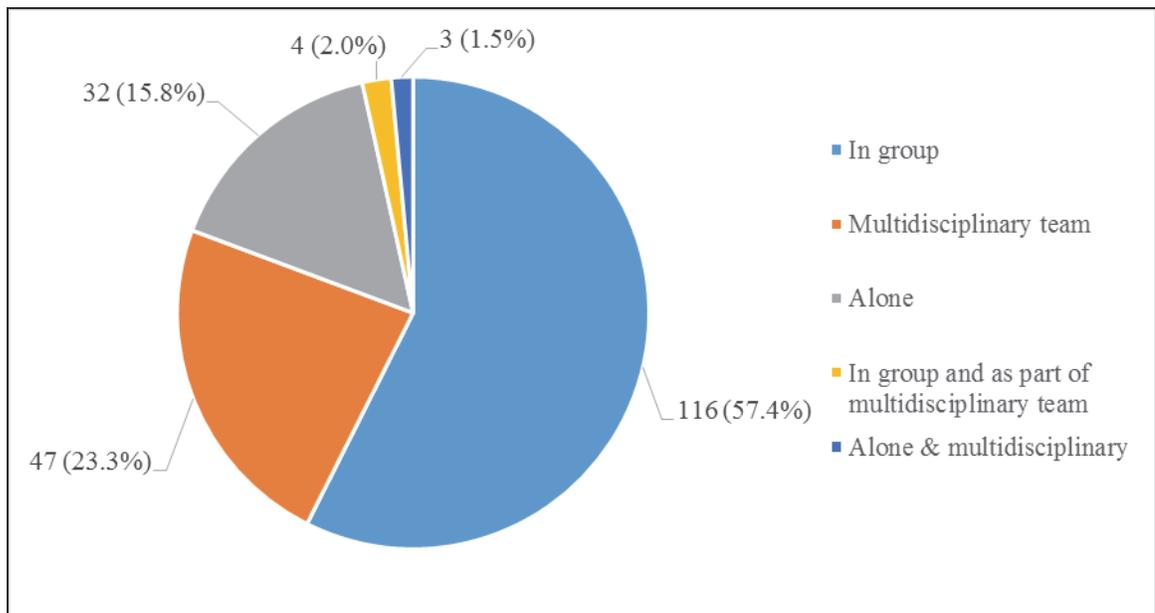


Figure 4.5 Practice setting of respondents prescribing BZDs (Actual  $N = 202$ ; Missing =31)

Table 4.1 The descriptive statistics of the respondents who prescribe BZDs (Sample size  $N = 233$ )

Variable	$N = 233$		Actual $N$ (100%)	Missing
	Count	Percent		
<b>Year of completion of medical studies</b>			226	7
1975 to 1984	73	32.3		
1985 to 1994	66	29.2		
1995 to 2004	52	23		
1965 to 1974	26	11.5		
2005 to 2007	6	2.7		
1955 to 1964	3	1.3		
<b>Practice Setting</b>			202	31
Office practice	108	53.5		
Hospital based	77	38.1		
Hospital based and Office practice	10	5		
Public clinic	6	3		
Nursing Home	1	0.5		

Variable	N = 233		Actual N (100%)	Missing
	Count	Percent		
<b>Specialty</b>			<b>203</b>	<b>30</b>
General Practitioners	129	63.5		
Others	74	36.5		

The following is the detailed breakdown of all the respondents by “specialty”:

63.5% General practitioners, 3.5% adult psychiatrists, 1.4% child psychiatrists, 0.5% forensic psychiatrists, 2.0% neurologists, 4.4% surgeons. 24.6% were classified as “other” and belonged to approximately 30 different specialties including surgeon, geriatrician, internist, urologist, paediatrician, occupational medicine, and resident.

## **Section 2**

The second section on the questionnaire had detailed questions regarding the prescribing patterns of the respondents who answered “yes” to question 9 (in Section 1).

### **1.Types of BZDs currently prescribed:**

The prescribers were first asked to mark the name(s) of medication(s) (drug molecule and brand name) they prescribe with respect to BZD types of drugs.

Table 4.2 below shows a dominance of high potency BZDs. Over 90% of the respondents indicated to currently prescribe a short-acting BZD: lorazepam (high potency short- to intermediate-acting BZD). The second most prescribed drug was zopiclone which is a BZD type hypnotic, which was followed by clonazepam (high potency long-acting BZD), temazepam (low potency short- to intermediate-acting BZD) and diazepam (medium potency long-acting BZD) (in that order).

Table 4.2 The descriptive statistics of the types of BZDs which are currently prescribed by respondents

<b>Drug molecule (Brand name)</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
1. Lorazepam (Ativan <sup>®</sup> )	216	93.9
2. Zopiclone (Imovane <sup>®</sup> )	159	69.1

<b>Drug molecule (Brand name)</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
3. Clonazepam(Rivotril <sup>®</sup> )	144	62.6
4. Temazepam (Restoril <sup>®</sup> )	137	59.6
5. Diazepam (Valium <sup>®</sup> )	123	53.5
6. Oxazepam (Apo-Oxazepam <sup>®</sup> )	108	47.0
7. Alprazolam ( Xanax <sup>®</sup> )	91	39.6
8. Bromazepam (Lectopam <sup>®</sup> )	67	29.1
9. Midazolam ( Apo-Midazolam Injectable <sup>®</sup> )	57	24.8
10. Triazolam ( Halcion <sup>®</sup> )	45	19.6
11. Chlordiazepoxide ( Apo- Chlordiazepoxide <sup>®</sup> )	43	18.7
12. Nitrazepam (Mogadon <sup>®</sup> )	21	9.1
13. Flurazepam (Dalmane <sup>®</sup> )	17	7.4
14. Clobazam (Frisium <sup>®</sup> )	16	7.0
15. Zaleplon (Starnoc <sup>®</sup> )	13	5.7
16. Clorazepate (Novo- Clopat <sup>®</sup> )	12	5.2
17. Estazolam (ProSom <sup>®</sup> )	2	0.9

<b>Drug molecule (Brand name)</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
18. Zolpidem (Ambien <sup>®</sup> )	1	0.4
19. Carisoprodol (Soma <sup>®</sup> )	1	0.1
20. Quazepam(Doral <sup>®</sup> )	0	0
21. Other(s) (please specify)	0	0

Note: 1. Sample Size  $N = 230$  (3 missing responses). 2. Options were not mutually exclusive hence one prescriber could mark more than one BZDs.

Significant results:

As shown in Table 4.3 below, gender and years of medical practice played an important role in prescribing of triazolam. Psychiatrists tend to prescribe clonazepam more than general practitioners. Older (48 to 71 years) physicians were more inclined to prescribe chlordiazepoxide, flurazepam, temazepam and clobazam than their younger (27 to 47 years old) counterparts. Physicians practicing in a demographic population of less than 25,000 were more inclined to prescribe nitrazepam, bromazepam and chlordiazepoxide than those practicing in an area with 25,000 or more people. Physicians who practice in group or multi-disciplinary unit were more likely to prescribe lorazepam than those who practice alone. Each of these results had a small effect size.

