Pharmacoepidemiology and Drug Utilization of Benzodiazepines and Z-Drugs among adults in Manitoba, Canada

By

Jaden Brandt

A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

College of Pharmacy, Rady Faculty of Health Sciences

University of Manitoba

Winnipeg, MB, CAN

i) Abstract

Background: The use of benzodiazepines and z-drugs remains controversial given their potential for misuse and harm. Investigation of their use in Manitoba remains important for monitoring and improving prescribing patterns.

Methods: Administrative data was used to conduct i) drug utilization study from 2001-2016, and ii) incident-user cohort study of patients with anxiety/insomnia.

Results: i) Z-drug use increased on all measures while only dose intensity increased for benzodiazepines. Higher utilization occurred among females and those ≥65 years.

ii) The proportion of patients who became long-term users (>6months) in their first episode of use ranged from 4.5-9.6%. Males, older age, socioeconomically deprived, use of opioids or psychotropic agents, and poor physical health, were associated with long-term use.

Conclusion: While less than one in 10 were considered a long-term user of these agents, further investigation into whether specific factors associated with long-term use requires consideration during the prescribing of these agents is warranted.

ii) Preface

This thesis is composed of four manuscripts (some published as scientific articles, others submitted or to be submitted for publication), supplemented with additional writings, that have been organized and expounded upon to create a cohesive, comprehensive document. This thesis follows the AMA (American Medical Association) citation style. While the first and shortest chapter (introduction) is followed by the longest written chapter (literature reviews), it is the chapters that follow which are the most important in my training as a junior scientific investigator. Chapters 3 and 4 represent the original research project as it was conceived, proposed and conducted from the beginning of my graduate studies.

Overall, it is the hope that this thesis has accomplished two things. First, that some of the work herein is an important contribution to the fields of drug utilisation and pharmacoepidemiology as they relate to benzodiazepines and Z-Drugs. Second, that the original research conducted in the Manitoban population may be of some use (directly or indirectly) to academics, health professionals and health policy-makers in Manitoba to improve upon the use of these medications.

iii) Acknowledgements

Firstly, I offer my sincerest gratitude to my advisor Dr. Christine Leong, who was most patient with me and who provided valuable, expert insight to me at various stages of the thesis. Additionally, the members of my thesis committee (Drs. Zelenitsky, Alessi-Severini, Chateau and Singer) provided me with important advice throughout the research process.

I was most happy to share my research journey with my student peers and colleagues (all friends) in the pharmacoepi training group. I thank my friend Mr. Kevin Friesen, especially, both for his frequent friendly conversation/debate on various intellectual matters (both in and beyond pharmacy) and for his frequent SAS advice and occasional vetting of my programming code.

I thank my analyst Randy Wallid (and Heather Prior and others at MCHP) for his/their diligence on updating my datasets and resolving related issues on my behalf. I also thank Randy for the book recommendations and our shared passion for world literature (Russian especially!).

I thank the Manitoba Government and College of Pharmacy for funding support to make this research possible.

I thank Lori Bielefeld at the bookstore both for her jovial conversation and the provision of various books which kept my mind occupied on topics beyond my academic research.

I thank Edgar and Cyndi for the support.

I thank Darren King, Stuart Bellingham, Kelly Borisenko, Shannon Venne, Kelly Kennedy, Heather Charron and the rest of the staff at Clarke's Pharmacy in Thompson for: 1) teaching me the business and human side of the profession when I was a new pharmacist in a way that is

inaccessible in any classroom and 2) being the best work friends and colleagues a person can ask for.

Lastly, I thank my parents (Debbie and Russ), brother (Taben), my girlfriend (Kelleigh) and her family (John, Cathy, Caitlin, Nana etc..) and my many friends for their love and support that continues to carry me forward in life. I couldn't do this without you.

iv) Dedication

This thesis is dedicated to all persons who have used, use, or will use, Benzodiazepines or Z-Drugs…for better, or for worse.

v) Table of Contents

vi) List of Tables

vii) List of Figures

viii) List of Abbreviations

ACG – Adjusted Clinical Group(s)

AD – Antidepressant

ATC – Anatomical Therapeutic Chemical

BZD – Benzodiazepine(s)

CADTH – Canadian Agency Drugs & Technology in Health

CCI – Charlson Comorbidity Index

CCSA – Canadian Centre on Substance Abuse

CIHI – Canadian Institute for Health Information

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

CPG – Clinical Practice Guideline

CTADS - Canadian Tobacco, Alcohol and Drug use Survey

DAG – Directed Acyclic Graph

DDD – Defined Daily Dose

DME – Diazepam Milligram Equivalence

DPIN – Drug Programs Information Network

GABA – Gamma-Amino-Butyric Acid

GAD – Generalised Anxiety Disorder

ICD – International Classification of Diseases (CM – Clinical Modification, CA – Canadian Adaptation)

INCB – International Narcotics Control Board

MCHP – Manitoba Centre for Health Policy

MHSAL – Manitoba Health, Seniors and Active Living

OCD – Obsessive Compulsive Disorder

PD – Panic Disorder

PHIN – Personal Health Information Number

PRDR – Population Research Data Repositor

PTSD – Post Traumatic Stress Disorder

ROC – Receiver Operator Curve

RUB – Resource Utilization Band

SDLP – Standardized Deviation of Lateral Position

SAD – Social Anxiety Disorder

SEFI – Socio-Economic Factor Index

UN – United Nations

US – United States

WHO – World Health Organization

Chapter 1 - Introduction

1.1) Background

Benzodiazepines and Z-Drugs are among the most commonly prescribed medications used to manage anxiety disorders and insomnia, respectively.[1–3] Although the short-term use of benzodiazepines and Z-Drugs are known to improve symptoms of acute anxiety and sleeplessness in the general patient population, many patients are continued on these agents for much longer than intended. Moreover, the overall benefit-risk ratio remains controversial, especially in vulnerable populations such as older adults or the cognitively impaired.[2,4] Emerging literature has generated additional safety concerns (dementia, infections, cancer etc.) that require further investigation to either substantiate or refute early findings.[5–7] These issues have further added to the controversial reputation that has remained with this class of psychotropic medications since the mid-1970's.[8]

Clinical practice guidelines for anxiety disorders tend to differ slightly in their dosing and duration of use recommendations for benzodiazepines and Z-Drugs.[9–13] However, they generally advise durations of use no longer than 3 months from initiation unless the agent is being employed as a 2nd line option for maintenance treatment after the failure of one or more adequate trials of anti-depressant medication use (Appendix 1). The latest Canadian guidelines for anxiety and associated disorders implicitly recommend a duration of no longer than 8 weeks for panic disorder and to keep to short-term use (unspecified duration) for general and social anxiety disorders.[13] In attempts to abide by guidelines and reduce inappropriate, potentially harmful use, a culture of "deprescribing" has found greater emphasis in recent years among those in the medical community.[14–18] In light of the established and perceived safety risks and ongoing efforts to reduce potentially inappropriate use, it is valuable to characterize both the population of patients receiving

benzodiazepine/Z-Drug therapy based on duration of use as well as changes in estimated total adult population use over time. Such information is expected to inform prescribing policies and practices given what is already known from the current state of clinical science on benzodiazepines and Z-Drugs.

The work included in this thesis serves as: 1) an appraisal of the major adverse outcome associations linked to benzodiazepine and Z-Drug use, 2) an evaluation of methods for measuring population exposure to these agents and 3) a comprehensive assessment of their use in the Manitoba adult population over the years from 2001 to 2016.

1.2) Research Questions

Overall, this thesis sought to answer six research questions which are formulated as follows (**corresponding chapter or section containing answer**):

I) What is already known about the pharmacoepidemiology of benzodiazepines and Z-Drugs in terms of different patterns of use? **(2.1)**

II) What is the evidence for each of the various major adverse health outcomes from benzodiazepine / Z-Drug use reported on in the literature? **(2.2)**

III) What are the relative advantages or disadvantages of each of the various prescription-based methods for measuring the utilization of benzodiazepines / Z-Drugs in large patient populations? **(2.3)**

IV) How has the utilization of benzodiazepines / Z-Drugs changed in the Manitoba adult population over the past 15 years? **(3)**

V) What factors are associated with the progression to long-term benzodiazepine use in the Manitoba adult population with anxiety and sleep disorders? **(4)**

VI) How does the average duration of benzodiazepine / Z-Drug use in the Manitoba adult population with anxiety and insomnia compare with common recommendations from clinical practice guidelines? **(4)**

Each of these research questions have been formulated in the broadest possible sense, consistent with the work of this thesis. It is therefore hoped that the reader will appreciate, over the course of this document, how each of these inquiries were necessarily divided into smaller, more manageable questions that are implicit within the broader scope of each stated research question. It should also be understood that answers to research questions IV, V and VI were dependent upon the conduct of original research, whereas the former research questions (I-III) were answerable only after thorough literature review and mental digestion of published content.

Chapter 1 References

1. Starcevic V. The reappraisal of benzodiazepines in the treatment of anxiety and related disorders. *Expert Rev Neurother*. 2014;14(11):1275-1286. doi:10.1586/14737175.2014.963057.

2. Baldwin DS, Aitchison K, Bateson A, et al. Benzodiazepines: risks and benefits. A reconsideration. *J Psychopharmacol*. 2013;27(11):967-971. doi:10.1177/0269881113503509.

3. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry*. 2013;28(1):7-20. doi:10.1016/j.eurpsy.2011.11.003.

4. Stevens JC, Pollack MH. Benzodiazepines in clinical practice: Consideration of their long-term use and alternative agents. *J Clin Psychiatry*. 2005;66(SUPPL. 2):21-27.

5. Pariente A, De Gage SB, Moore N, Bégaud B. The Benzodiazepine-Dementia Disorders Link: Current State of Knowledge. *CNS Drugs*. 2016;30(1):1-7. doi:10.1007/s40263-015-0305-4.

6. Iqbal U, Nguyen P-A, Syed-Abdul S, et al. Is long-term use of benzodiazepine a risk for cancer? *Medicine (Baltimore)*. 2015;94(6):e483. doi:10.1097/MD.0000000000000483.

7. Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: Eszopiclone, ramelteon, zaleplon, and zolpidem. *J Clin Sleep Med*. 2009;5(4):377-383.

8. López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. *J Anxiety Disord*. 2011;25(4):554-562. doi:10.1016/j.janxdis.2011.01.002.

9. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus

statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol*. 2010;24(11):1577-1601. doi:10.1177/0269881110379307.

10. Stein MB, Goin MK, H.Pollack M, Roy-Byrne P, Sareen J, Campbell-Sills L. Practice guideline for the Treatment of Patients With Panic Disorder (2nd ed.). *Am Psychiatr Assoc*. 2010;2:1-90. doi:10.1176/appi.books.9780890423905.154688.

11. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi:10.3109/13651501.2012.667114.

12. Bandelow B, Zohar J, Hollander E, Kasper S, Moller H-J. World Federation of Societies of Biological Psychiatry (WfSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Psttraumatic Stress Disorders. *World J Biol Psychiatry*. 2008;9(4):248-312. doi:10.1080/15622970802465807.

13. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.

14. Ng BJ, Couteur DG Le, Hilmer SN. Deprescribing Benzodiazepines in Older Patients : Impact of Interventions Targeting Physicians , Pharmacists , and Patients. *Drugs Aging*. 2018. doi:10.1007/s40266-018-0544-4.

15. Pollmann AS, Murphy AL, Bergman JC, Gardner DM. Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review. *BMC Pharmacol Toxicol*. 2015;16:19. doi:10.1186/s40360-015-0019-8.

16. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA Intern Med*. 2014;174(6):890-898. doi:10.1001/jamainternmed.2014.949.

17. Lader M, Kyriacou A. Withdrawing Benzodiazepines in Patients With Anxiety Disorders. *Curr Psychiatry Rep*. 2016;18(1):8. doi:10.1007/s11920-015-0642-5.

18. Pottie K, Thompson W, Davies S, et al. Deprescribing benzodiazepine receptor agonists. *Can Fam Physician*. 2018;64(5):339 LP-351. http://www.cfp.ca/content/64/5/339.abstract.