Table 4.3 The significant results from the chi-square analyses between demographic variables and the types of BZDs which are currently prescribed

Type of BZDs prescribed by physician (N)	Demographic characteristic of physician (NN)	% of NN = Yes'	Chi-square / Fisher's exact	p	Effect size= small/moderate /large
Triazolam (229)	Male (146)	24	5.877	0.015	0.160 =small
	Female (83)	10.8			
Clonazepam (140)	General practitioner (129)	69.8	0.023		
	Psychiatrist (11)	100			
Triazolam (226)	Phys with 20 to 50 years of medical practice( 119)	24.4	0.036		
	Phys with 0 to 19 years of medical practice (107)	14			

Type of BZDs prescribed by physician (N)	Demographic characteristic of physician (NN)	% of NN = Yes'	Chi-square / Fisher's exact	p	Effect size= small/moderate /large
Clobazam (208)	Older (48 to 71 years) phys (103)	11.7	4.502	0.034	0.147 =small
	Younger (27 to 47 years) phys (105)	3.8			
Bromazepam (227)	Phys practicing in area with more than 25000 people (129)	21.7			
	Phys practicing in area less than 25000 people (98)	38.8	7.869	0.005	0.186 =small

Type of BZDs prescribed by physician (N)	Demographic characteristic of physician (NN)	% of NN = Yes'	Chi-square / Fisher's exact	p	Effect size= small/moderate /large
Chlordiazepoxide (227)	Phys practicing in area less than 25000 people (98)	27.6	8.323	0.004	0.191 =small
	Phys practicing in area with more than 25000 people (129)	12.4			
Nitrazepam (227)	Phys practicing in area less than 25000 people (98)	13.3	4.259	0.039	0.137 =small
	Phys practicing in area with more than 25000 people (129)	5.4			

Type of BZDs prescribed by physician (N)	Demographic characteristic of physician (NN)	% of NN = Yes'	Chi-square / Fisher's exact	p	Effect size= small/moderate /large
Flurazepam (208)	Older (48 to 71 years) phys (103)	11.7	4.502	0.034	0.147 =small
	Younger (27 to 47 years) phys (105)	3.8			
Temazepam (208)	Older (48 to 71 years) phys (103)	69.9	10.647	0.001	0.226 =small
	Younger (27 to 47 years) phys (105)	47.6			

Type of BZDs prescribed by physician (N)	Demographic characteristic of physician (NN)	% of NN = Yes'	Chi-square / p Fisher's exact	Effect size= small/moderate /large
Lorazepam (199)	Phys who practice in group or multi-disciplinary unit (167)	95.8	0.027	
	Phys who practice alone (32)	84.4		

Note: 1. The degree of freedom for all reported results in Table 4.3 is 1. 2. No effect size is calculated for results reporting Fisher's exact test.

## 2. Reasons to prescribe BZDs:

Prescribers were asked to indicate the reason for prescribing BZDs (Table 4.4). The results show that anxiety was the leading reason to prescribe BZDs. This was followed by insomnia and then by panic attack. Though less than 50% of the respondents indicated alcohol withdrawal and convulsive disorders as the indications for BZDs, they do occupy fourth and fifth place in the top five slots.

Table 4.4 The descriptive statistics of reasons to prescribe BZDs by respondents

<b>Reasons for prescribing</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
1. Anxiety	194	84.3
2. Insomnia	169	73.5
3. Panic attacks	146	63.5
4. Alcohol withdrawal	110	47.8
5. Convulsive disorders (ex: Seizures)	104	45.2
6. Single-dose for phobia	91	39.6
7. Sedation	88	38.3

<b>Reasons for prescribing</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
8. Grief reaction	78	33.9
9. Muscle relaxant	73	31.7
10. Movement disorders	55	23.9
11. Depression	25	10.9
12. Anti-vertigo	19	8.3
13. Bipolar disorder	19	8.3
14. Amnesic	12	5.2
15. Other(s) (please specify)	43 (Responded)	18.7

Note: 1. Sample Size  $N = 230$  (3 missing responses). 2. Options were not mutually exclusive hence one prescriber could mark more than one response as his/her reason to prescribe BZDs.

The following are responses recorded under the 'other' option : procedural sedation (16 or 37.20%), adjunctive therapy to SSRI (4 or 9.30%), palliative care, restless leg syndrome and dementia associated agitation (3 responses or 6.97% each), travel and inherited patient (2 responses or 4.65% each), muscle contraction, dementia associated agitation, emergency use only, individual patient's clinical response to drugs, anticipatory

nausea, part of medications for chronic pain, anti nausea, ventilator facilitation, spasticity, tinnitus, and finally, myoclonus (1 response or 2.32% each).

Significant results (Table 4.5) : Male physicians were more inclined to prescribe BZDs for single dose for phobia and sedation than their female equivalents.

General practitioners and psychiatrists were more inclined to prescribe for muscle relaxant and bipolar disorders respectively.

Physicians practicing for 0 to 19 years were more inclined to prescribe BZDs for insomnia than physicians practicing for 20 to 50 years. Physicians practicing for 20 to 50 years were more inclined to prescribe BZDs as a muscle relaxant and for convulsive disorders.

Physicians practicing in an area with more than 25,000 people were more inclined to prescribe for insomnia than physicians practicing in a less populated area. Physicians practicing in an area with less than 25,000 people were more inclined to prescribe for alcohol withdrawal, as muscle relaxants and for panic attacks.

27 to 47 year old physicians were more predisposed to prescribing BZDs for depression than their older counterparts.

Table 4.5 The significant results from the chi-square analyses between demographic variables and the reasons for prescribing BZDs

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i> Fisher's exact</b>	<b>Effect size= small/moderate /large</b>	
Single dose for phobia (228)	Male (145 )	55.6	4.153	0.042	0.135 =small
	Female (83)	44.4			
Sedation (228)	Male phys (145)	44.1	5.161	0.023	0.150 =small
	Female phys (83)	28.9			
Muscle relaxant (140)	General practitioners (129)	41.1	0.004		
	Psychiatrist (11)	0			

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i></b>	<b>Effect size= small/moderate /large</b>
Bipolar disorder (140)	General practitioners (129)	7.8	0.000	
	Psychiatrist (11)	54.5		
Insomnia (225)	Phys with 20 to 50 years of medical practice (119)	68.1		
	Phys with 0 to 19 years of medical practice (106)	80.2	4.258	0.039
				0.138 =small

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i> Fisher's exact</b>	<b>Effect size= small/moderate /large</b>	
Muscle relaxant (225)	Phys with 20 to 50 years of medical practice (119 )	38.7	4.446	0.035	0.141 =small
	Phys with 0 to 19 years of medical practice (106 )	25.5			
Convulsive disorders (225)	Phys with 20 to 50 years of medical practice (119)	52.9	6.620	0.010	0.172 =small

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i> Fisher's exact</b>	<b>Effect size= small/moderate /large</b>
	Phys with 0 to 19 years of medical practice (106)	35.8		
Insomnia (226)	Phys practicing in area with more than 25000 people (128)	80.6	4.550	0.033
	Phys practicing in area less than 25000 people (98)	68		0.142 =small

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i> Fisher's exact</b>	<b>Effect size= small/moderate /large</b>	
Alcohol withdrawal (226)	Phys practicing in area less than 25000 people (98 )	56.1	4.818	0.028	0.146 =small
	Phys practicing in area with more than 25000 people (128)	41.4			
Muscle relaxants (226)	Phys practicing in area less than 25000 people (98)	41.5	7.195	0.007	0.178 =small

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i> Fisher's exact</b>	<b>Effect size= small/moderate /large</b>
	Phys practicing in area with more than 25000 people (128)	25		
Panic attacks (226)	Phys practicing in area less than 25000 people (98)	71.4		
	Phys practicing in area with more than 25000 people (128)	56.2	5.476	0.019
				0.156 =small

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / <i>p</i> Fisher's exact</b>	<b>Effect size= small/moderate /large</b>
Depression (207)	Older (48 to 71 years) phys (103)	4.9		
	Younger (27 to 47 years) phys (104)	14.4	5.428	0.020
				0.162 =small

Note: 1. The degree of freedom for all the reported results in table 4.5 is 1. 2. No effect size is calculated for results reporting Fisher's exact test.

### 3. Reasons to prescribe BZDs beyond 90 days:

Prescribers were asked to indicate the reason for prescribing BZDs beyond 90 days.

‘Patient on long-term BZDs’ (chronic users) was the most cited reason for prescribing BZDs beyond 90 days. Furthermore, the extended prescribing was practiced in case the patient suffered from chronic anxiety, chronic insomnia, and if the patients were in palliative care. The results also show that 77.2% continue to prescribe BZDs after 90 days (Table 4.6).

Table 4.6 The descriptive statistics of reasons to prescribe BZDs beyond 90 days by respondents

<b>Reasons to prescribe beyond 90 days</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
1. Patient on long term BZDs	119	51.3
2. Chronic anxiety	116	50.0
3. Chronic insomnia	86	37.1
4. Palliative care	68	29.3
5. Never	53	22.8
6. Convulsive disorders	48	20.7
7. No response to other medications	49	21.1

<b>Reasons to prescribe beyond 90 days</b>	<b>Response: Yes (Count)</b>	<b>Response: Yes (Percent)</b>
8. Chronic muscle spasms	34	14.7
9. Extended crisis in patient's life	31	13.4
10. Bipolar disorder	16	6.9
11. Other(s) (please specify)	29 (Responded)	12.9

Note: 1. Sample Size  $N = 232$  (1 missing responses) 2. Options were not mutually exclusive hence one prescriber could mark more than one response as his/her reason to prescribe BZDs beyond 90 days.

The other responses ( $n=29$ ) were (Figure 4.6): inheriting patients who were either chronic users or unable to wean off BZDs (13 or 44.88%), dementia associated with agitation (2 or 6.89%); restless leg syndrome (2 or 6.89%); panic attack prophylaxis if SSRIs are not helpful (1 or 3.45%); tinnitus (1 or 3.45%); continued ventilation (1 or 3.45%); anti-

spasticity agents (1 or 3.45%); adjunct to SSRI (1 or 3.45%); p r n basis for insomnia (1 or 3.45%); extended ICU admission (1 or 3.45%); movement disorders (1 or 3.45%); anticipatory nausea (chemotherapy related) (1 or 3.45%); and only when alternative groups have failed to achieve their effect (1 or 3.45%).

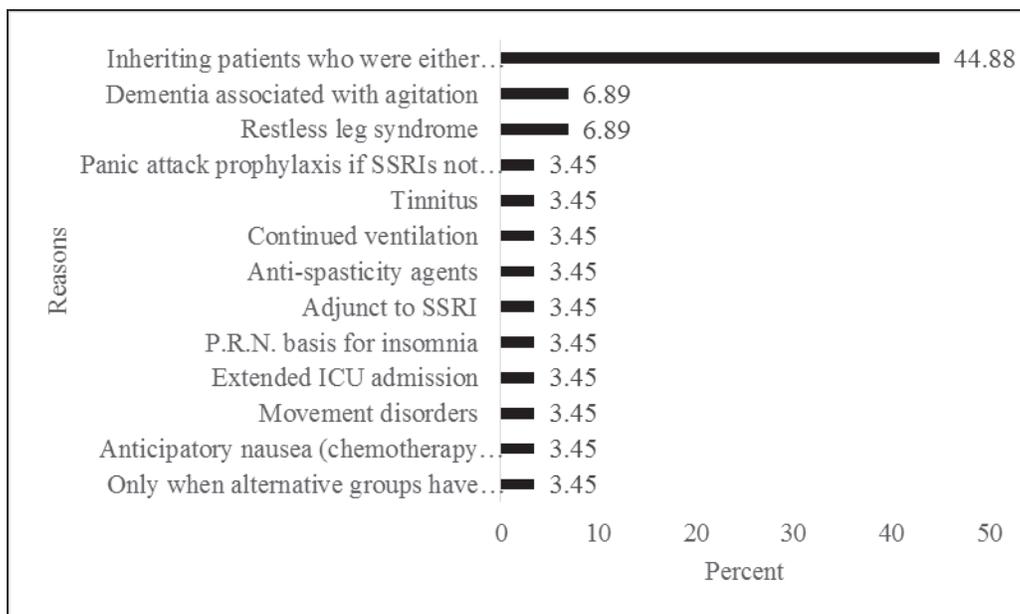


Figure 4.6 Other reasons to prescribe BZDs beyond 90 days as stated by respondents

Significant results (Table 4.7):

Psychiatrists were more inclined to prescribe BZDs for longer than 90 days for bipolar disorder than general practitioners.

Physicians practicing for 20 to 50 years were more inclined to cite “extended crises in person’s life”, “chronic muscle spasm” and “convulsive disorders” as a reason for prescribing BZDs for longer than 90 days.

Older (48 to 71 years) physicians were more predisposed to citing “for extended crises in person’s life”, “chronic anxiety” and “convulsive disorders” as a reason for prescribing BZDs for more than 90 days.

Table 4.7 The significant results from the chi-square analyses between demographic variables and the reasons for prescribing BZDs beyond 90 days

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / Fisher's exact</b>	<b>p</b>	<b>Effect size= small/moderate /large</b>
Bipolar disorder (140)	General practitioners (129)	8.5	0.018		
	Psychiatrist (11)	36.4			
Extended crises in person's life (225)	Phys with 20 to 50 years of medical practice (118)	17.8	4.278	0.039	0.138 =small
	Phys with 0 to 19 years of medical practice (107)	8.4			

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / Fisher's exact</b>	<b>p</b>	<b>Effect size= small/moderate /large</b>
Chronic muscle spasm (225)	Phys with 20 to 50 years of medical practice (118)	19.5	4.615	0.032	0.143 =small
	Phys with 0 to 19 years of medical practice (107)	9.3			
Convulsive disorders (225)	Phys with 20 to 50 years of medical practice (118)	29.7	11.554	0.001	0.227 =small
	Phys with 0 to 19 years of medical practice (107)	11.2			

<b>Reason for BZD prescription by physician(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / Fisher's exact</b>	<b>p</b>	<b>Effect size= small/moderate /large</b>
Extended crises in person's life (207)	Older (48 to 71 years) phys (102)	18.6	5.582	0.019	0.163 =small
	Younger (27 to 47 years) phys 105	7.6			
Chronic anxiety (207)	Older (48 to 71 years) phys (102)	59.8	8.117	0.004	0.198 =small
	Younger (27 to 47 years) phys (105)	40			
Convulsive disorders (207)	Older (48 to 71 years) phys (102)	30.4	8.850	0.003	0.207 =small
	Younger (27 to 47 years) phys (105)	13.3			

Note 1. The degree of freedom for all the reported results in Table 4.7. is 1. 2. No effect size is calculated for results reporting Fisher's exact test.

#### 4. Concurrent prescription of more than one BZD:

The WHO guidelines on BZDs explicitly state that no more than one BZD should be prescribed to the same patient. In spite of this recommendation, 17.9~18.0% of the respondents concurrently prescribe more than one BZD to the same patient (Figure 4.7).

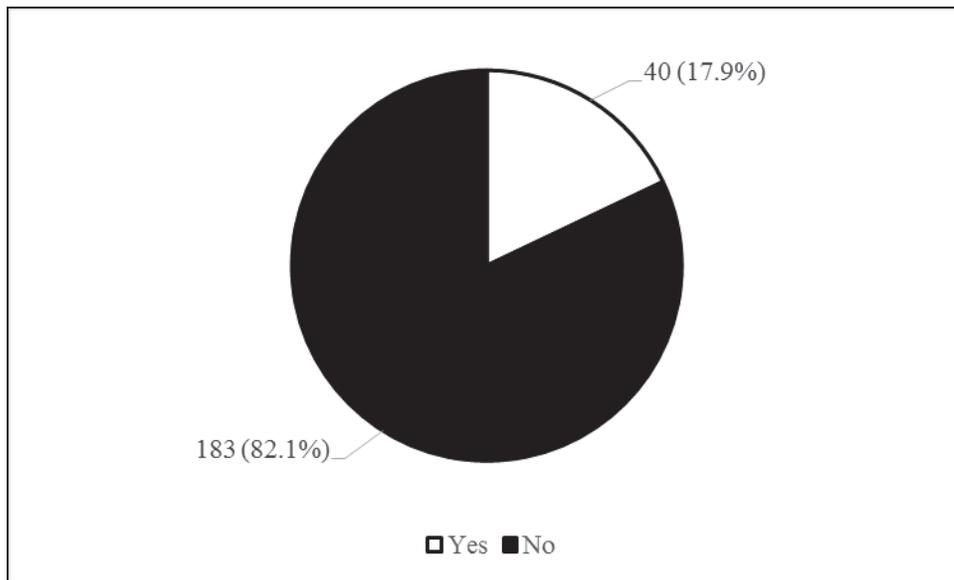


Figure 4.7 Percent of respondents concurrently prescribing more than one BZD

Note : Sample size  $N = 223$  (10 missing)

Of the 40 “yes” responses to the above question, only 36 mentioned the reason for prescribing more than one BZD concurrently to the same patient. As seen below, the co-morbidity of insomnia with anxiety was the principle indication for more than one BZD to the same patient (Table 4.8).