Chapter 2: Literature Reviews and Investigation

2.1) Descriptive Pharmacoepidemiology of Benzodiazepines and Z-Drugs

2.1.1) General Usage

Globally estimated measures of benzodiazepine consumption by country are reported annually in a comprehensive report prepared by the International Narcotics Control Board (INCB), an organization affiliated with the United Nations.[1*] Benzodiazepine statistics are reported by the INCB in three categories; sedative-hypnotic, anxiolytic and anti-epileptic, of which the first two comprise the majority of benzodiazepine use.[2] The latest INCB psychotropic substances report provides global benzodiazepine consumption data for the years 2008 to 2016; measured in annualized Defined Daily Doses (DDD) per 1000 inhabitants per day.[2**]

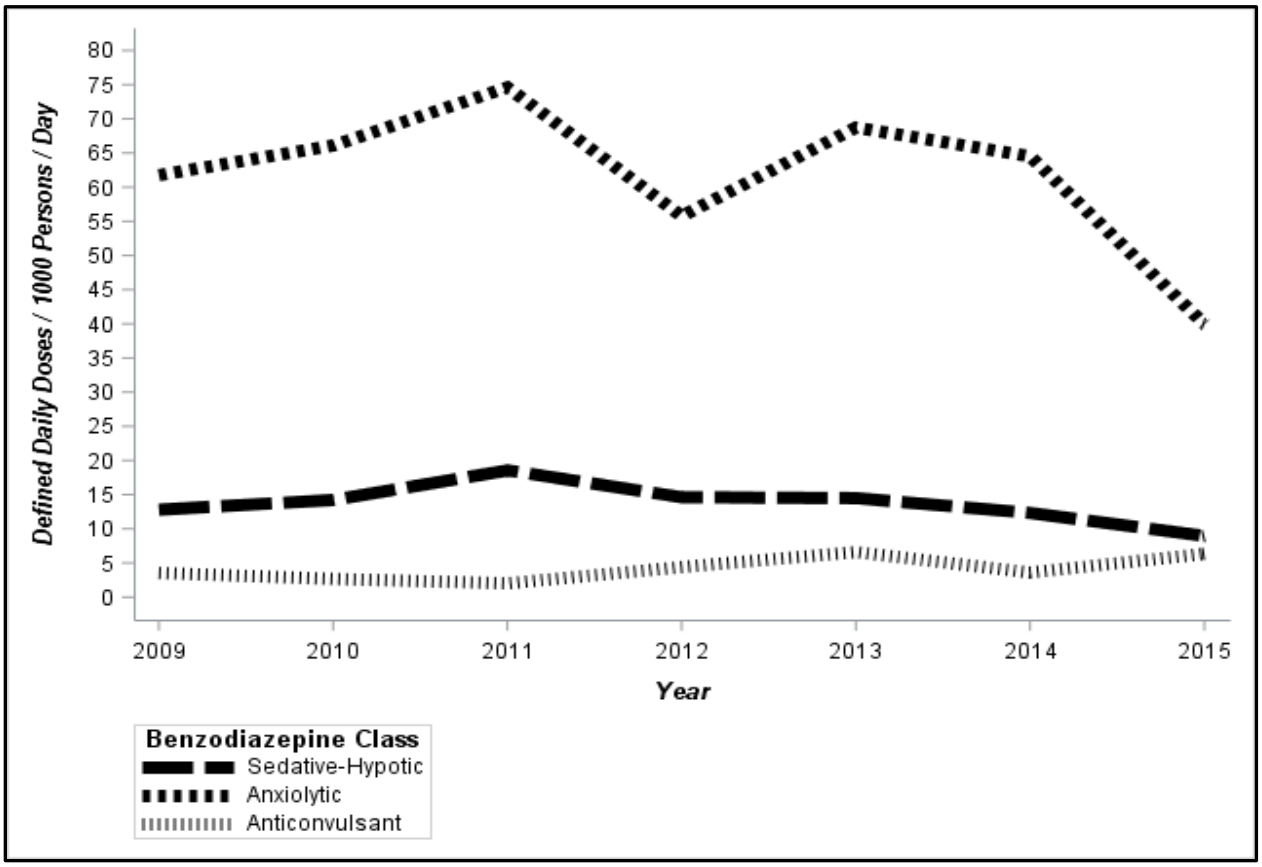
Consumption, in the category of sedative-hypnotics, has been the highest in Europe of all continents from 2008-2016, remaining stable in the range of 18-21 DDD / 1000-person-days. Sedative-hypnotic consumption in the Americas increased only slightly from 6.5 DDD / 1000-person-days in 2008-2010 to 7.8 DDD / 1000-person-days in 2014-2016. The Asia and Oceania regions have maintained a higher per-capita consumption of sedative-hypnotic benzodiazepines over the Americas while consistently remaining behind Europe by a difference of no less than 5 DDD / 1000 person-days. Africa has the lowest calculated consumption at less than 2 DDD / 1000

[*] The INCB and its affiliated member nations operate under the mandate of articles 18 and 16, respectively, of the *1971 United Nations Psychotropic Drug Convention*. Country based statistics are derived from import/export ledgers and manufacturer reported data and thus cannot precisely represent the true consumption in any given jurisdiction.

[**] A review of the DDD section is the topic of section 2.3.1. Nonetheless, the reader should find that this metric lends itself to simple interpretation in regards to trends and regional comparisons for this section.

person-days. For Canada, sedative-hypnotic use peaked in the year 2011 at 18.5 DDD / 1000 person-days and has slightly declined thereafter as depicted in Figure 2.1.

Figure 2.1 – Estimated Canadian Benzodiazepine Consumption by General Indication



INCB based reporting of anxiolytic benzodiazepine use in most parts of the world is on a scale of significantly larger magnitude than that of sedative-hypnotic consumption. As with the sedative-hypnotic benzodiazepines as recognized by the INCB (temazepam, flurazepam, triazolam etc..), Europe has also been the top consumer of anxiolytic benzodiazepines as well (alprazolam, diazepam, lorazepam etc..) with a DDD / 1000 person-days of 44 in 2008-2010 but dropping to 36 in the 2014-2016 period. Contrary to the reduction of sedative-hypnotic benzodiazepine consumption, the Americas have seen a consistent increase in anxiolytic benzodiazepine use rising

gradually from 26 in 2008-2010 to 32 in 2014-2016. Canada's anxiolytic consumption has fluctuated at a level nearly 2 times greater than that of the Americas as a whole, and 1.5 times greater than Europe as a whole (Figure 2.1). Anxiolytic benzodiazepine use in the Asia and Oceania regions has generally remained lower than the Americas which is the opposite comparison of these regions in terms of sedative-hypnotic benzodiazepine use. While Africa's anxiolytic benzodiazepine use has traditionally been the lowest of all regions (just over 5 DDD/ 1000 person-days during 2014-2016), it nevertheless surpassed Asia in the 2014-2016 period at 7 DDD / 1000 person-days owed to a simultaneous decrease in use for the latter region. Interestingly, manufacture of benzodiazepines over the past decade, for both categories, has predominated in Italy; which accounts for approximately 40% of all annualized benzodiazepine production in the world.[2]

Zolpidem was the only Z-Drug agent tracked by the INCB but is mentioned to be one of the most consumed psychotropic drugs based on its production, export, import and calculated consumption.[2] Nevertheless, in comparison to the benzodiazepines, consumption per capita is not explicitly defined for zolpidem in terms of DDD / 1000 person-days nor are continental statistics made available. Throughout the world, France had the highest domestic requirement at 30 million grams, the United States had the 2nd highest domestic requirement of this drug at 10,376,000 grams and Canada was the 6th highest consuming nation requiring ~4 million grams for domestic and scientific usage.[2] Considering that Canada's total population as of the latest United Nation's World Population Prospect revision report was ~36 million which is roughly one-ninth of the United State's population of ~322 million, the national domestic requirement of zolpidem is disproportionate and possibly overestimated.[3] A greater discrepancy is the fact that zolpidem utilisation is miniscule in comparison to zopiclone as the latter made up 26% of all sedative-

hypnotic prescription claims in Canada between 2012 and 2013 according to the Canadian Rx Atlas report by the University of British Columbia Centre for Health Services and Policy Research.[4] This is consistent with a drug utilisation study by Alessi-Severini et al. which demonstrated that incident Z-Drug use has been increasing substantially in Manitoba compared to new benzodiazepine use.[5]

Estimated annual prevalence of "any use" for benzodiazepines and Z-Drugs among the Canadian population has remained stable since 2008, at approximately 10%, according to the Canadian Centre on Substance Abuse (CCSA).[6] This is consistent with the most recent 2015 Canadian Tobacco, Alcohol and Drug use Survey (CTADS) from Statistics Canada which also reported an overall annual prevalence of 10% for the survey population.[7] The CCSA reports usage as being more common in females (14%) than males (7%) and in those over the age of 65 (14.1%) compared to younger adults (11.5%) and this is also confirmed by reports from the Canadian Institute for Health Information (CIHI) on psychotropic drug use among seniors.[6,8] Pharmacoepidemiologic studies assessing prescription benzodiazepine and Z-Drug use have demonstrated similar disproportionate use in females and elderly persons in disparate countries including France[9,10], Switzerland[11], United States[12], Italy[13], South Korea[14], Pakistan[15], Norway[16] and Great Britain.[17]

2.1.2) Long-term/Chronic Use

The definition of "long-term" or "chronic" use in pharmacoepidemiologic studies of benzodiazepines and Z-Drugs is quite variable within the international biomedical literature.[18,19] Notable efforts to standardize the operational definition of "long-term" use have been made recently by a group of researchers studying population use patterns of these medications. In 2015,

this issue was comprehensively addressed by Kurko et al., in a systematic review of register-based studies of long-term use.[19] This review found a total of 41 studies that met the inclusion criteria of their search strategy. Of those, 36 studies examined "long-term" use ranging in definition from one month to several years. A duration greater than 6 months was the most common definition and was operationalized in 10 of 36 studies reported as either ≥180 days or ≥6 months. The authors of this systematic review offer a concluding recommendation that "in future studies, long-term benzodiazepine use should be defined as the use of 6 months or longer during a year."[19]

The 6-month duration of use definition can be argued as appropriate for ideal clinical practice comparison as it is twice as long as the standard acute phase duration of treatment (<12 weeks) recommended by practice guidelines (Appendix 1). In terms of insomnia treatment, this proposed 6-month duration may be argued as being too long as most of the practice guidelines for insomnia recommend duration of treatment that is even shorter than that recommended for anxiety (Appendix 1). Thus, if the difference in comparative durations is too great, it may lead to misclassification and subsequent underestimation of potentially inappropriate use in pharmacoepidemiologic studies.

Despite the fact that there has been inconsistency in measurement methodology constituting long-term/chronic use duration of benzodiazepines and Z-Drugs, the available Canadian studies do demonstrate a high degree of correlation in their patient characteristic findings. In this specific area of population health research there is sufficient quality evidence to conclude that, in terms of basic demographics, long-term Canadian users of benzodiazepines and Z-Drugs have a higher probability of being female and of older age.[20–25] These two basic demographic findings associated with long-term use of benzodiazepines and Z-Drugs have been independently replicated in countries from regions all over the globe including (in no particular

order): Switzerland[11], United States of America[12,26], Italy[13], South Korea[14], Denmark[27], Norway[16], the Netherlands[28,29], Australia[30], and Great Britain[17]. Lastly, it should be understood that these basic demographic characteristics (female and elderly) are positively associated with usage in general and not just long-term chronic use, therefore these factors may be interpreted as potential confounders rather than effect-modifiers or causal associations. Following this, research by Neutel et al. shows that previous use of benzodiazepines is perhaps the most significant predictor of long-term use in the Canadian population.[23,31] Assuming that this relationship between "any use" and "long-term use" truly holds, we may expect the population of long-term users to be a representative sub-sample of the overall population of general users of benzodiazepines and Z-Drugs. The elderly and female predictor variables alone lend support to this hypothesis. Table 2.1 displays the factors that have determined to be associated with long-term benzodiazepine use along with their corresponding explanations for the association.