Table 4.8 The reasons to prescribe BZDs concurrently as stated by the respondents

<b>Reasons</b>	<b>Frequency</b>	<b>Percent</b>
Insomnia and Anxiety	11	30.6
To continue previous prescriptions	4	11.1
Additional PRN dose	2	5.6
Anxiety and Panic attacks	2	5.6
ICU setting	2	5.6
Long term use	2	5.6
Anxiety and Seizures	1	2.8
Chronic anxiety and Acute anxiety	1	2.8
Clona. for muscles ATIVAN for anxiety/insomnia	1	2.8
Insomnia and Panic	1	2.8
Insomnia and Panic attacks	1	2.8
No response to one BZD and other medications	1	2.8
Occ. when short term enhancement of effect required	1	2.8
Palliative setting	1	2.8
Patient specific reasons	1	2.8
Premed prior to intraprocedural sedation	1	2.8

Reasons	Frequency	Percent
To continue previous precriptions; Unable to discontinue; Anxiety and Insomnia	1	2.8
Unable to discontinue one medication	1	2.8
Use combination of Xanax and Ativan	1	2.8

### 5.Factors influencing BZD prescribing:

The next question asked the prescribers to rate each of the 14 factors on the Likert scale of 1 (strongly disagree) to 7 (strongly agree).

With respect to descriptive analysis, the mean was calculated for each variable. Table 4.9 itemizes the results.

Table 4.9 The mean of the responses indicated for factors influencing BZD prescribing

<b>Variable</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>Interpretation</b>
Risk of abuse/ misuse	5.64	1.873	6 (Moderately agree)
Effectiveness of drug	5.64	1.356	6 (Moderately agree)
Indication	5.50	1.590	6 (Moderately agree)
Side effects	5.22	1.567	5 (Agree)
Drug interactions	4.89	1.744	5 (Agree)

<b>Variable</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>Interpretation</b>
Clinical practice guidelines	4.66	1.766	5 (Agree)
Continuing prescription	4.44	1.834	4 (Neither Agree/Disagree)
Availability of counseling	4.01	1.951	4 (Neither Agree/Disagree)
Affordability of counseling	3.96	1.993	4 (Neither Agree/Disagree)
Peer group	3.89	1.863	4 (Neither Agree/Disagree)
Cost	3.84	1.809	4 (Neither Agree/Disagree)
Drug availability	3.68	1.851	4 (Neither Agree/Disagree)
Patient's request	3.59	1.753	4 (Neither Agree/Disagree)

<b>Variable</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>Interpretation</b>
Insurance coverage	3.49	1.914	4 (Neither Agree/Disagree)
Manufacturer's information	3.43	1.657	3 (Disagree)
Pharmaceutical rep	2.65	1.602	3 (Disagree)

Note: Sample size: 225 (missing responses were variable for each factor).

The inferential analysis of the scale was conducted by collapsing the 3 levels of opinion (except level 4 which signifies neither agree nor disagree); i.e. 1 (strongly disagree), 2 (moderately disagree) and 3 (disagree) into a one single opinion of disagreement. The levels for agreement (5, 6 and 7) were also recoded as a single opinion of agreement. This was done to simplify the presentation of results.

Significant results (Table 4. 10): Physicians practicing in group or multi-disciplinary unit were more inclined to mention “peer group” as a factor influencing their BZD prescribing than their counterparts who practiced alone. A greater percent of female physicians agreed with “clinical practice guidelines” influencing their BZD prescribing than their male equivalents. Physicians practicing in less populated area (less than 25,000 people) were more inclined to cite “availability of counseling” as a factor influencing their BZD prescribing than their counterparts in the areas which had 25,000 or more people.

Table 4.10 The significant results from the chi-square analyses between demographic variables and factors influencing BZD prescribing

<b>Factor affecting BZD prescribing</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / Fisher's exact</b>	<b>p</b>	<b>Effect size= small/moderate /large</b>
Peer group (184)	Phys practicing in group or multi-disciplinary (158)	50	12.094	0.002	0.256=small
	Phys practicing alone (26)	15.4			

<b>Factor affecting BZD prescribing</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes'</b>	<b>Chi-square / Fisher's exact</b>	<b>p</b>	<b>Effect size= small/moderate /large</b>
Clinical practice guidelines (215)	Male (137)	49.6	6.276	0.043	0.171 =small
	Female (78)	59			
Availability of counseling (204)	Phys practicing in area with less than 25000 people (89)	57.3	6.465	0.039	0.178 =small
	Phys practicing in area with equal or more than 25000 people (115)	40			

Note 1. The degree of freedom for all the reported results in Table 4.10 is 2. 2. No effect size is calculated for results reporting Fisher's exact test.

## 6.Guidelines embraced by prescribers:

Question 15 explored the usage of guidelines among the respondents. 51 (35.91%) of 142 prescribers (91 missing responses) reported that they did not use guidelines. The respondents were supposed to give the name of guidelines employed, source of the same and their disagreement with the used guidelines for this question. 91 (64.10%) prescribers who gave a detailed response mentioned the name of the guideline issuing institution in place of actual title of the guideline hence the data analysis was performed combining both categories: name of guideline and source of guideline.

Following are the major guidelines/sources of guidelines mentioned by the prescribers:

Canadian Clinical Practice Guidelines (9.8%), Literature (9.2%), Canadian Medical Association (7.0%), Hospital/Administration (4.2%) and CME (4.2%), Canadian Anaesthesia Use Practice Guideline (2.8%), Canadian College of Family Physicians (2.8%), Canadian Psychiatric Association (2.8%), guidelines from medical school (2.8%), Canadian Journal Psychiatry (2.1%), Anxiety and Canadian Paediatric Society (2.1%). 1.2% responded by citing multiple sources (CMA, AMA, Canadian Psychiatric Association, American Psychiatric Association) and 1.4% cited CPSNL. The remaining guidelines/sources mentioned were AAFP, American Academy of Sleep Medicine, American Association of Paediatrics, CPA, Canadian Therapeutic Choice book,

CANMAT, CMHA, CPS & AAP, Critical Care Medicine, Manufacturer's info, Royal Australian College of GP, Tintanalli ER (0.7% each).

Following were the disagreement with the guidelines:

1. "Corporate potential bias"
2. "Sometimes lacks context"
3. "I have my own rational approach to prescribing benzodiazepines"
4. "differentiating efficacy of analgesia, sedatives and antipsychotics in given situations"
5. "guidelines are guidelines, you are allowed not to follow them in all cases as this would be against guidelines"
6. "guidelines not clear on pharmacotherapy for patients intolerant to or cannot (sic) afford first line drugs (SSRI, SNRI): benzodiazepines mentioned as long term adjunctive drugs"
7. "Don't reflect reality of addiction"

### 7. Tools to optimize prescription standards:

The second to last question looked at the perceptions of the prescribers with regards to the most helpful method/tool to optimize their prescribing standards (Table 4.11).

61.5% of the respondents preferred to improve their prescribing standards by utilizing professional guidelines. CME by expert (44.1%) and availability and affordability of counseling (38.8%) were the second and third choices respectively for the same. The respondents did not regard regulation by the government as a helpful tool and 52.4% ranked it as an least helpful method to better their prescribing standard.

Table 4. 11 The perceptions of the prescribers with regards to the most helpful method/tool to optimize their prescribing standards

<b>Variable</b>		<b>Most helpful (1)</b>	<b>Moderately helpful (2)</b>	<b>Somewhat helpful (3)</b>	<b>Least helpful (4)</b>	<b>Total</b>
Professional guidelines	Frequency	107	43	18	6	174
	Valid Percent	61.5	24.7	10.3	3.4	100.0
CME by expert	Frequency	71	53	28	9	161
	Valid Percent	44.1	32.9	17.4	5.6	100.0
Regulation by government	Frequency	12	16	32	66	126
	Valid Percent	9.5	12.7	25.4	52.4	100.0
Availability and affordability of counseling	Frequency	59	21	38	34	152
	Valid Percent	38.8	13.8	25	22.4	100.0

## 8. Personal use of BZDs by prescribers:

The last question pertained to the personal use of BZDs by the prescribers themselves.

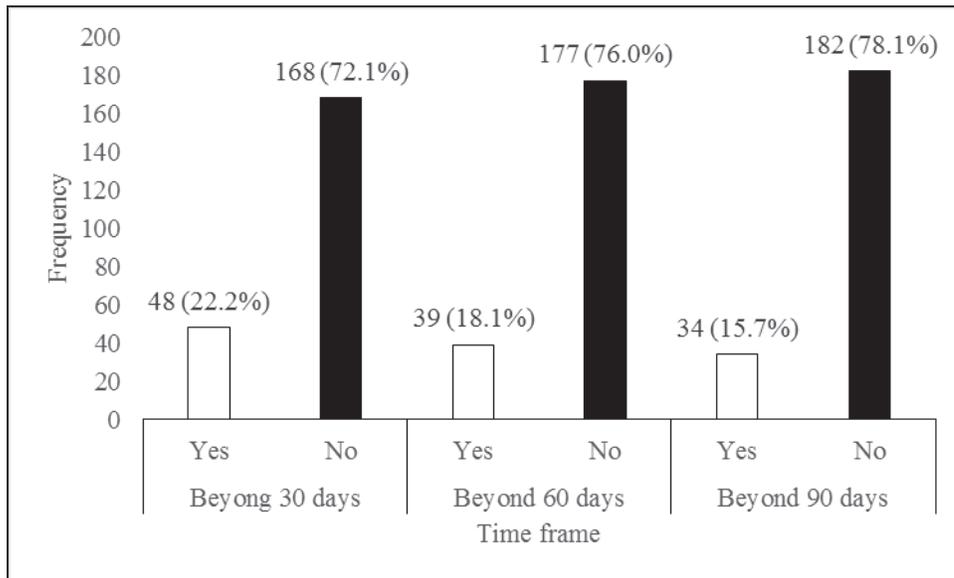


Figure 4.8 Personal use of BZDs by prescribers beyond 30/60/90 days.(Sample size: *N*: 233)

As seen in Figure 4.8, though a majority of respondents indicated that, personally, they would not use BZDs after 30, 60 and 90 days, 22.2 %, 18.1% and 15.7% were open to the consideration of personally using BZDs after 30, 60 and 90 days respectively.

Significant results (Table 4.12):

It was found that older (48 to 71 year) physicians were more open to using BZDs beyond 60 days and 90 days.

Table 4.12 The significant results from the chi-square analyses between demographic variables and personal use of BZDs by the prescribers (respondents)

<b>Personal use of BZDs by physicians(N)</b>	<b>Demographic characteristic of physician (NN)</b>	<b>% of NN = Yes?</b>	<b>Chi-square / Fisher's exact</b>	<b>p</b>	<b>Effect size= small/moderate /large</b>
Beyond 90 days (194)	Older phys (48 to 71 year) (96)	21.9	7.171	0.007	0.192 =small
	Younger phys (27 to 47) (98)	8.2			
Beyond (60) days 194	Older phys (48 to 71 year) (96)	22.9	4.696	0.030	0.156 =small
	Younger phys (27 to 47) (98)	11.2			

Note: 1. The degree of freedom for all the reported results in Table 4.12 is 1. 2. No effect size is calculated for results reporting Fisher's exact test.

## **Chapter 5: Discussion, Limitations, and Conclusions:**

This study is an effort to understand the BZD prescribing patterns of physicians as well as the variables which influence them. In this chapter I will discuss pertinent findings from the survey, enumerate limitations of the study as well as present conclusions for this study.

### Discussion:

BZD prevalence is not uniform throughout Canada; provincial variations have been reported with Quebec being the highest consumer and Atlantic Canada (including Newfoundland and Labrador) being the lowest consumer of BZD (Hogan et al., 2003). Lorazepam was the most prescribed BZD in the present survey. In spite of regional variations observed by Hogan et al. (2003), this result is in tandem with the findings by Smith et al. (2008) who stated that in the Canadian province of Nova Scotia, lorazepam was the most commonly used BZD (though only among seniors and those persons receiving social security benefits). Furthermore, lorazepam was observed to be the drug (BZD) of choice for elderly patients in Quebec receiving a BZD prescription for the first time (Sylvestre et al., 2012). High potency BZDs such as lorazepam are associated with an increased risk of dependence (Nelson & Chouinard, 1999) and increased propensity to cause fall-related injuries among seniors (Sylvestre et al., 2012). As fall-related injuries may have implications for an individual (patient) and for society (cost of hospitalization

etc), the need for lorazepam prescriptions among the population, especially the elderly, should be evaluated via further research. In this survey, older physicians (48 to 71 years) were more inclined to prescribe chlordiazepoxide and flurazepam than their younger (27 to 47 years old) counterparts. Flurazepam and chlordiazepoxide undergo both Phase I and Phase II metabolism and are considered long-acting BZDs. As Phase I metabolism slows with age, these BZDs are best avoided in the elderly (Nelson & Chouinard, 1999). Additionally, higher doses of flurazepam and chlordiazepoxide are associated with risks of injury among the elderly (Tamblyn, Abrahamowicz, Berger, McLeod, & Bartlett, 2005). Furthermore, the guidelines do not recommend long-acting BZDs for patients aged 65 years and older (APA, 1990). As this survey did not link indications with the type (long- or short-acting) of BZDs prescribed, more research needs to be conducted to understand such prescriptions.

This survey also revealed that a higher number of male physicians prescribed BZDs in comparison to female physicians. Despite the increase in the proportion of females joining the Canadian physician work force, male physicians still outnumber their female counterparts in clinical practice (CIHI, 2012). Furthermore gender bias was observed among the total number of respondents to this survey as only 36% of respondents were females. Both of these factors may explain the increased BZD prescribing by male physicians in Newfoundland and Labrador. The association between gender (male) and BZD prescribing was also reflected in a Norway based study by Bjørner and Lærum

(2003) which reported that male doctors were significantly associated with ‘high-volume’ BZD prescribing. It also reported that ‘high-volume’ prescribers consider BZDs a difficult class of medication to use in accordance with the current guidelines, and knowingly prescribe contrary to the current guidelines. Swedish physicians too had similar prescribing habits; a case study based survey which tested the significance between BZD prescribing habits and physician characteristics concluded that female physicians were significantly less likely to consider prescribing BZD for generalized anxiety syndrome than male physicians (Jarbrink, Carlsten, & Otto Frederiksen, 1999). Similarly, more number of male physicians were prescribing BZDs to patients than their female counterparts in British Columbia (Thomson & Smith, 1995). Another significant finding which demonstrated differing practices among male and female respondents to this survey is increased incidence of the prescribing of triazolam by male physicians. Triazolam, a short-acting BZD, is not recommended as a sedative-hypnotic since it causes behavioural changes (Jensen & Regier, 2010). Increased reliance on pharmacotherapy as a treatment modality along with less time spent with the patient during consultation has been noted among Canadian psychiatrists (Garfinkel et al., 2004). The changing sex ratio among the Canadian physician workforce is being reflected by a continuing increase in the number of female physicians as general practitioners (CIHI, 2012). Hence, the translation of theory into practice is likely because, while respondents of both genders agreed with having CPG bearing upon their BZD

prescribing habits, female physicians were significantly more associated with perusing the guidelines in the BZD prescribing process than their male counterparts. Thus increased concordance with evidence-based medicine with respect to BZD prescribing may be expected at the primary care level. Though physicians agree with CPG being one of the determining factors in their prescribing of BZDs, in this survey, 77.2 % of physicians indicated prescribing BZDs for more than 90 days. Since the guidelines advise using BZDs for the shortest period of time possible and mention 2-4 weeks as an ideal period of time for its use, there is clearly a disjoint between clinical practice and guideline recommendations. Discordance between perceptions held by physicians and their clinical practice regarding BZD prescribing habits was also observed in an Irish survey. The evidence-based statement 'Low rate of benzodiazepine prescribing for prolonged periods (>2-4 weeks)' was ranked third most important and relevant indicator of the physicians' daily practice but a simultaneous prescription database audit proved otherwise; the majority of BZD prescriptions were for a duration of more than 4 weeks (Okechukwu, Benett, & Feely, 2006). Uptake of CPG has been the focus of many studies (Parker et al., 2008; Sekimoto, Imanaka, Kitano, Ishizaki, & Takahashi, 2006; Sinuff, Kahnamoui, Cook, & Giacomini, 2007). One such study (Parker et al., 2008) found comprehensiveness of the guidelines to be an important factor in its uptake by physicians, i.e. guidelines which do not include all the necessary treatment modalities for a disease state can face barriers to its use in clinical practice. In disease states such as

insomnia, psychological counselling or behavioural therapy is often required in addition to pharmacotherapy to achieve the desired outcome ( Jensen & Regier, 2010).