Table 2.1 – Factors Associated with Long-Term Use of Benzodiazepines and Z-Drugs

Factor	Proposed Rationale	Citations (original studies)
Increased utilisation of healthcare services	Indicator of poor health which itself predicts for 'health anxiety' and psychiatric comorbidity	9,30,32
Psychiatric comorbidities	Correlation between the extent of psychiatric comorbidity and the magnitude of psychotropic medication required to manage symptoms	9,10,25,28–30,32–37
Multiple Pharmacy and Prescriber use	Behavioral indicator of potential prescription drug misuse/abuse	10
Low socioeconomic status or long-term unemployment	Social and financial stressors worsen mental health or are correlated with poor mental	13,15,24,32,34

Factor	Proposed Rationale	Citations (original studies)
High socioeconomic status	Lavish lifestyle and social 'culture' afford opportunity for extended benzodiazepine use/misuse	27
Poor subjective health status or chronic physical illnesses	Indicator of poor health which itself predicts for 'health anxiety' and psychiatric comorbidity	24,29,32–34
Single Marital Status from divorce, separation, death of spouse	Benzodiazepine use becomes a "coping mechanism" for dealing with interpersonal grief	25,27,28,30,32,34
Rural residence	Less availability of services or activities that may replace the need for ongoing benzodiazepine use	37
Concurrent or previous opioid use	Indicator of predisposition to possible prescription drug misuse/abuse disorder as opioids are also controlled drugs	38,39
Concurrent or previous antidepressant/antipsychotic use	Indicator of more severe psychiatric comorbidity requiring longer treatment durations	32,35
Previous use of benzodiazepines or Z-Drugs	Past use predicts greater willingness to repeat/continue treatment	23,31,33,34
Use of shorter-acting or "potent" benzodiazepines over longer acting agents	Greater desire to maintain use to avoid pharmacological withdrawal symptoms (pharmacokinetics predict more rapid/severe withdrawal)	31,32,40
Male prescriber	Male personalities are less 'rule-abiding' and so may disregard guideline recommendations in favor of their own clinical judgment more regularly	41,42
Prescriber is older or has many years of practice	Clinician may not be 'up-to-date' on the latest evidence or the changing practice recommendations	42

Factor	Proposed Rationale	Citations (original studies)
Prescriber has large average daily patient case load or excessively busy	Clinician busyness precludes opportunities to engage patients in deprescribing interventions	43

By independently following up on the citations provided in Table 2.1, one would find that there are varying degrees of evidence for all of the above predictors in terms of their association with long-term, potentially inappropriate benzodiazepine use. Single study results must be interpreted very cautiously because international populations differ in their generalizability to each other as well as to the Canadian population of interest. Furthermore, there are significant differences in how these characteristics have been measured between studies which presents further difficulty in determining whether or not there is a true association between a given patient/prescriber characteristic and the risk of long-term use. Lastly, associations between many of these characteristics with long-term benzodiazepine/Z-Drug use could either lack causal significance or be causally bi-directional. For example, aberrant patient behaviors such as "doctor shopping" and "pharmacy hopping" would not necessarily be expected to typically precede physical dependence, long-term use or intentional prior misuse. It would also be false to conclude that antidepressant or antipsychotic use "cause" benzodiazepine/Z-Drug use. Rather, the use of all of these medication classes is the result of perceived psychiatric need and so causality must not be confused with a simple positive association. Other predictors, such as basic physician characteristics, become even more difficult to draw strong inferences from due to confounders such as practice setting, personality traits, physician knowledge etc. In other words, these characteristics, while purporting to "predict" for long-term benzodiazepine use *by patients*, are

actually only attempting to predict (or not predict) *prescriber* behavior; a nebulous, complex phenomena incapable of being adequately accounted for by almost any form of available data.

Of all the above factors, it seems psychiatric comorbidities, poor physical health, low income/unemployment and high healthcare utilization carry the most evidence to support associations with long-term use. Nonetheless, most, if not all of these are likely associated with increasing age, which is already strongly associated with long-term use, thus making confounding a very likely possibility. A large number of the variables are also correlated with each other and therefore complicate the causal chain (i.e chronic physical illness → healthcare utilization or psychiatric comorbidities → concurrent psychotropic medication). Further well-designed research is needed to determine which, if any, of the characteristics above are significantly associated, in a meaningful way, with problematic long-term benzodiazepine use.

2.1.3) High-dose Use

As with long-term use, definitions constituting high-dose usage of benzodiazepines and Z-Drugs have been variable and a consensus has been slow to develop in the literature because of this. The adoption of the Diazepam Milligram Equivalence (DME) system or the Defined Daily Dose (DDD) system by many researchers aids in the conversion to a commonly accepted, standardized unit of dose measurement regardless of which specific drug entity is being examined.* When DME was used previously in studies as the metric of dose used, 40 DME's/day and 20 DME's/day have been used as thresholds for high-dose intensity users in the 18-64 year and 65+

* As mentioned previously, a complete discussion of the DDD and DME metrics (with references) is the focus of section 2.3

age ranges respectively.[35,44] Another study, using the DDD metric defined "excessive users" as those eventually requiring ≥2 DDD per day.[45]

Based on a basic understanding of sedative-hypnotic pharmacology, dependence and tolerance, it seems plausible to hypothesise that a large proportion of long-term users will have become high-dose users. However, this pharmacological hypothesis has not been borne out by the pharmacoepidemiologic investigations into this line of inquiry. It seems that high-dose users usually meet criteria for long-term use, however, the reverse is rarely the case as less than <8% of chronic users in one study[44] and only 1.6% in another study escalated to high dose use (≥40 DME's / day).[35] A Norwegian study, found that only 0.9% of benzodiazepine naïve patients escalated to high dose use (>2 DDD / day) for 3 months or longer[45] but a follow-up study by the same authors found that excessive use, of the same definition, had a period-prevalence over 5 years of 2.3%.[46]

Contrary to patterns observed with long-term use, high-dose users have been reported in some studies to be younger in age rather than older.[35,44] Characteristics in common with long-term users that are statistically predictive also of high-dose use include low income[44,46], anti-depressant medication use,[35,44,46], history of substance use disorders[44,46] and use of particular benzodiazepines.[44,46] Higher dose benzodiazepine use has also been correlated in one study with higher consumption of nicotine, caffeine and alcohol.[47]

Overall, there is a current dearth of evidence on patterns of high-dose use in various jurisdictions. As with long-term use, study findings in certain geographic regions may lack generalizability for patient risk prediction for clinical practice in other areas, but the characteristics thus far supported remain plausible given current knowledge regarding abuse liability with benzodiazepines. As of yet, there does not appear to be any published studies that purely examined

population based high-dose use of Z-Drugs. Such a study may be important given increases in their use over the last number of years as well as their narrowed indication for use as compared to benzodiazepines.

2.2) Pharmacoepidemiology of Major Adverse Drug Events

***Disclaimer*:** This section is an adapted version of the published manuscript:

Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017. doi:10.1007/s40268-017-0207-7.

Student contribution: conceptualised topic, conducted all research on topic, wrote first draft, wrote revised draft and wrote final version. Student was corresponding author.

2.2.1) Motor Vehicle Accidents

According to the World Health Organization, road injury was the 9th leading cause of death globally between 2002-2012.[48] The prevalence of prescription drug-positive fatal motor vehicle accidents has increased by an estimated 49% in the United States over the past twenty years, with benzodiazepines in particular more than doubling their rate of involvement in such accidents.[49] In Canada, 11.2% of drivers killed in vehicle accidents, between 2000 and 2010, tested positive for sedative-hypnotic type prescription drugs post-mortem.[50] For the past decades, benzodiazepines and Z-Drugs have been the focus of much public safety research, both epidemiological and experimental, on motor vehicle driving performance and outcomes.

Experimental studies have involved the dosing of a sedative-hypnotic medication on individuals prior to a measured test of driving performance, be it simulated or in an actual vehicle. Though

experimental study designs may differ, many studies have utilized a commonly validated measure of safe driving performance called the Standardized Deviation of Lateral Position (SDLP); an index of maintaining vehicle positioning during driving on a stretch of road (usually straight) at a constant speed.[51] A 2009 meta-analysis by Rapoport et al. carefully selected a total of 5 on-road experimental studies of similar methodology to determine differences in SDLP between users and controls with a reported pooled estimate of Standardized Mean Difference between groups at 0.80 ($p = 0.0004$) at a ≤5 mg dose equivalent of diazepam.[52] The SMD further increased to 3.07 standard deviations at a ≥10 mg diazepam dose equivalent thus implying a dose-dependent loss of vehicle control in users compared to controls.[52] Another meta-analysis of 14 randomized controlled trials by Roth et al. in 2013 concluded that "…the half-life, dose of the hypnotic, as well as time between treatment and driving, as measured by SDLP, all significantly impact the ability to drive a car after taking hypnotic drugs."[53] More specifically, driving performance diminished significantly with longer half-life agents, as doses increased and when time between single dosing and driving was reduced.[53] Furthermore, based on some studies, blood plasma concentrations of benzodiazepines in impaired drivers has been shown to correlate, with some degree reliability, with risk of potential accidents.[54,55] These findings are consistent overall with clinical pharmacokinetic-pharmacodynamic principles applicable to benzodiazepines and Z-Drugs.[56]

Z-Drugs in particular have also been the subject of experimental studies, though, as may be expected, less so than benzodiazepines. A pooled analysis of 4 studies on zopiclone's potential for residual sedation contributing to driving risk, demonstrated that impairment lasted for up to 11 hours after dosing, was not significantly dependent on sex nor age and was comparable in magnitude to a blood alcohol concentration of up to 0.8 mg/L, which, in turn, corresponds to at least twice the risk of motor-vehicle accidents.[57] Perhaps because of this, zopiclone has been used

as a positive control for studies on other drugs in driving because of its reliability in causing significant impairment.[58] Studies on zolpidem and zaleplon in healthy subjects have not been shown to cause significant residual impairment leading to traffic accident risk with early or middle-of-the-night dosing.[59–62] Zolpidem has been shown to cause significant changes in SDLP, standard deviation in speed and alertness in healthy drivers between the ages of 55-65.[63] A literature review by Gunja also ranks zopiclone over the other Z-Drugs in terms of potential for residual impairment but also places rightful emphasis on safety concerns arising from sleep behaviors (including sleep driving) reported more frequently in zolpidem users.[64] A simplified, summative, evidence based categorization guide produced by the International Council on Alcohol, Drugs & Traffic Safety has ranked various medications based on their potential for causing impaired driving (I = presumed safe, II = minor to moderate impairment, III = severe impairment) with most benzodiazepines and zopiclone ranked at III and the remaining benzodiazepines, zolpidem and zaleplon ranked at II.[65,66]

Epidemiologic studies examining real-world accident outcomes, as opposed to experimental surrogate outcomes (SDLP and others), are perhaps easier to place into relevant context for clinicians and those in public health. Twenty-five of 28 epidemiologic studies examined in a review by Gjerde et al. found positive associations between road traffic accidents and benzodiazepine/Z-Drugs.[67] In terms of quantifying this association, the meta-analysis by Rapaport et al., previously cited above, also provided pooled odds ratio estimates for case-control studies (n = 6) and cohort studies (n = 3) on accident risk with Benzodiazepine exposure; reporting a 60% higher odds of accident in Benzodiazepine users.[52] Another 2011 Meta-analysis by Dassanayake et al. also included an assessment of Benzodiazepine association with motor vehicle accidents via 3 distinct pooled odds ratio estimates based on case-control studies (n = 6, OR = 1.59), cohort studies (n = 3, OR = 1.81) and accident culpability studies (n = 5, OR = 1.41), all of

which significantly indicated an association.[68] The last estimate, on accident culpability, when considered in conjunction with the experimental studies, strengthens the causal argument by showing that those involved in vehicle accidents who consumed benzodiazepine medication were ~40% more likely to be at fault than the other parties involved. The latest 2013 meta-analysis by Elvik separated pooled risk estimates by outcome (fatal, injury or property damage) rather than by study type for benzodiazepines.[69] For benzodiazepines, after adjusting for publication bias, these estimates remained significant for fatal accidents (n = 10, OR = 2.30), injury accidents (n = 51 , OR = 1.17) and property damage (n = 4, OR = 1.35).[69]

The epidemiologic association made between Z-Drugs and motor vehicle accidents is less robust than with the benzodiazepines yet is still significant enough to warrant concern among clinicians, public health researchers and policy makers. Studies of differing methodologies and sample populations have reported overall risk/odds ratios ranging from a 38% increased risk/odds to over double the risk/odds of traffic accidents in zolpidem users over non-users.[70–73] Despite the compelling experimental evidence for driving impairment, the epidemiological evidence for zopiclone in vehicle accidents is less clear as some studies have found an association[74,75] and others have not.[73] An exhaustive 2016 systematic review of epidemiologic studies on numerous medications and motor vehicle collisions by Rudsill et al. found 4 of 5 studies to be statistically significant for zolpidem and 2 of 6 studies to be statistically significant for zopiclone.[76]

Though sedative-hypnotic drugs undoubtedly seem to pose a hazard in driving safety, increased risk has been tentatively identified in certain users or medication related behaviors albeit with much uncertainty. Younger age[74] and new use of medication[72] have been reported as additional risk factors in users of these medications. A literature review on gender risk difference in drugged driving has found that, with the exception of zolpidem and flurazepam, no differences

in impairment have been noted between the sexes but this has been foremost due to a lack of study data differentiating the magnitude of impairment between men and women.[77] An observational finding has also been made that drug impaired driving, in some jurisdictions, may be primarily among a younger population using these medications non-medically with or without the concurrent use of illicit street drugs.[78] This raises the question as to what proportion of vehicle crashes associated with sedative-hypnotics is from irresponsible or non-medical use as opposed to as prescribed use? Driving behavior among younger drivers may simply be different enough in general and so confounding could have played a role in these associations.

There is an overwhelming degree of evidence, both experimental and epidemiologic, implicating benzodiazepines in particular, but Z-Drugs as well, with fatal and non-fatal motor vehicle accidents. Both streams of evidence (experimental and epidemiologic), when considered together, support a strong causal argument for exposure of these drugs resulting in motor vehicle accidents. It seems more research is necessary to elucidate with certainty which medications in which patients further increases the risk so as to enable effective targeted interventions to reduce motor vehicle harm.