Furthermore, physicians in the same study (Parker et al., 2008) were found to be reticent about using constantly revised guidelines since they feared that their clinical credibility would be threatened if they suggested frequent changes to the treatment modality of their patients. Also, since most guidelines are more than 2 pages in length, a shorter version may help improve its uptake. In this case, a recent Canadian study concluded that physicians were more enthusiastic to utilize a concise one-page guideline (Pimlott et al., 2009). Multifactorial intervention(s) aimed at not only prescribers (physicians primarily) but also patients and pharmacists and the simultaneous implementation of government legislation may be an answer to the dilemma of resistance to change in BZD prescribing habits of physicians. Two studies (Australian and Danish) were able to significantly reduce BZD usage in their respective regions using physician education (including provision of guidelines and motivational lectures), patient information campaigns involving local/regional media, government issued strictures on the length of BZD prescriptions, and mandatory in-person (and not telephonic) consultations to prescribe BZDs. Though the long-term impact of both these studies are not known, and the study by Dollman et al. (2005) focused on rural participants only, inclusion of the main stakeholders to modulate BZD prescribing may help optimize prescribing practices in Canada (Dollman et al., 2005; Jørgensen, 2007). In this survey, physicians have cited

'professional guidelines' as a variable which can help them optimise their BZD prescribing behaviour. A similar opinion is echoed in the study by Sinuff et al. (2007) which found that guidelines are viewed as a multipurpose instrument which can help make a clinical decision, improve knowledge about current practices, and can be used as an autonomy aid (to make independent decisions) in accordance with the professional stature of the respondents (physicians). While adoption of guidelines on BZDs were measured to be negligent in some studies, it was perceived to be adequate among Canadian physicians in 2001 (Neutel, Skurtveit, & Berg, 2012; Siriwardena et al., 2006; Svarstad & Mount, 2001; Tu, Mamdani, Hux, & Tu, 2001). However, the proposed conclusion by Tu et al. (2001) was refuted by an intervention study which concluded that guidelines had little effect on existing patterns of prescribing long-acting BZDs to seniors and the continuation of BZDs for long durations without any clinical evidence of effectiveness (Pimlott et al., 2003). The major limitation of these studies include conflation of the availability of guidelines with awareness, adoption, and finally adherence of these guidelines. Development and publication of CPG are steps preceding its awareness, uptake, and finally, its continued adoption by clinicians. Accessibility and agreement with guidelines were cited as barriers to the use of sedation protocols among physicians practicing critical care medicine (Tanios, de Wit, Epstein, & Devlin, 2009 ). Incorporation of physician views to develop comprehensive guidelines which address management of non-clinical issues such as patient expectation may enhance the adoption

of a CPG. Time limitation is postulated to be an impediment in providing quality of care by physicians for patients with mental health issues. This concern can be alleviated by improved dissemination of BZD knowledge to the public to increase the awareness of clinical evidence on the prescribing and usage of medication for a correct length of time and indication(s). Also, a prescriber better equipped to identify mental health issues may be at an advantage through the utilization of a guideline recommended treatment algorithm (Smolders et al., 2010).

In our survey 'patient's request' as a variable influencing BZD prescribing received equivocal response from physicians. However, studies by Sekimoto et al. (2006) and Tracy, Coelho Dantas, & Upshur (2003) revealed that when faced with a trade-off between satisfying their patients or limiting their prescriptions for genuine cases and stopping medication when it loses its effectiveness, physicians chose the former option. Tracy et al. (2003) further stated that physicians would change their common practice(s) in disease management to provide treatment which is deemed favourable by the patient. In the present survey, the primary reason to continue BZDs after 90 days was to continue longstanding prescriptions; also, respondents cited similar reasoning behind the decision to prescribe more than one BZD concurrently to the same patient. Discontinuation of BZDs in long-term users requires both patient and physician support. Records of Dutch patients who were long-term BZD users were assessed retrospectively after the

completion of a BZD discontinuation program. Only 12 % of patients were BZD free and the concurrent use of more than one BZD accounted for failure to discontinue the drug in 33% of patients. While practice settings did not significantly affect continuation or resumption of BZD prescriptions, the authors surmised that patient pressure may have played a role in BZD prescribing patterns (Couvee, Timmermans, & Zitman, 2002). As noted in a Swedish qualitative study (Bendtsen, Hensing, McKenzie, & Stridsman, 1999) among general practitioners, the primary reason for patients to ask for BZDs is to continue their existing prescriptions. Swedish physicians reported that 37% of BZD users asking for prescriptions wanted to continue (and not start) their BZD consumption. These physicians cited anticipated refusal by elderly patients to discontinue BZDs and resistance to access specialized mental health services as barriers to the implementation of evidence-based prescribing practices. Conversely, 39% of Swedish general practitioners chose not to prescribe BZDs when faced with pressure from patients. 91% of these physicians noted abuse or risk of abuse as a factor in refusing to prescribe BZDs to patients in their daily practice. Risk of abuse was also one of the main variables that influenced the prescribing of BZDs among the respondents in the current survey. In the current climate of collaborative decision-making, patient perception and views are heavily weighed prior to deciding upon the clinical course of treatment. With respect to BZDs, (elderly) patients' and physicians' opinions of benefit-risk vary significantly; patients perceive BZDs as beneficial while physicians consider them as

risky long-term treatment for insomnia (Mah & Upshur, 2002). Patient education as a part of multifactorial intervention may be a viable option to reduce the prevalence of BZDs in the elderly population (Ostini, Jackson, Hegney, & Tett, 2011). A patient who is given the opportunity to compare his/her long held beliefs on the effectiveness of BZDs may revise them upon being presented with clinical evidence on the risks associated with its use (Martin, Tamblyn, Ahmed, & Tannenbaum, 2013).

With respect to specialty, we found that a greater number of general practitioners (64%) indicated prescribing BZDs to their current patients. This may be due to the greater number of general practitioners than psychiatrists found in Newfoundland and Labrador (Canadian Medical Association, 2011). This result is echoed in a Swedish survey which concluded that psychiatrists prescribed less BZD than general practitioners (Jarbrink et al., 1999). However, a national prescription database study in Norway concluded that psychiatrists were contributing significantly more to the increased prevalence of BZD prescriptions in patients with insomnia (Hausken, Furu, Skurveit, Engeland, & Bramness, 2009). General practitioners are the primary point of contact for people with mental as well as physical ailments, while psychiatrists focus upon diagnosing and treating the mental disorders. Therefore, this can translate into a high volume of BZD prescriptions by general practitioners as BZDs are indicated as anxiolytics, hypnotics, anticonvulsants,

amnestics, and myorelaxants. Also many primary care physicians are averse to the idea of initiating BZD withdrawal in the elderly if they were unable to achieve success in their previous attempts and if the patients were chronic users (Cook, Marshall, Masci, & Coyne, 2007).

This survey found that 18% of physicians were concurrently prescribing more than one BZD to the same patient. This result is substantiated by the findings of an office-based study which revealed that office-based psychiatrists were more likely to prescribe two or more sedative-hypnotics for anxiety disorders (Mojtabai & Olfson, 2010). The WHO guidelines (1996) explicitly state that more than one BZD should not be given to the same patient as they act on the same binding sites in the brain. The '65 years and over' segment of the population is expected to increase in the coming years in Canada (Statistics Canada, 2007) and BZDs have been linked to falls and hip fractures in this aforementioned group (Cumming & Le Couteur, 2003). The current BZD prescribing trend needs to be corrected in the immediate future in order to avoid unnecessary medicating of patients, especially seniors.

Zopiclone was rated as the second most frequent medication to be prescribed by the physicians in this survey. In Canada, zopiclone is considered a 'good choice' to manage insomnia because it is considered to have less side effects (tolerance). It is considered a

safer and effective alternative to BZDs with lesser chances for the occurrence of rebound insomnia as well as withdrawal symptoms (Jensen & Regier, 2010). Our results regarding zopiclone also complements the views of general practitioners in the UK who believe Z-drugs to be a safer and, more effective class of medication (with fewer side effects) for insomnia in older patients (Siriwardena et al., 2006).

A study in 2002 estimated 3.3 million Canadians aged 15 or older, or about one in every seven had insomnia (Statistics Canada, 2005). In this study, prescribing BZDs due to insomnia was significantly associated with physicians practicing in areas with more than 25,000 people. This significant association may be on account of the high prevalence of insomnia in urban areas (Morin, LeBlanc, Daley, Gregoire, & Mérette, 2006).