2.2.2) Falls and Bone Fractures

Osteoporosis, a state of bone mineral density deterioration, is a medical condition in which the health burden increases with advancing age, particularly in females after menopause.[79] This higher disease incidence in elderly females corresponds to the higher sedative-hypnotic medication usage incidence and prevalence witnessed in this same portion of the general population. Importantly, fractures, being the main devastating outcome to be prevented in osteoporosis, are

linked directly to increases in mortality rates.[80] This is especially true for hip-fractures with an estimated excess mortality ranging from 8% to 36% over a 1 year period.[81]

A multitude of individual studies, summarized by comparative systematic reviews and meta-analyses, have consistently demonstrated various psychotropic medication classes, including anti-depressants, anti-psychotics, opioids and sedative-hypnotics, to be linked to falls[82–84] and fractures[85]. In terms of a speculative causal association to fractures with GABA-A receptor modulating drugs, a direct effect on bone mineral metabolism seems untenable and so the association has instead been attributed to their adverse pharmacodynamic effect on cognition, gait and balance leading to falls in susceptible patients such as the elderly or those with mobility issues.[193] Furthermore, prior literature reviews show conclusively that benzodiazepines and Z-Drugs have a dose-dependent deleterious effect on postural stability and balance thus implying an inextricable link to fractures, with falling as the critical intermediary event.[88,89] Fall related harm from Benzodiazepine use was estimated to cost 1.8 billion Euro in the European Union in the year 2000.[90] This is one of the few cost-estimates of benzodiazepine related harm but nonetheless shows the negative expenses of such drug use in the population.

Attempts to quantify the overall risk of fractures associated with benzodiazepine use has been carried out by careful compilation of existing study data. A meta-analysis published by Khong et al. in 2012, consisting of data from 14 studies, used an ecological study design to examine hip fracture rates in association with benzodiazepine consumption in the United States and five European countries.[91] They concluded a pooled relative increased risk of 24-58% in benzodiazepine users over non-users for hip fracture. Another, more recent, meta-analysis from 2014 by Xing et al, included 25 distinct studies (19 case-control and 6 cohort) and determined a

conservative adjusted overall estimate indicating a 13-30% increased risk of fractures attributable to benzodiazepine use.[92]

When it comes to discerning differences in falls and fracture risk among benzodiazepines, there have been some discrepancies in the findings of individual studies. For example, a few studies demonstrated a seemingly greater risk with long-acting benzodiazepines supposedly explained by their pharmacokinetic profile in the eldelry.[93–95] Another study, hypothesizing increased rates of fractures with oxidative benzodiazepines (i.e requiring phase 1 hepatic metabolism for elimination) found no difference to support that non-oxidative benzodiazepines are of lesser risk in causing fractures among elderly persons.[96] Other studies, including the aforementioned 2014 meta-analysis, have attributed a higher risk to short-acting agents.[92,97–99] These discordant pharmacokinetic findings on population drug safety have been partially explained by selection bias and confounding by indication. For instance, prescribers may select shorter-acting or non-oxidative agents on a frequent basis for higher risk patients thus making lower risk drugs appear higher in risk when falls and fractures finally do occur.[86,99] However, evidence has shown, with limited conflicting results and adherence to expected pharmacological principles, that the risk of falls and fractures increases with higher doses.[95,99–102], drug interactions[99] and after treatment initiation particularly during the first 1-2 weeks of drug exposure[99–101,103]. Of particular concern is that some limited evidence indicates that elderly Canadians at a higher baseline risk for falls (pre-existing risk factors) may be more likely to receive new benzodiazepine prescriptions than a lower-risk elderly cohort.[104]

Despite the fact that, in comparison to the benzodiazepine class, there is substantially less study data elucidating the degree of association between Z-Drugs and fractures, a meta-analysis of the available studies on zolpidem by Park et al. was published recently in 2016.[105] This meta-

analysis was comprised of 9 studies (4 cohort, 4 case-control and 1 case-crossover) and reported a pooled estimate of 92% excess risk of fractures in zolpidem users. Given the comparably lower meta-analytic risk estimates attributed to benzodiazepines, this estimate may be inflated due to heterogeneity, confounding and the reduced sample size of included studies. Nonetheless, three of the studies included in the meta-analysis had reported event rate comparisons with benzodiazepines yet the relative risk of fracture with zolpidem still exceeded that of benzodiazepines.[106–108] Predictably, a trend towards greater risk in the early treatment period and with increasing doses has been shown to hold true for Z-Drugs in the same way as benzodiazepines.[95,105]

It is unclear what further studies (non-intervention based) on this topic will accomplish considering the overall weight of the current evidence establishing the use of these drugs with falls leading to fractures (especially of the hip). Interventional studies indicating effective health policy implementation and clinical approaches to reduce fall related harm from sedative-hypnotics should perhaps be the continued focus of future research.

2.2.3) Drug Overdose

The risk of fatal overdose with benzodiazepines alone is quite rare. However, involvement of benzodiazepines with other agents known to cause CNS and respiratory depression, such as alcohol, opioids, or muscle relaxants substantially increases risk of acute harm.[109] Concurrent use of benzodiazepines and opioids in particular, is a complex topic reviewed in detail elsewhere[110,111]. Simultaneous co-administration of these drug classes purportedly enhances the 'euphoric high' as per synergistic pharmacologic CNS mechanisms.[112] This likely reinforces dangerous medication taking behavior among those with substance use disorder thus increasing risk of overdose. Issues

surrounding combination sedative-opioid use remain highly relevant for clinical practice as studies from various jurisdictions have shown co-prescription use of these drug classes to be frequent or increasing.[39,113–116]

Drug overdose fatality data, made available, by the United States' National Institute for Drug Abuse (NIDA) reveals that death involving benzodiazepine overdose has been steadily on the rise since 2002 (2,022 deaths) to current (8,791 deaths in 2015) with ~75% of these overdoses involving opioids.[117] These government reported statistics are generally in alignment with a 2016 study analyzing trends in benzodiazepine prescription and overdose deaths in the United States from 1996-2013, which found that the dispensed benzodiazepine prescription drug volume more than tripled during this period and overdose deaths involving benzodiazepines became five times more frequent.[118]

Remaining in the U.S, from 2004-2011, emergency department visits involving non-medical combined use of benzodiazepines and opioids increased threefold (11 to 34.2 / 100,000 persons) and increases in death from co-overdose was nearly proportional to this (0.6 to 1.7 / 100,000).[119] In terms of poisoning leading to hospitalization (i.e beyond the emergency department) in the U.S, from 1999-2006, benzodiazepines were involved in more poisoning events and had the largest increase in rate of poisoning among all drug classes studied (39% increase from 26,321 in 1999 to 36,700 in 2006).[120] A case-control study in a U.S Veterans population concluded a dose-dependent relationship between benzodiazepine prescription issuance with overdose mortality (overall adjusted hazard ratios of 2.33 and 3.86 for previous prescription and current prescription of benzodiazepines respectively).[121] As with dose response, as duration of use increases, the odds of overdose seem to increase as well according to results from a retrospective cohort study of prescription opioid users.[122] Despite the logic underlying dose-duration

relationships with mortality at the population level, these findings require confirmation by result replication in other populations and study designs.

Similar statistics on overdose related outcomes (mortality, emergency visits etc..) involving benzodiazepines are not readily available in Canada at this time but CIHI seems intent on delivering this information in the future.[123] It is probably fair to speculate that, given the current opioid epidemic in Canada, benzodiazepine involvement in overdose scenarios has likely increased as well commensurate with the United States.

Recent large observational studies specifically on benzodiazepine overdose in countries other than the U.S appear to be lacking and this is even more true for the Z-Drugs. It is currently difficult to determine with accuracy the extent of Z-Drug overdose morbidity and mortality in general populations (national, provincial or otherwise) as they are frequently grouped with benzodiazepines. Nevertheless, a comparative epidemiologic study of single drug overdose fatalities from the United Kingdom from 1983-1999 found a reduced frequency of fatalities for Z-Drugs in overdose compared to benzodiazepines (~2 deaths vs ~5.6 deaths / million prescriptions).[124] Though, these findings warrant caution in concluding Z-Drugs as being generally safer in overdose as the death rates amongst individual benzodiazepines differed tremendously (flurazepam being the highest and medazepam the lowest at 20.5 and 0.0 deaths / million prescriptions respectively) and user populations for particular agents may be inherently different.[124]

Given their relative safety in mono-drug overdose, benzodiazepines have seldom been studied on an epidemiologic basis in this context unless opioids are also involved. Though, it is only sensible that opioids are afforded research priority over benzodiazepines in the

pharmacoepidemiology of prescription drug overdose because of their comparably greater toxicity. Future studies examining benzodiazepine overdose mortality, similar in design as the U.K study by Buckley et al. would be invaluable.[124]

2.2.4) *Pancreatitis*

Less reported on in the literature is the possible association between benzodiazepines and/or Z-Drugs with acute episodes of pancreatitis. Thus far, one Taiwanese retrospective cohort study has raised the association for benzodiazepines[125] and two Taiwanese case-control studies have raised the issue with zopiclone[126] and zolpidem[127].

After adjusting for potential confounders, Liaw et al. observed a 5.33 fold (95% CI 2.26-12.60) increased risk of pancreatitis within one month of benzodiazepine poisoning over controls.[125] Lai et al. reported a confounding adjusted odds ratio of 2.36 (95% CI 1.70-3.28) for those with receipt of zopiclone prescription within 30 days of pancreatitis compared to never-users of this drug.[126] Of note is that the association remained significant even when a prescription was dispensed ≥31 days prior to the episode of pancreatitis (95% CI 1.60-2.66) thus suggesting a possible spurious association. The authors address this by claiming possible "as needed" use of the drug prior to the episode however this is not verifiable with the database study design. The same group of researchers, in an almost identical study design, reported an adjusted odds ratio for pancreatitis of 7.20 (95% CI 5.81-9.82) in those who received a prescription for zolpidem within 7 days of pancreatitis diagnosis compared to those who never received zolpidem.[127] Unlike the study with zopiclone, the authors examined and discovered a dose-response trend where the association was greater for doses >10 mg (OR = 8.70) compared to ≤10 mg (OR = 6.76).

A precise mechanism behind benzodiazepine or Z-drug induced pancreatitis remains elusive, though the authors of the previous studies have proposed direct noxious effects on

pancreatic tissue from these drugs.[125–127] However, a pharmacological mouse-model study of cerulein-induced pancreatitis yielded anti-thetical results wherein pre-treatment diazepam at 5 mg/kg (intra-peritoneal) was observed to produce anti-inflammatory effects; reducing pancreatic edema along with lipase and amylase serum levels compared to a negative control.[128] Recent review articles also make no mention of either benzodiazepines or Z-drugs as agents being associated with drug-induced pancreatitis.[129,130]

In summary, few original research studies exist on the presence or absence of an association between benzodiazepines and Z-drugs with pancreatitis. The three population-level observational studies that do exist are all of a retrospective design in the Taiwanese population. Despite this, all of these studies are in concordance with each other in presenting odds ratios of sufficient magnitude to raise an alert for this serious association. There is a dearth of experimental studies specifically addressing the effects of benzodiazepines and Z-Drugs on pancreatic tissues. Further high-quality research, both observational and experimental, from multiple countries would be invaluable towards determining with greater certainty whether there is any causal truth behind this drug exposure to adverse outcome association.