In my study, BZD prescriptions for panic disorders were significantly associated with physicians practicing in areas with less than 25,000 people, and ‘Availability of counseling’ was found to be a significant factor associated with physicians practicing in areas containing less than 25,000 people. Panic attacks can be managed with cognitive-behavioral therapy which is considered efficacious during either acute or long-term treatment (Pollack et al., 2003). Non-pharmacological therapy such as cognitive behavioural therapy is postulated to be cost effective in international literature, though this finding is yet to be ascertained in a Canadian context (Myhr & Payne, 2006).

About 20% of the Canadian population, or around one-fifth of the older population, lives in rural areas (Statistics Canada, 2006 ; Havens, n.d.). Given that it is difficult to access health care (especially mental health specialists) in rural areas (Starkes, Poulin, & Kisely, 2005), the optimization of BZD prescribing may be greatly assisted if relevant resources (such as certified counsellors, counselling centres etc) were provided to them.

Additionally, health care education aimed at the public with less education may help improve their usage of such services as increased utilization of specialized mental health facilities was associated with better educated patients within Atlantic Canada (Starkes et al., 2005).

The adverse effects resulting from acute as well as chronic use of BZDs are well-known to prescribers due their educational background, clinical experience and constant exposure to the sources of CME. Hence, it was perplexing to note that around 22.2 % of the prescribers were open to the consideration of personally using BZDs after 30 or more days. A study focused upon exploring medication use among Swiss physicians reported similar findings: it revealed that self- medication among physicians was more common for tranquilizers including hypnotics and less frequent in case of antidepressant drugs (Schneider, Gallacchi, Goehring, Künzi, & Bovier, 2007). Though the same study (Schneider et al., 2007) reported self-medication to be more among younger physicians, we found that older physicians were significantly more inclined to

self-medicate with BZDs for more than 60 or 90 days. The following factors (combined or individually) may explain the personal use of BZDs among older physicians: impaired mental and/ or physical health, a tendency to treat themselves i.e. self-referral (Töyry et al., 2000) and fewer barriers to procure medication. Furthermore, a prescribing pattern of sedative hypnotics for patients is found to have a significant association with the self-medicating behaviour of older physicians (Verger et al., 2004) because high volume BZD prescribing in their practice is correlated to increased personal use. Note that there may be other individual factors which contribute to self-medication, though literature on the subject is limited. Education regarding self-treatment (including self-medication), information on the BZD class of drugs and interventions to diminish the threshold for seeking counsel from health care providers may help reduce personal usage of BZDs.

Limitations:

This is a cross-sectional survey. No causal inference could be drawn from its results, only associations between factors can be concluded.

Given the methodology, bias is introduced through the limitations of informational recall via memory.

Physicians practicing for 20 to 50 years as well as older (48 to 71 years) physicians were more inclined to cite ‘extended crises in person’s life’ as a reason for prescribing BZDs for longer than 90 days. Though this was a much cited opinion, it is also subjective in

nature. Therefore, it was difficult to draw a definite conclusion from it. Further research may need to be conducted to understand the precise definition of this phrase from the physician's viewpoint.

Research which focuses on the reasons and variables that account for personal use of BZDs by physicians and the questions related to BZD prescribing with respect to each segment of the population (age-wise) may provide us with more information on BZD prescribing patterns.

Online resources (such as web-based questionnaires) were not explored to seek responses for this survey.

#### Conclusions:

The prescribing patterns of BZDs vary. Gender-based variations were observed; female physicians are more inclined towards uptake of CPG. Male physicians were significantly associated with more BZD prescribing among Newfoundland and Labrador physicians; this may be attributed to the increased male presence in the Canadian physician work force. These practice patterns may have implications in the primary care setting due to the increasing feminization of the Canadian physician workforce (especially in family/general practice).

In this survey, discordance between agreement with the recommendations of the CPG and its implementation in the clinical practice was observed. Barriers to the adoption and adherence of the CPG need to be addressed. Continuation of long-term prescriptions as a reason to further prescribe BZDs was identified as a common theme behind inappropriate prescriptions. Patient pressure or their expectations may be one of the factors behind such clinical decisions. Improving public awareness on the benefits-risks of taking BZDs for short- and long-term durations may help remodel patient views on BZDs. Furthermore, implementation of multipronged interventions involving all stakeholders such as physicians, patients, health care organizations as well as federal/ provincial regulatory bodies may decrease the inappropriate prescribing of BZDs by physicians.

Older physicians significantly prescribe more chlordiazepoxide and flurazepam to their patients; both these agents are associated with risk of injury among the elderly population. As the proportion of the senior population is growing at a faster rate in the developed world, geriatric medicine needs to evolve and involve physicians to ensure harm reduction due to inappropriate medications. Additionally, general practitioners were more likely to prescribe BZDs than psychiatrists. Given that primary care physicians are the first point of contact (for patients) in the health care setup, the initiation or continuation of BZD prescriptions by general practitioners is concerning. Informational

or training modules addressing the educational needs of general practitioners in both urban and rural areas may help remedy the situation. Further research needs to be carried out to link each prescribed BZD with its indication(s) to understand the reasoning behind such prescriptions.

Lastly, personal use of BZDs beyond the recommended period of time by physicians may be due to self-referral and perceived benefits of the drug. Older physicians were significantly more prepared to take BZDs for long-term use. Personal choices of physicians in disease management may have an impact on their work place functioning. Thus, an assessment of the health beliefs held by older physicians may help elucidate the factors affecting their personal preferences of treatment algorithms.

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## **Appendices:**

## APPENDIX A: COVER LETTER FOR FIRST CONTACT



Faculty of Medicine

Clinical Epidemiology Unit  
300 Prince Philip Drive, Health Sciences Centre  
St. John's, NL Canada A1B 3V6  
Tel: 709-777-7390/7346: Fax: 709-777-7877  
[www.med.mun.ca/graduate/pages/epidemiology.htm](http://www.med.mun.ca/graduate/pages/epidemiology.htm)

June 4, 2007

Dear Doctor:

As you are aware, benzodiazepines are a class of drugs that have a wide range of actions including, but not limited to, anxiolytic, hypnotic, anticonvulsant, amnesic, and myorelaxant.

In 2002, a team of concerned physicians, academics, allied health professionals, private and public insurers, government agencies, and concerned citizens formed an organization to evaluate prescribing and usage patterns of benzodiazepines. Initially, a Canada /United States collaboration, the organization has grown significantly in the past few years, and now has an international membership.

At this time we are soliciting your help to evaluate current benzodiazepine prescribing patterns as well as factors that may be influencing benzodiazepine prescribing. Through your efforts, we hope to increase our understanding of how benzodiazepines are prescribed and eventually make available evidence based guidelines.

The accompanying questionnaire is voluntary and can be completed in approximately 10 minutes. Though every effort is made to ensure the anonymity of the accompanying questionnaire, it can not be guaranteed. The numeric code on the return envelope is only to identify non-respondents so that a reminder can be sent. The code will **not** be linked to the responses. **We understand that your time is valuable and would like to thank you, in advance, for your contribution to this timely and important research.**

Please return the completed questionnaire in the postage-paid pre-addressed envelope by June 30. Return of the questionnaire will serve as your consent to participate in this study.

If you would like to discuss the study further, please do not hesitate to contact Dr Gerry Mugford ([gmugford@mun.ca](mailto:gmugford@mun.ca) ; tel. (709) 777-7390 / pager (709) 570-9090) or Shweta Pai ([k42ssp@mun.ca](mailto:k42ssp@mun.ca) ; tel. (709) 777-6305).

Sincerely,

Dr. Gerry Mugford

Ms. Shweta Pai

Dr. Terrence Callanan

APPENDIX B: COVER LETTER FOR SECOND CONTACT



Faculty of Medicine

Clinical Epidemiology Unit  
300 Prince Philip Drive, Health Sciences Centre  
St. John's, NL Canada A1B 3V6  
Tel: 709-777-7390/7346: Fax: 709-777-7877  
[www.med.mun.ca/graduate/pages/epidemiology.htm](http://www.med.mun.ca/graduate/pages/epidemiology.htm)

July 16, 2007

Dear Doctor:

As you are aware, benzodiazepines are a class of drugs that have a wide range of actions including, but not limited to, anxiolytic, hypnotic, anticonvulsant, amnesic, and myorelaxant.