2.2.5) Infections

Speculation linking benzodiazepines to infections originally began when multiple in-vivo pharmacology studies demonstrated immune dysfunction and bacterial infections of greater frequency among rodents exposed to diazepam.[131–133] Despite these results, the immunopharmacology of peripheral and central benzodiazepine GABA-A receptors remains complex as other in-vitro studies have shown potentiation of immune response from triazolo-benzodiazepines such as alprazolam and triazolam.[134–136]

Scaling back focus to an epidemiologic level, evidence is conflicting as some observational studies have detected associations between mortality from community acquired pneumonia with benzodiazepine/Z-Drug use[137–140] and others have not.[141,142] The largest and most recent observational study by Nakafero et al (2016) in the U.K., employed a survival analysis methodology on a retrospective cohort of >800,000 patients with "Influenza-like-illness" (ILI).[137] This study reported resultant adjusted hazard ratios of 4.24 and 20.69 for ILI and ILI-related mortality respectively in current benzodiazepine/zopiclone users.[137] This team of researchers and another independent group, Obiora et al., not only found strong statistical significance for an association but also observed a dose-response trend for many benzodiazepines and Z-Drugs under study as the hazard ratios generally trended higher from "non-users" to "past-users" to "current-users" albeit with many instances reflecting a J-curve.[137,138] Discrepant findings in an elderly population (those not found to be at greater risk from exposure)[142] have been explained by both Nakafero et al. and Obiora et al. by the higher comorbidity burden in older patients which independently increases pneumonia and mortality risk by a magnitude substantially greater than benzodiazepine exposure thus limiting statistical detection in this sub-population.[137,138] Considering Z-Drugs separately from benzodiazepines, a meta-analysis of published studies and FDA randomized clinical trial data by Joya et al. found a 25-64% increased risk of infection (various types) in those exposed to Z-Drugs (and Ramelteon) over placebo.[143] There was enough data only for sub-analysis of eszopiclone and zolpidem, both of which were statistically significant with adjusted hazard ratios at 1.48 and 1.99 respectively.[143]

Infection risk with benzodiazepines and Z-Drugs is yet to be widely recognized by clinicians as a concern deserving of attention as the population-based evidence supporting this association is rather recent and not yet confirmed by the scientific rigor required of causal

associations. With a proposed mechanism derived from lab-based pharmacologic experiments in place to substantiate infection risk from this class of drugs, the concerning results from some observational studies is granted some degree of plausibility for a causal association. Unlike the literature on falls, fractures and motor vehicle accidents however, there is a scarcity of pharmacoepidemiologic research on this association. It may also be argued that the pharmacological plausibility for infection is made less tenable given the basic pharmacology, as commonly understood, for this class of drugs. Therefore; confirmation of this tentative adverse drug event should be sought from high-quality prospective study designs or, at the very least, replicated by more, large retrospective studies from various jurisdictions.

2.2.6) Respiratory Disease Worsening

It is rational to hypothesize that patients with significant respiratory dysfunction are more susceptible to the otherwise minor respiratory depressive effects of benzodiazepines at approved doses. A review by Roth reported that benzodiazepines diminish respiratory function by reducing airway smooth muscle tone and/or increasing the threshold for arousal by desensitizing neurons in airway obstructed sleep states.[144] Roth observed that "unlike benzodiazepines, [Z-Drugs] have been found to have no significant effect on ventilatory drive and central control of breathing in normal subjects or in patients with mild to moderate COPD."[144] Another review by Stege et al. assessed the results of drug-effect studies on oxygen saturation, inspiratory flow rate and a variety of other objectively determined respiratory parameters on COPD patients with insomnia receiving benzodiazepines and Z-Drugs. However, the overall verdict was inconclusive as some experiments showed deleterious changes in these domains and others did not.[145] In terms of a difference in safety between benzodiazepines and Z-Drugs in COPD, the authors of this review, unlike Roth, refrain from declaring either sub-class as being safer in this context given that 4 of 6 studies found

no difference in respiratory changes between these classes.[145] In the context of Obstructive Sleep Apnea (OSA) the results of two meta-analyses largely found an absence of any worsening of sleep disordered breathing.[146,147]

Contrary to the experimental literature just discussed, mounting evidence from observational studies over the past number of years has raised the suspicion that use of benzodiazepines or Z-Drugs in those with COPD increases risk of respiratory exacerbations and mortality beyond that expected from the course of the disease state alone.[148–151] For the first time, an association with asthma exacerbation has also been raised from the results of a large observational study in the U.K.[152] The results for a few of these studies have been subject to extensive reviewer discussion with criticism but will not be taken up in detail here.[153,154]

Despite the similar findings and model adjustments by the authors of these studies, issues of confounding, bias and other methodological limitations can probably be raised as usual.[148–152] Of special potential confounding interest is the common usage of benzodiazepines for dyspnea in palliation.[155] Despite the fact that palliative drug usage is poorly captured in most pharmacoepidemiologic study designs (databases typically limited to outpatients), it is reasonable to speculate that even later stage ambulatory COPD patients with poor survival prognoses would be granted prescriptions for benzodiazepines and Z-Drugs more frequently than those with milder disease severity to assuage breathlessness, anxiety or insomnia related to their illness (i.e confounding by indication). Nonetheless, this was anticipated by Vozoris et al. who stratified their Canadian patient cohort by severity and still discovered that the highest hospitalisation or pneumonia rate ratio was in the healthiest sub-group of the COPD patients initiating benzodiazepines.[148]

The effect of benzodiazepines and Z-Drugs on non-infectious diseases of the respiratory tract is not yet perfectly clear due to the disparity of results between acute respiratory effects as measured in smaller experimental studies and longer-term clinical outcomes in observational studies. Given that population-based studies examining outcomes from exposure to these drugs has been predominantly of the case-control and retrospective cohort designs, prospective evidence, or even a meta-analysis of the available studies would be useful to persuade researchers and clinicians of any causal truth behind these associations. This is yet another example where findings from one discipline are not clearly in accord with that of another for these drugs and efforts should be made to reconcile this discrepant mistranslation in findings between pharmacology and epidemiology.

2.2.7) Dementia

Dementia, comprising Alzheimer's disease, vascular, lewy-body and other sub-types, remains among the most feared disease states associated with aging because of its poor prognosis, lack of effective treatment modalities and increasing global prevalence in the aging population.[156] It is long-standing basic knowledge that benzodiazepines and Z-Drugs cause acute, reversible cognitive dysfunction (slurred speech, transient amnesia, etc.) in many patients. It is also well known that older individuals are more sensitive to the psychotropic adverse effects of benzodiazepines. Beyond acute drug effect, an association extending to progressive, neurodegenerative disease has been raised on numerous occasions by independent researchers.

Barker et al. published a 2006 meta-analysis of 13 experimental studies, all of which employed a battery of various neuropsychological tests, finding overall statistically significant reductions for 12 of 12 cognitive domains thus strongly affirming the cognitive decline associated

with long-term use of benzodiazepines.[157] However, these findings, though compelling in establishing the range of cognitive deficits that may occur from benzodiazepine use do not confer direct knowledge on whether these drugs lead to neurodegenerative changes in cerebral tissue. Pariente et al., in a recent review article, speculate on a few potential drug-induced disease mechanisms but favor the hypothesis whereby exposed subjects are less likely to resort to a "cognitive reserve" that is; alternative neural signaling pathways unaffected by undetected pre-clinical lesions which may have otherwise been protective of cognitive faculties.[158] Ultimately, the true mechanism, if there even is one, remains unknown and so these authors call for more experimental research to clarify this.

Pariente et al., also reviewed the pharmacoepidemiologic body of evidence for this association and critically appraised the methodology of 10 observational studies as per the Newcastle-Ottawa scale for non-randomized studies.[159] Of the studies, 9 reported an increased risk of dementia from benzodiazepines.[159] A systematic review of 10 studies and meta-analysis of 8 studies, many of which overlapped with the prior review, used a random-effects model and found an overall 78% increased odds of dementia in benzodiazepine users over non-users.[160] A slightly older meta-analysis included 6 studies and reported a 49% increased odds in those ever having used benzodiazepines.[161] The association is strengthened considerably in those using benzodiazepines chronically for long-periods with a potentially further increased risk with higher doses and use of long-acting agents.[158–160] The meta-analyses, though quite recent themselves, may already warrant an updated estimate given three recent publications two of which reported increased risk of dementia from benzodiazepine use.[162–164] Notably, Takada et al. conducted various analyses on Canadian, American and Japanese data sources (adverse event databases, claims databases) and found that data from all 3 countries supported an association between long-

term and long-acting benzodiazepine use and dementia.[162] The majority of studies on this association have been retrospective but a recent prospective study by Gray et al. reported discordant findings. Despite having shown "any-use" of benzodiazepine to be significantly associated with dementia, they failed to find higher dementia incidence in those individuals with the longest exposure duration to these drugs.[165]

In terms of evidence regarding any association of Z-Drugs specifically to dementia, the evidence is primarily restricted to a few sub-analyses in benzodiazepine studies previously alluded to which suggest similar risk of dementia as was seen with benzodiazepines.[166] A single Taiwanese case-control study reported an increased risk of dementia with zolpidem compared to non-users but other than this, there appears to be a lack of studies solely on Z-Drugs and dementia with benzodiazepines excluded.[167]

There has been general consensus among researchers in this area that methodological limitations and differences giving rise to bias or confounding have been the primary challenge that remains to be overcome in order to conclude judgement on this association with high-level confidence. The most popular alternative explanations and criticisms for the reported association is founded upon protopathic bias (reverse-causality) whereby early onset symptoms of clinically undetected dementia are first treated with benzodiazepines prior to a formal dementia diagnosis.[159,168–170]Similarly, the association is further confused through the common clinical use of benzodiazepines to treat behavioral and psychological symptoms of dementia.[171] In this case, confounding by indication is a danger for proper interpretation and, with reverse-causality, represents a temporal continuum of potential bias in pharmacoepidemiologic studies on this topic. Therefore, despite the large proportion of studies concluding an association between benzodiazepines and dementia, the criteria required to strongly substantiate a causal relationship

remains only partially fulfilled.[159] Clear evidence of a drug-induced neuropathological mechanism as well as a large well-designed prospective study with sufficiently long follow-up period (30+ years) are current gaps in the research that have already been called to be filled by previous authors who have examined the body of evidence.[158–161] Nevertheless, the truth behind this association carries potentially major public health implications for prevention of an, as of yet, incurable, but always devastating, neurodegenerative disease.

2.2.8) Cancer

With the burden of cancer having increased substantially over the past decades, the medico-scientific community, in response, has been ever more vigilant in identifying potential causal exposures leading to cancers (i.e environmental hormone disruptors, dietary red meat, etc.). Mechanisms underlying benzodiazepine and Z-Drug induced tumorigenesis remain tentative and unclear based on a review by Brambilla et al. of carcinogenicity and genotoxicity study results.[172] These authors reviewed study data for 51 benzodiazepine and Z-Drugs and at the very least, it is clear that there does not appear to be a consistent class effect for these agents in causing neoplasms in various animal tissue types. However, at the time of reporting the authors state that only 8 of 41 marketed molecules had all the necessary data needed for fulfillment of the FDA guidelines for carcinogenicity testing of pharmaceuticals.[172]

Despite the lack of conclusive experimental data, alarm signals for cancer risk have been raised by researchers for benzodiazepines and the Z-Drugs based on observational study findings.[173–176] In attempts to get a clear answer to this quandary, Kim et al. published a 2016 meta-analysis of 22 observational studies (18 case-control and 4 cohort) which concluded an overall estimate of 19% increased cancer risk, with a significant dose-response trend, among

benzodiazepine users over non-users.[177] There does exist a fine degree of granularity when it comes to the determination of cancer risk from benzodiazepines/Z-Drugs as certain types of cancer (i.e esophageal, brain, pancreatic) and certain agents (lorazepam, clonazepam, zopiclone) carry greater statistical weight driving the overall association.[174,177] Given that most of the studies included in the meta-analysis are retrospective, the authors address the limitations fairly by reminding us of confounding by indication (cancer patients more likely to use anxiolytic medication) and unmeasured confounding (alcohol and smoking).[177]

Perhaps most strikingly and of special interest is the odds/risk ratio of 2.08 (CI 1.77-2.44) for brain tumors which was of considerably greater magnitude than other types of cancer in the above cited meta-analysis. Harnod et al., in the only study solely devoted to this cancer sub-type found a more than three fold greater incidence of benign brain tumors in those exposed to benzodiazepines.[178] However, the benzodiazepine users in this study were significantly confounded as they were more likely to have had histories of dementia, epilepsy, head injuries and brain scan imaging. The authors claim to have adequately adjusted for confounding but also rightfully mention the potential for unmeasured confounding as well as protopathic bias (undiagnosed brain tumors giving rise to insomnia, seizures and psychiatric symptomatology) which may have skewed the results.[178] Nevertheless, an alarming finding of this magnitude is hypothesis generating and should require either confirmation or refutation from further study. Can it be more than coincidence that the anatomical location of highest potential neoplasm risk and the primary site of action for these agents is one and the same?

There is currently a lack of complete, high-quality experimental and epidemiologic evidence to confirm an association between benzodiazepine/Z-Drug use and cancer. Ultimately, if these drugs are later proven from now to be carcinogenic it seems reasonable to question why this

association was not detected with certainty many years earlier given their widespread usage? Malignancy caused by any regulated prescription medication is usually extremely rare and slow to develop. Even after diagnosis, it is not likely to be frequently identified in the minds of clinicians in terms of a causal association. Further to this, confounding by indication and unmeasured confounding are real limitations which place doubt on the association as it currently stands according to the observational study data. For these reasons, as with the dementia association, a prospective study of sound methodology and sufficient sample size is needed to address the seriousness of the claims raised recently in the literature.

2.2.9) Conclusion

Standard considerations for the causality of harm associations have been discussed and implied throughout this review. A concise summary assessing each adverse outcome association (excluding overdose for obvious reasons) for causality has been provided in Table 1 based on the well recognized Bradford Hill criteria[179], which has been operationalized in pharmacoepidemiology in the past.[180] However, the reader is cautioned that a systematic objective process to determine whether a criterion was fulfilled was not undertaken in this narrative review. Therefore, Table 1 simply serves as a summative, visual display of the authors' interpretation, which may be vulnerable to bias. It is clear that, despite the voluminous body of biomedical literature on benzodiazepines and Z-drugs, there is still a research need to answer vital questions relevant to the optimization of their effectiveness and safety in society. As with legal matters (i.e., innocent until proven guilty), doubt persists in the biomedical community regarding the relatively new safety accusations (dementia, infections, pancreatitis, and cancer) levelled against these drugs by pharmacoepidemiologic researchers (i.e., association until proven causation).

Table 2.2: Hill Causality Criteria Fulfillment for Benzodiazepine/Z-Drug Harm Associations

	Traffic Accidents	Falls leading to Fractures	Dementia	Infections	Pancreatitis	Respiratory Worsening	Cancer
Consistency	+	+	+/-	+/-	+/-	-	+/-
Strength	+	+	+	+/-	+	+/-	+/-
Temporality	+	+	-	+	-	-	-
Specificity	-	-	-	-	-	-	-
Dose-Response	+	+	+/-	-	+/-	-	+/-
Coherence	+	+	+/-	+/-	-	+/-	-
Experimental Evidence	+	+	-	+/-	-	+/-	-
Analogy	+	+	-	-	+/-	+	-

+ = positive evidence, - = lack of evidence, +/- = inconclusive evidence

Although serious clinical doubt persists, if even one of these newer associations stands the rigorous test of scientific scrutiny and is practically proven, it will have potentially tremendous public health implications given the already existent controversy surrounding certain patterns of use. Furthermore, serious negative health outcomes that are known to be associated with these agents such as falls, hip fractures, overdose, and motor vehicle accidents still need to be continually addressed in policies and clinical practice.

2.3) Methods for Measurement of Aggregate Benzodiazepine Utilisation

***Disclaimer*:** This section is an adapted, condensed version of the published manuscript:

Brandt J, Alkabanni W, Alessi-severini S, Leong C. Translating Benzodiazepine Utilization Data into Meaningful Population Exposure : Integration of Two Metrics for Improved Reporting. *Clin Drug Investig*. 38(7). 565-572 2018. doi:10.1007/s40261-018-0648-y.

Student contribution: *conceptualised topic, researched topic, wrote first draft, revised draft and wrote final version. Student was corresponding author to editor and peer-reviewers.*

2.3.1) Defined Daily Dose (DDD) Methodology

Measuring benzodiazepine and Z-Drug (i.e zopiclone, zolpidem, zaleplon) utilisation in populations helps to reaffirm current prescribing practices or identify problematic usage patterns that could be predictive of major adverse outcomes (section 2.2). Drug utilisation studies commonly follow the internationally accepted, standard methodology established by the WHO Collaborating Centre on Drug Statistics in which the Anatomical Therapeutic Chemical (ATC) classification system is used in conjunction with drug specific Defined Daily Doses (DDD).[181,182] The DDD for a particular drug is defined as the *"*average maintenance dose per day for its main indication in adults*"*.[181] Population consumption is typically reported as the quantity of DDD/1000

inhabitants per day or the quantity of DDD/1000 inhabitants per year. A major advantage of this system is the organized classification of drugs and doses based on therapeutic categories, primary indications and routes of administration. Assignment of DDD values are regularly reviewed and updated. Lastly, guidelines explaining the appropriate use of the ATC/DDD system ensure consistency in the calculation and reporting of drug utilisation statistics. For these reasons, past reviews of consumption measures have recognized the value of the DDD unit system for drug utilisation research.[183,184]

Despite the advantages of the DDD metric, the listed DDDs for certain drugs have become contentious due to differences in approved indications and dosing patterns between countries.[183,184] In terms of benzodiazepines, clonazepam serves as the best example of this limitation. The DDD for clonazepam orally is 8 mg for its main indication as an anticonvulsant.[182] However, its use as an anxiolytic is quite common for conditions such as panic disorder, where a typical daily dose would be in the lower dosage range of 0.5-4 mg.[185,186] Based on this, many countries may underestimate the use of clonazepam relative to other benzodiazepines. This limitation is somewhat obviated when researchers also report the average Prescribed Daily Dose (PDD) in addition to the DDD. The PDD is the dose, maintained in its original milligram units, derived from the day supply, metric quantity dispensed (i.e number of tablets) and the strength of the dosage form. The PDD can be easily determined for a single dispensing observation according to formula 1 below. Alternatively, formula 2 may be used to yield the average PDD based on all dispensing observations in a given time period (i.e fiscal year).

$$(1) \quad \text{PDD} = \frac{\text{Q x S}}{\text{D}}$$

$$(2)\quad \mathrm{PDD}_{\mathrm{avg}} = \frac{\sum(\mathrm{Q\ x\ S})}{\sum \mathrm{D}}$$

where:
$\mathrm{Q} = \text{Metric Quantity Dispensed}$
$\mathrm{S} = \text{Milligram Strength of Dosage Unit}$
$\mathrm{D} = \text{Day Supply of Medication}$

Nonetheless, it has been shown that the ratio of the PDD:DDD varies greatly not only between individual agents in the same pharmacologic class (intra-class variation), but also between common drug classes (inter-class variation). For example, Grimmsmann and Himmel showed that the PDD:DDD ratio increased, on average, from 0.79 to 2.17, if patients were switched from a beta-blocker to an Angiotensin Converting Enzyme (ACE) inhibitor.[187]

2.3.2) Diazepam Milligram Equivalence (DME) Methodology

The DME metric system was first established in the United Kingdom by Dr. Ashton based on her clinical observations of dose-response and cross-tapering in benzodiazepine dependent patients with anxiety and sleep disorders.[188,189] It has been used in pharmacoepidemiologic studies in the past to define thresholds for dose-intensity between distinct user populations.[35,44] Although this system has the advantage of being specific to benzodiazepines and Z-Drugs, it is not routinely favored due to discrepancies between sources as to the accuracy and precision of conversion values. Though multiple dose equivalency tables exist, the original Ashton table remains as the most prominent.[189] Other dose equivalency tables have been derived from clinical observations on cross-tolerance to determine the minimum doses necessary for the probable prevention of withdrawal symptoms, with diazepam as the reference drug.[190,191] Of interest, a very recent study has purported to establish benzodiazepine conversions from serum concentrations as correlated with driving impairment.[192]

Despite different attempts and approaches to establish "equivalence", it should be noted that benzodiazepines produce somewhat variable effects from one another. This implies that 'dose-equivalencies' cannot reliably represent similarities in the magnitude of sedative, hypnotic, anxiolytic or amnestic effects between agents. Major differences in the pharmacokinetics of benzodiazepines, such as the half-life or accumulation of active metabolites, are also not well accounted for by the DME system. This is undeniably problematic. However, the saving grace of this conversion system rests on the theoretical underpinning that there is *some* principle of pharmacodynamic equivalence that, however currently ill-defined, can still be discovered or for which sufficient consensus can be reached. For example, most clinicians would probably expect a closer proximity in the magnitude of central nervous system depression between 10 mg of diazepam and 1 mg of lorazepam than between 20 mg of diazepam and 0.5 mg of lorazepam. This estimate should become more accurate with collective clinical experience in large populations.

2.3.3) Integrated 'DME-DDD' Methodology

Despite the aforementioned limitations, the DME system does offer a more useful comparative estimate of potency than the DDD system, as the latter was not designed to do so between drugs in a class. Therefore, we contend that when it is combined with the DDD system and when researchers understand the limitations behind both, the integrated metric discussed here would outperform either alone in terms of the estimation and subsequent interpretation of overall population pharmacologic exposure to the benzodiazepine drug class.

For simplicity, this metric will be referred to as the Diazepam Milligram Equivalent Defined Daily Dose (DME-DDD) to clearly suggest the contribution of each component metric. However, the concept underlying this proposed metric was previously characterised by Svendson

et al. when they combined Morphine Milligram Equivalence (MME) with the DDD system to improve opioid utilisation reporting.[193] Unfortunately, the DME conversion system is less well-established and recognised than the MME conversion system. For example, the MME conversion system, having found its way into clinical practice guidelines, is frequently employed to assist in the cross-tapering or switching of opioids to mitigate withdrawal symptoms and/or reduce overdose risk.[194] Similar investigations to compare the DDD system with equivalence adjusted units for antipsychotics have also been conducted.[195,196]

By using values for both systems outlined in Table 2.3., an adjustment factor can be derived for each individual agent by dividing the listed DDD by the dose approximately equivalent to 10 mg of diazepam. The adjustment factor can therefore be conceived of as a ratio representing the number of diazepam DDDs which would be equal to a single DDD of the original drug.

$$3) \quad Adjustment\ Factor\ = \frac{DDD}{DME}$$

In some cases, this makes no difference suggesting that there is already agreement between the DDD and DME. In other cases, such as with the commonly used benzodiazepines; clonazepam, lorazepam and alprazolam, the estimates can change considerably. For some benzodiazepines including brotizolam, camazepam, fludiazepam and midazolam, a DME value has yet to be clearly determined from reputable scientific sources. Although some internet-based equivalency tables may provide some estimate, confidence in their reliability is too low for inclusion or citation.

Table 2.3 – Defined Daily Doses, Diazepam Milligram Equivalence and Derived Adjustment Factor for Prescribed Benzodiazepines and Z-Drugs

	ATC Code [182]	Defined Daily Dose (oral route)[182]	Equivalence to 10 mg Diazepam [189]	Adjustment Factor
Alprazolam	N05BA12	1 mg	0.5 mg	2
Bentazepam	N05BA24	75 mg	N/A	N/A
Bromazepam	N05BA08	10 mg	5-6 mg	1.66-2
Brotizolam	N05CD09	0.25 mg	N/A	N/A
Camazepam	N05BA15	30 mg	N/A	N/A
Chlordiazepoxide	N05BA02	30 mg	25 mg	1.2
Clobazam	N05BA09	20 mg	20 mg	1
Clonazepam	N03AE1	8 mg	0.5 mg	16
potassium Clorazepate	N05BA05	20 mg	15 mg	1.33
Diazepam	N05BA01	10 mg	10 mg	1
Estazolam	N05CD04	3 mg	1-2 mg	1.5-3
Fludiazepam	N05BA17	0.75 mg	N/A	N/A
Flurazepam	N05CD01	30 mg	15-30 mg	1-2
Flunitrazepam	N05CD03	1 mg	1 mg	1
Halazepam	N05BA13	100 mg	20 mg	5
ethyl Loflazepate	N05BA18	2 mg	N/A	N/A
Loprazolam	N05CD11	1 mg	1-2 mg	0.5-1
Lorazepam	N05BA06	2.5 mg	1 mg	2.5
Lormetazepam	N05CD06	1 mg	1-2 mg	0.5-1

	ATC Code [182]	Defined Daily Dose (oral route)[182]	Equivalence to 10 mg Diazepam [189]	Adjustment Factor
Medazepam	N05BA03	20 mg	10 mg	2
Midazolam	N05CD08	15 mg	N/A	N/A
Nitrazepam	N05CD02	5 mg	10 mg	0.5
Nordazepam	N05BA16	15 mg	10 mg	1.5
Oxazepam	N05BA04	50 mg	20 mg	2.5
Prazepam	N05BA11	30 mg	10-20 mg	1.5-3
Quazepam	N05CD10	15 mg	20 mg	0.75
Temazepam	N05CD07	20 mg	20 mg	1
Triazolam	N05CD05	0.25 mg	0.5 mg	0.5
Zaleplon	N05CF03	10 mg	20 mg	0.5
Zolpidem	N05CF02	10 mg	20 mg	0.5
Zopiclone	N05CF01	7.5	15 mg	0.5

N/A – Not Applicable given insufficient source data

2.3.4) Comparison of Methodologies

To demonstrate an application of the DME-DDD method, annualised benzodiazepine consumption data was retrieved from the most recent drug utilisation study (at the time of writing). Berman et al. recently published benzodiazepine consumption data for Israel for the years 2005-2013.[197] They reported overall class consumption and consumption by individual agent in the standard DDD/1000 inhabitants/day units. To get their raw data for each drug by year we used

data from the supplement that accompanied the main publication and reproduced the data in Table 2.4.