In 2002, a team of concerned physicians, academics, allied health professionals, private and public insurers, government agencies, and concerned citizens formed an organization to evaluate prescribing and usage patterns of benzodiazepines. Initially, a Canada /United States collaboration, the organization has grown significantly in the past few years, and now has an international membership.

At this time we are soliciting your help to evaluate current benzodiazepine prescribing patterns as well as factors that may be influencing benzodiazepine prescribing. Through your efforts, we hope to increase our understanding of how benzodiazepines are prescribed and eventually make available evidence based guidelines. A copy of the enclosed questionnaire was previously mailed to you; however we have not yet received your response. If you have returned your questionnaire please accept our sincere thanks and disregard this correspondence. If not, please take a few moments to complete the enclosed replacement questionnaire and return it in the postage-paid pre-addressed envelope. Please return the completed questionnaire by August 16.

The accompanying questionnaire is voluntary and can be completed in approximately 10 minutes. Return of the questionnaire will serve as your consent to participate in this study. Though every effort is made to ensure the anonymity of the accompanying questionnaire, it can not be guaranteed.

**We understand that your time is valuable and would like to thank you, in advance, for your contribution to this timely and important research.**

If you would like to discuss the study further, please do not hesitate to contact Dr Gerry Mugford ([gmugford@mun.ca](mailto:gmugford@mun.ca) ; tel. (709) 777-7390 / pager (709) 570-9090) or Shweta Pai ([k42ssp@mun.ca](mailto:k42ssp@mun.ca) ; tel. (709) 777-6305).

Sincerely,  
Dr .Gerry Mugford

Ms. Shweta Pai

Dr. Terrence Callanan

**SECTION I: Q 1 to Q 9**

**Q1. Your gender (Place a ✓ in the appropriate box)**

- Male  Female

**Q2. Your present age**

---

**Q3. Year you completed medical studies**

---

YYYY

**Q4. How many years have you practiced medicine?**

---

**Q5. Population of the community where you practice? (Place a ✓ in the appropriate box)**

- Less than 2,000  
 2,000-4,999  
 5,000-9,999  
 10,000-24,999  
 25,000-49,999  
 50,000-99,999  
 100,000 or more

**Q6. Your practice is best described as (Place a ✓ in the appropriate box)**

- Office practice  
 Hospital based  
 Public clinic

**Q7. You (Place a ✓ in the appropriate box)**

- Practice alone  
 Practice in a group (all physicians)  
 Practice as part of a multidisciplinary team

**Q8. Which best describes you? (Place a ✓ in the appropriate box)**

- General practitioner  
 Child psychiatrist  
 Adult psychiatrist  
 Forensic psychiatrist  
 Neurologist  
 **Other (please specify)**
- 

**Q9. Do you currently prescribe benzodiazepines? (Place a ✓ in the appropriate box)**

- Yes (**Please continue to Q 10**)  
 No (**Please stop here. Thank you for your support.**)

**SECTION II: Q 10 to Q 17**

**Q10. From the list below, please indicate the drugs you currently prescribe (Circle all that apply)**

- |   |   |
|---|---|
| 1. Alprazolam (e. g.: Xanax <sup>®</sup> )                | 12. Nitrazepam (Mogadon <sup>®</sup> )    |
| 2. Bromazepam ( Lectopam <sup>®</sup> )                   | 13. Oxazepam (Apo-Oxazepam <sup>®</sup> ) |
| 3. Chlordiazepoxide ( Apo-Chlordiazepoxide <sup>®</sup> ) | 14. Quazepam (Doral <sup>®</sup> )        |
| 4. Clobazam ( Frisium <sup>®</sup> )                      | 15. Temazepam (Restoril <sup>®</sup> )    |
| 5. Clonazepam (Rivotril <sup>®</sup> )                    | 16. Triazolam ( Halcion <sup>®</sup> )    |
| 6. Clorazepate (Novo-Clopate <sup>®</sup> )               | 17. Zaleplon (Starnoc <sup>®</sup> )      |
| 7. Diazepam (Valium <sup>®</sup> )                        | 18. Zopiclone (Imovane <sup>®</sup> )     |
| 8. Estazolam ( ProSom <sup>®</sup> )                      | 19. Zolpidem (Ambien <sup>®</sup> )       |
| 9. Flurazepam ( Dalmane <sup>®</sup> )                    | 20. Carisoprodol (Soma <sup>®</sup> )     |
| 10. Lorazepam (Ativan <sup>®</sup> )                      | 21. <b>Other(s) (please specify)</b>      |
| 11. Midazolam ( Apo-Midazolam Injectable <sup>®</sup> )   | <hr/>                                     |

**Q11. Please indicate your reason(s) for prescribing benzodiazepines (Circle all that apply).**

- |                           |  |
|---------------------------|--|
| 1. Anxiety                | 9. Convulsive disorders (ex: Seizures) |
| 2. Insomnia               | 10. Anti-Vertigo                       |
| 3. Depression             | 11. Sedation                           |
| 4. Movement disorders     | 12. Panic attacks                      |
| 5. Alcohol withdrawal     | 13. Amnesic                            |
| 6. Muscle relaxant        | 14. Bipolar disorder                   |
| 7. Grief reaction         | 15. <b>Other(s) (please specify)</b>   |
| 8. Single-dose for phobia | <hr/>                                  |

A survey assessing current benzodiazepine prescribing patterns and factors influencing benzodiazepine prescribing in Newfoundland and Labrador physicians

**Q 12. Please indicate your reason(s) to continue benzodiazepines beyond 90 days (Circle all that apply).**

- |                                      |   |
|--------------------------------------|---|
| 1. Never                             | 7. Chronic muscle spasms                |
| 2. Extended crisis in patient's life | 8. Convulsive disorders                 |
| 3. Chronic insomnia                  | 9. Bipolar disorder                     |
| 4. Chronic anxiety                   | 10. Patient on long term benzodiazepine |
| 5. Palliative care                   | 11. <b>Other(s) (please specify)</b>    |
| 6. No response to other medications  | _____                                   |

**Q13a. Do you prescribe more than one benzodiazepine concurrently to the same patient : Y/ N**

**Q13b. If 'Yes' to Q 13a then please specify the reason(s) for prescribing more than one benzodiazepine concurrently:**

**Q14. Please indicate the degree to which the following variables influence your benzodiazepine prescribing habits. (Please circle the appropriate number)**

Variable	Strongly Disagree		Neither Agree/ Disagree			Strongly Agree	
1. Clinical practice guidelines	1	2	3	4	5	6	7
2. Peer Group	1	2	3	4	5	6	7
3. Side effects	1	2	3	4	5	6	7
4. Drug interactions	1	2	3	4	5	6	7
5. Insurance coverage	1	2	3	4	5	6	7
6. Drug availability	1	2	3	4	5	6	7
7. Cost	1	2	3	4	5	6	7
8. Risk of abuse/misuse	1	2	3	4	5	6	7
9. Manufacturers' information	1	2	3	4	5	6	7
10. Pharmaceutical rep	1	2	3	4	5	6	7
11. Patients' request	1	2	3	4	5	6	7
12. Indication	1	2	3	4	5	6	7
13. Effectiveness of drug	1	2	3	4	5	6	7
14. Continuing an existing prescription	1	2	3	4	5	6	7
15. Availability of counseling	1	2	3	4	5	6	7
16. Affordability of counseling	1	2	3	4	5	6	7
17. Other(s) (please list): _____	1	2	3	4	5	6	7

**Q15. In Q14 above you have indicated the degree to which practice guidelines influence your benzodiazepine prescribing patterns. Could you please indicate:**

- 1 Which guidelines do you use? \_\_\_\_\_
- 2 Who provides them? \_\_\_\_\_
- 3 Disagreements with these guidelines. (If any)

**Q16. Please indicate which of the following would most help you to optimize your benzodiazepine prescribing. (Please rank them 1(most helpful), 2, 3, 4(least helpful) :**

- Professional guidelines     CME by an expert in the field     Regulation/Law by the government
- Availability and affordability of counseling based treatments for anxiety disorders     **Other (please specify):** \_\_\_\_\_

**Q17. Please indicate whether you would personally use benzodiazepines beyond: a. 30 days (Y/N) b. 60 days (Y/N) c. 90 days (Y/N).**

**Thank you**