Table 2.4 –Benzodiazepine Consumption Data from Israel in DDD / 1000 person-days[197]

	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Alprazolam	2.01	2.18	2.57	2.12	2.27	2.16	2.28	2.17	2.58
Brotizolam	7.74	4.97	5.41	13.46	13.19	13.58	14.08	14.01	14.22
Clobazam	0.091	0.092	0.101	0.101	0.115	0.121	0.131	0.155	0.170
Clonazepam	0.0015	0.0014	0.0014	0.0014	0.61	1.23	1.25	1.23	1.19
Diazepam	3.09	3.33	3.04	2.99	2.87	2.97	2.81	2.71	2.58
Flunitrazepam	0.26	0.24	0.22	0.17	0.12	0.12	0.10	0.10	0.08
Lorazepam	4.23	4.16	4.08	3.99	3.92	3.85	3.78	3.71	3.64
Midazolam	0.26	0.25	0.33	0.31	0.33	0.33	0.32	0.28	0.31
Nitrazepam	0	0	1.13	0.96	0.91	0.93	0.77	0.75	0
Oxazepam	2.08	2.04	1.92	1.75	1.78	1.61	1.59	1.56	1.52
Zolpidem	0.33	3.68	4.93	3.00	3.33	3.66	3.98	4.70	5.19
Zopiclone	1.89	1.86	1.84	1.81	2.29	2.66	2.81	2.92	3.01
Total	21.99	22.80	25.57	30.66	31.73	33.21	33.90	34.29	34.49

The accuracy of the reported results using the standard DDD methodology are neither doubted nor disputed. However, it is difficult to conceptually grasp the true meaning of the DDD/1000 inhabitants/day for the overall class totals in the last row of Table 2.4, despite that it is simply the sum of the values for each drug individually. For instance, one may ask if there is an inherent difference in the measurement of DDD of “benzodiazepine” / 1000 inhabitants / day in

Israel compared to another jurisdiction (e.g., Canada). Table 2.5 shows the Israel consumption data transformed to DDD/1000 inhabitants/day based on an approximate 10 mg dose of diazepam.

Based on the original results from Table 2.4, an Ashton-equivalency adjustment factor was applied on 10 of the 12 agents to produce the results displayed in Table 2.5. There was no Ashton conversion value for brotizolam and midazolam, therefore these values were left unchanged. Though an adjustment, especially for brotizolam, may have changed the results, it is suspected that it would have been minor in contribution to the overall totals. The DDD values increased for alprazolam, clonazepam, lorazepam and oxazepam and decreased for nitrazepam, zolpidem and zopiclone. Clobazam, diazepam and flunitrazepam were already at unity between the DME and DDD resulting in no shift of the reported values.

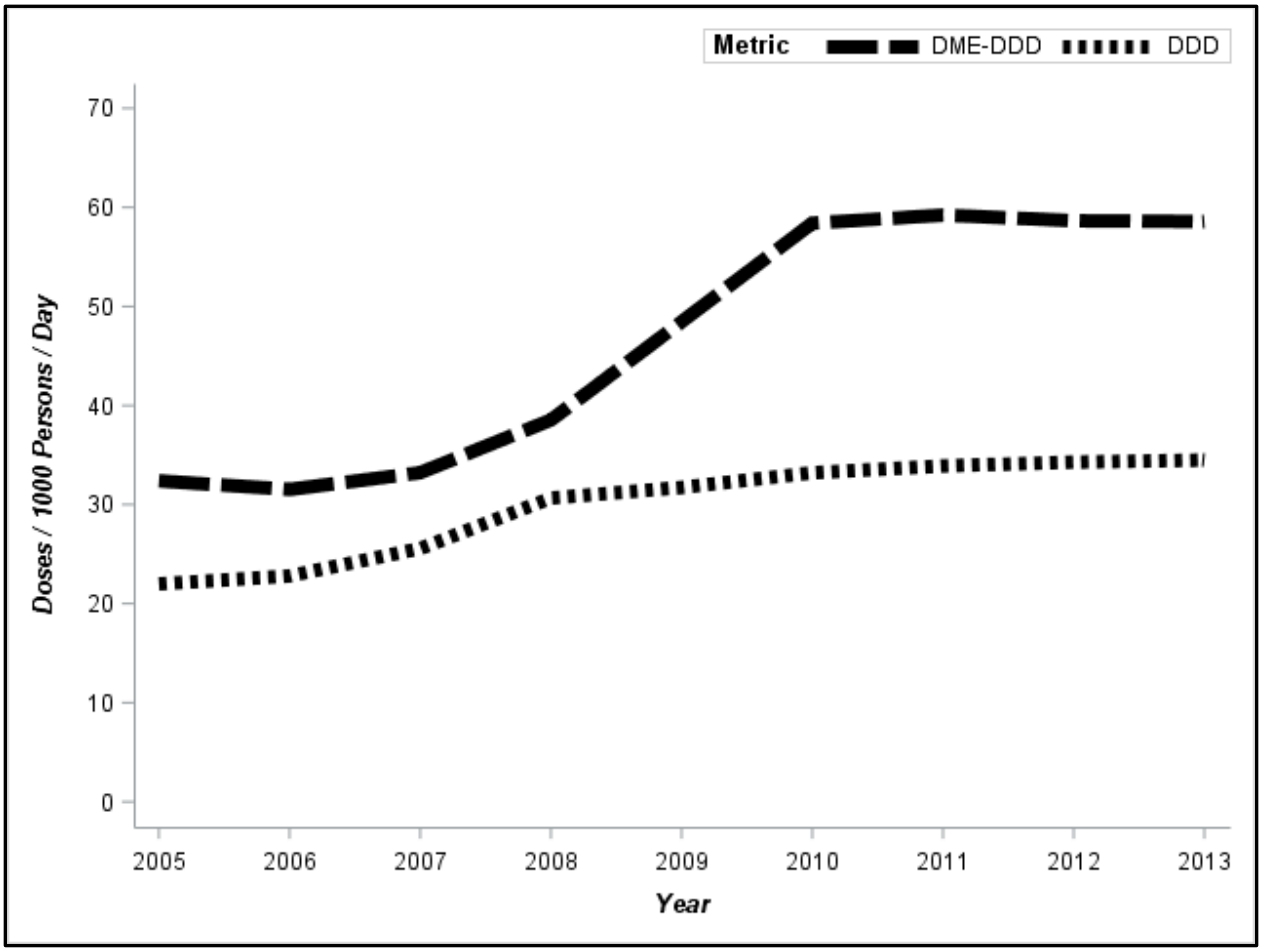
Table 2.5 – **Benzodiazepine Consumption Data from Israel in DME-DDD / 1000 person-days**

	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Alprazolam	4.02	4.36	5.14	4.24	4.54	4.32	4.56	4.34	5.16
Brotizolam[a]	7.74	4.97	5.41	13.46	13.19	13.58	14.08	14.01	14.22
Clobazam	0.091	0.092	0.101	0.101	0.115	0.121	0.131	0.155	0.170
Clonazepam	0.024	0.0224	0.0224	0.0224	9.76	19.68	20	19.68	19.04
Diazepam	3.09	3.33	3.04	2.99	2.87	2.97	2.81	2.71	2.58
Flunitrazepam	0.26	0.24	0.22	0.17	0.12	0.12	0.10	0.10	0.08
Lorazepam	10.58	10.4	10.2	9.98	9.8	9.63	9.45	9.28	9.1
Midazolam[a]	0.26	0.25	0.33	0.31	0.33	0.33	0.32	0.28	0.31
Nitrazepam	0	0	0.57	0.48	0.46	0.47	0.39	0.38	0
Oxazepam	5.2	5.1	4.8	4.38	4.45	4.03	3.98	3.9	3.8
Zolpidem	0.17	1.84	2.47	1.5	1.67	1.83	1.99	2.35	2.60
Zopiclone	0.95	0.93	0.92	0.91	1.15	1.33	1.41	1.46	1.51
Total	32.39	31.53	33.22	38.54	48.46	58.41	59.22	58.65	58.57

[a]No adjustment made as DME value insufficiently known

The original results showed a steady increase of 56.8% in the DDD/1000 inhabitants/day from 2005-2013. Our transformation of the results demonstrates a larger difference wherein the DME-DDD/1000 inhabitants/day increased by 80.8% (Figure 2.2).

Figure 2.2 – Overall Benzodiazepine Utilization in Israel (2005-2013)



The original results could be argued as more correct because they strictly adhere to the WHO DDD values without deviating via conversion. However, a rise in 56.8% of the DDD/1000 inhabitants/day for benzodiazepines and Z-Drugs does not reveal what the class-based DDD value actually means in a way that is interpretable via another layer of important information. In contrast,

using the adjustment method, it can be claimed that there was a relative 80.8% increase in the number of defined daily doses of approximately 10 mg of diazepam consumed per 1000 inhabitants per day from 2005-2013. This difference is important because the pooled estimates for the total utilisation of "benzodiazepines" (or other drug class for that matter) in DDD/1000 inhabitants/day would be confounded when comparing over time, or between regions, if the proportional use and potency of individual agents are left unaccounted for.

Although the functionality of this method for interpretation has been demonstrated, the DME-DDD metric itself has some important limitations. These limitations lie solely with the DME portion. Firstly, the DME metric is currently plagued by inconsistency and disagreement between sources in conversion values.[189–192] Therefore, use of the DME-DDD metric should be accompanied by the chosen equivalency table for the purpose of cross-verification. Secondly, many benzodiazepines currently lack an approximate conversion value, making the application of the method one of varying completeness depending on the geographic origin of the data. Thirdly, the DME is founded upon pharmacological principles and varied clinical observation in adults. Not only is it therefore prone to considerable inter-individual and intra-individual variation, but results may also become biased if it is used improperly in smaller, non-representative populations (i.e children, pregnant women). Lastly, a final dilemma is accounting for varying levels of tolerance in populations where benzodiazepine use is being measured. Accordingly, the DME-DDD would be best understood in conjunction with prevalence estimates of short-term and chronic users to provide context for complete interpretation.

Any and all discrepancies in the DME values between sources would be expected to lessen as data from large samples and expert opinion accumulate to correct or confirm conversion estimates. As decades of empirical clinical observation and experience with benzodiazepines have

accrued in almost all countries, representing millions of patients, it is not unrealistic to attempt to establish a consensus on DME values amongst prescribers and pharmacists familiar with each benzodiazepine. This may be achieved through a well-designed international survey, of sufficient sample size, with representation of experts from diverse geographies.

Alternatively, dose-response studies on large, generalizable samples using well defined, valid and clinically relevant psychometric tests, would be a superior empirical approach for yielding more accurate equivalency values. This approach has been taken in the past on numerous occasions, albeit in small samples and with limited success. The only exceptions were for saccadic eye movement velocity and visual analogue scale measured "alertness", both of which produced some reliability for determining dose-response relationships and tentative equivalencies.[198] The latter measure may be more appropriate if it is taken as a surrogate measure for the central nervous system depressive effects of benzodiazepines. Unfortunately, pursuing further controlled pharmacological experimentation is far less practical and may be of limited current interest to benzodiazepine researchers. Ashton's work was conducted on benzodiazepine dependent individuals with potency equivalence being determined on the basis of whether withdrawal symptoms manifested or not. A continued exploration of this context in clinical practice may resolve discrepancies between equivalency sources.

2.3.5) Conclusion

Measuring benzodiazepine and Z-Drug (i.e zopiclone, zolpidem, zaleplon) utilisation in populations helps to reaffirm current prescribing practices or identify problematic usage patterns that could be predictive of major adverse outcomes (Section 2.2). By reconstituting and appraising a rarely used benzodiazepine utilisation metric, these tasks are made easier. It is recommended that

this new metric not replace the DDD but rather be used in addition to it for more meaningful reporting of estimated population pharmacologic exposure to the benzodiazepine / Z-Drug class. As shown previously, this method may be further translatable to other drug classes, hopefully where equivalencies are well-defined based on evidence and where this approach is sensible. In concept, this method aids in making utilisation estimates more meaningful by enabling a robust interpretation of population exposure by accounting for both consumption (DDD) and potency (DME). Though, the degree of accuracy by which it approximates *true* benzodiazepine population exposure (based upon pharmacokinetics, pharmacodynamics, adherence and population characteristics) remains ultimately unknown. Pharmacoepidemiology would further benefit from a systematic, evidence-based update on the current DME system to improve the accuracy of the DME-DDD metric for optimal use in benzodiazepine utilisation studies.

Chapter 2 References

1. United Nations. *Convention on Psychotropic Substances*.; 1971:1-39.

2. International Narcotics Control Board (INCB). *Techncal Report on Psychotropic Substances - Statistics for 2016*. New York, NY: United Nations; 2018. https://www.incb.org/documents/Psychotropics/technical-publications/2017/Technical_Publication_2017_English_04042018.pdf.

3. United Nations. World Population Prospect: The 2015 Revision World Population 2015 Wallchart. *World Popul Prospect 2015 Revis Popul 2015 Wallchart ST/ESA/SERA/378*. 2015:2. doi:ST/ESA/SER.A/378.

4. Morgan S, Smolina K, Mooney D, Raymond C, Bowen M. *Rx Atlas*.; 2013.

5. Alessi-Severini S, Bolton JM, Enns MW, et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. *C open*. 2014;2(4):E208-16. doi:10.9778/cmajo.20130076.

6. Canadian Centre on Substance Abuse. *Prescription Sedatives (Canadian Drug Summary)*.; 2015.

7. Government of Canada. Canadian Tobacco, Alcohol and Drug Survey: Summary of results for 2015. http://healthycanadians.gc.ca/science-research-sciences-recherches/data-donnees/ctads-ectad/summary-sommaire-2015-eng.php. Published 2015. Accessed January 5, 2017.

8. Canadian Institute for Health Information. The Use of Selected Psychotropic Drugs Among Seniors on Public Drug Programs in Canada , 2001 to 2010. 2012;(March).

9. Rosman S, Le Vaillant M, Pelletier-Fleury N. Gaining insight into benzodiazepine prescribing in General Practice in France: a data-based study. *BMC Fam Pract*. 2011;12(1):28. doi:10.1186/1471-2296-12-28.

10. Victorri-Vigneau C, Feuillet F, Wainstein L, et al. Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. *Eur J Clin Pharmacol*. 2013;69(11):1965-1972. doi:10.1007/s00228-013-1557-x.

11. Petitjean S, Ladewig D, Meier CR, Amrein R, Wiesbeck G a. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. *Int Clin Psychopharmacol*. 2007;22(5):292-298. doi:10.1097/YIC.0b013e328105e0f2.

12. Simon GE, VonKorff M, Barlow W, Pabiniak C, Wagner E. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *J Clin Epidemiol*. 1996;49(9):1067-1073. doi:10.1016/0895-4356(96)00139-4.

13. Magrini N, Vaccheri A, Parma E, et al. Use of benzodiazepines in the Italian general population: prevalence, pattern of use and risk factors for use. *Eur J Clin Pharmacol*. 1996;50(1-2):19-25. http://www.ncbi.nlm.nih.gov/pubmed/8739806.

14. Oh S-H, Oh KS, Lee K-U, et al. In-depth investigation for prescribing trends of benzodiazepines in South Korea. *Int J Clin Pharmacol Ther*. 2014;52(6):460-470. doi:10.5414/CP202008.

15. Iqbal SP, Ahmer S, Farooq S, et al. Benzodiazepine use among adults residing in the urban settlements of Karachi, Pakistan: A cross sectional study. *Subst Abuse Treat Prev Policy*. 2011;6(1):19. doi:10.1186/1747-597X-6-19.

16. Bjorner T, Tvete IF, Aursnes I, Skomedal T. [Dispensing of benzodiazepines and Z drugs by Norwegian pharmacies 2004-2011]. *Tidsskr Nor Laegeforen*. 2013;133(20):2149-2153. doi:10.4045/tidsskr.11.0543.

17. Dunbar GC, Perera MH, Jenner FA. Patterns of benzodiazepine use in Great Britain as measured by a general population survey. *Br J Psychiatry*. 1989;155(DEC.):836-841. doi:10.1192/bjp.155.6.836.

18. Zandstra SM, Furer JW, van de Lisdonk EH, et al. Different study criteria affect the prevalence of benzodiazepine use. *Soc Psychiatry Psychiatr Epidemiol*. 2002;37(3):139-144. doi:10.1007/s001270200006.

19. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

20. Egan M, Moride Y, Wolfson C, Monette J. Long term continuous use of benzodiazepines by older adults in Quebec: Prevalence, incidence and risk factors. *J Am Geriatr Soc*. 2000;48(7):811-816. http://sfx.nelliportaali.fi.libproxy.helsinki.fi/sfxlcl3?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&genre=article&sid=ProQ:ProQ:psycinfo&atitle=Long+term+continuous+use+of+benzodiazepines+by+older+adults+in+Quebec:+Prevalence%252.

21. Tu K, Mamdani MM, Hux JE, Tu JB. Progressive trends in the prevalence of benzodiazepine prescribing in older people in Ontario, Canada. *J Am Geriatr Soc*. 2001;49(10):1341-1345. doi:10.1046/j.1532-5415.2001.49262.x.

22. Kassam A, Patten SB. Hypnotic use in a population-based sample of over thirty-five thousand interviewed Canadians. *Popul Health Metr*. 2006;4:15. doi:10.1186/1478-7954-4-15.

23. Neutel CI. The epidemiology of long-term benzodiazepine use. *Int Rev Psychiatry*. 2005;17(3):189-197. doi:10.1080/09540260500071863.

24. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: Examining the impact of increasing research and guideline cautions against long-term use. *Health Policy (New York)*. 2010;97(2-3):122-129. doi:10.1016/j.healthpol.2010.03.008.

25. Esposito E, Barbui C, Patten SB. Patterns of benzodiazepine use in a Canadian population sample. *Epidemiol Psichiatr Soc*. 2009;18(3):248-254.

26. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-142. doi:10.1001/jamapsychiatry.2014.1763.

27. Anderson ABT et al. Long-term use of zopiclone, zolpidem and zaleplon among Danish elderly and the association with sociodemographic factors and use of other drugs. *Pharmacoepidemiol Drug Saf*. 2011;20:378-385. doi:10.1002/pds.

28. Zandstra SM, van Rijswijk E, Rijnders CAT, et al. Long-term benzodiazepine users in family practice: Differences from short-term users in mental health, coping behaviour and psychological characteristics. *Fam Pract*. 2004;21(3):266-269. doi:10.1093/fampra/cmh309.

29. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BHC. Determinants of chronic benzodiazepine use in the elderly: A longitudinal study. *Br J Clin Pharmacol*. 2008;65(4):593-599. doi:10.1111/j.1365-2125.2007.03060.x.

30. Jorm AF, Grayson DA, Creasey H, Waite L, Broe GA. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health*. 2000;24(1):7-10. doi:10.1111/j.1467-842X.2000.tb00715.x.

31. Neutel CI, Maxwell CJ. The benzodiazepine treadmill--does one prescription lead to more? *Pharmacoepidemiol Drug Saf*. 1996;5(1):39-42. doi:10.1002/(SICI)1099-1557(199601)5:1<39::AID-PDS211>3.0.CO;2-N.

32. Manthey L, Van Veen T, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: The Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol*. 2011;71(2):263-272. doi:10.1111/j.1365-2125.2010.03818.x.

33. Cheng J et al. Characteristics associated with benzodiazepine usage in elderly outpatients in Taiwan. *Int J Geriatr Psychiatry*. 2008;23:618-624. doi:10.1002/gps.

34. Gray SL, Eggen AE, Blough D, Buchner D, LaCroix AZ. Benzodiazepine use in older adults enrolled in a health maintenance organization. *Am J Geriatr Psychiatry*. 2003;11(5):568-576.

35. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-1011. doi:http://dx.doi.org/10.1176/appi.ps.54.7.1006.

36. Hausken AM, Furu K, Skurtveit S, Engeland A, Bramness JG. Starting insomnia treatment: The use of benzodiazepines versus z-hypnotics. A prescription database study of predictors. *Eur J Clin Pharmacol*. 2009;65(3):295-301. doi:10.1007/s00228-008-0565-8.

37. Mattos MK, Sereika SM, Naples JG, Albert SM. Differences in Benzodiazepine Receptor Agonist Use in Rural and Urban Older Adults. *Drugs - Real World Outcomes*. 2016;3(3):289-296. doi:10.1007/s40801-016-0080-7.

38. Sakshaug S, Handal M, Hjellvik V, et al. Long-term Use of Z-Hypnotics and Co-Medication with

Benzodiazepines and Opioids. *Basic Clin Pharmacol Toxicol*. 2016. doi:10.1111/bcpt.12684.

39. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002−2014. *Am J Prev Med*. 2016;51(2):1-10. doi:10.1016/j.amepre.2016.02.014.

40. van Hulten R, Teeuw KB, Bakker A, Leufkens HG. Initial 3-month usage characteristics predict long-term use of benzodiazepines: an 8-year follow-up. *Eur J Clin Pharmacol*. 2003;58:689-694. doi:10.1007/s00228-002-0548-0.

41. Bjorner T, Laerum E. Factors associated with high prescribing of benzodiazepines and minor opiates. A survey among general practitioners in Norway. *Scand J Prim Health Care*. 2003;21(2):115-120.

42. Amos TB, Keith SW, Del Canale S, et al. Inappropriate prescribing in a large community-dwelling older population: a focus on prevalence and how it relates to patient and physician characteristics. *J Clin Pharm Ther*. 2015;40(1):7-13. doi:10.1111/jcpt.12212.

43. Sirdifield C, Anthierens S, Creupelandt H, Chipchase SY, Christiaens T, Siriwardena AN. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC Fam Pract*. 2013;14:191. doi:10.1186/1471-2296-14-191.

44. Alessi-severini S, Bolton JM, Enns MW. Sustained Use of Benzodiazepines and Escalation to High Doses in a Canadian Population. *Psychiatr Serv*. 2016;67(9):1012-1018. doi:10.1176/appi.ps.201500380.

45. Tvete IF, Bjørner T, Aursnes IA, Skomedal T. A 3-year survey quantifying the risk of dose escalation of benzodiazepines and congeners to identify risk factors to aid doctors to more rationale prescribing. *BMJ Open*. 2013;3:e003296. doi:10.1136/bmjopen-2013-003296.

46. Fride Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. *Scand J Prim Health Care*. 2015;33(4):252-259. doi:10.3109/02813432.2015.1117282.

47. Lekka NP, Paschalis C, Beratis S. Nicotine, caffeine and alcohol use in high- and low-dose benzodiazepine users. *Drug Alcohol Depend*. 1997;45(3):207-212.

48. World Health Organization. WHO | The top 10 causes of death. WHO. http://www.who.int/mediacentre/factsheets/fs310/en/. Published 2014. Accessed January 26, 2017.

49. Rudisill TM, Zhao S, Abate MA, Coben JH, Zhu M. Trends in drug use among drivers killed in U.S. traffic crashes, 1999-2010. *Accid Anal Prev*. 2014;70:178-187. doi:10.1016/j.aap.2014.04.003.

50. Canadian Centre on Substance Abuse. *Facts about Drug-Impaired Driving*.; 2016.

51. Verster JC, Roth T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). *Int J Gen Med*. 2011;4:359-371. doi:10.2147/IJGM.S19639.

52. Rapoport MJ, Lanctot KL, Streiner DL, et al. Benzodiazepine use and driving: a meta-analysis. *J Clin Psychiatry*. 2009;70(5):663-673. doi:10.4088/JCP.08m04325.

53. Roth T, Eklov SD, Drake CL, Verster JC. Meta-analysis of on-the-road experimental studies of hypnotics: effects of time after intake, dose, and half-life. *Traffic Inj Prev*. 2014;15(5):439-445. doi:10.1080/15389588.2013.830211.

54. Smink BE, Lusthof KJ, de Gier JJ, Uges DRA, Egberts ACG. The relation between the blood benzodiazepine concentration and performance in suspected impaired drivers. *J Forensic Leg Med*. 2008;15(8):483-488. doi:10.1016/j.jflm.2008.04.002.

55. Bramness JG, Skurtveit S, Mørland J. Clinical impairment of benzodiazepines - Relation between benzodiazepine concentrations and impairment in apprehended drivers. *Drug Alcohol Depend*. 2002;68(2):131-141. doi:10.1016/S0376-8716(02)00188-6.

56. Altamura AC, Moliterno D, Paletta S, Maffini M, Mauri MC, Bareggi S. Understanding the pharmacokinetics of anxiolytic drugs. *Expert Opin Drug Metab Toxicol*. 2013;9(4):423-440. doi:10.1517/17425255.2013.759209.

57. Leufkens TRM, Vermeeren A. Zopiclone's residual effects on actual driving performance in a standardized test: a pooled analysis of age and sex effects in 4 placebo-controlled studies. *Clin Ther*. 2014;36(1):141-150. doi:10.1016/j.clinthera.2013.11.005.

58. Verster JC, Spence DW, Shahid A, Pandi-Perumal SR, Roth T. Zopiclone as positive control in studies examining the residual effects of hypnotic drugs on driving ability. *Curr Drug Saf*. 2011;6(4):209-218.

59. Hindmarch I, Patat A, Stanley N, Paty I, Rigney U. Residual effects of zaleplon and zolpidem following middle of the night administration five hours to one hour before awakening. *Hum Psychopharmacol*. 2001;16(2):159-167. doi:10.1002/hup.282.

60. Verster JC, Volkerts ER, Schreuder AHCML, et al. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*. 2002;22(6):576-583.

61. Verster JC, van de Loo AJAE, Moline ML, Roth T. Middle-of-the-night administration of sleep medication: a critical review of the effects on next morning driving ability. *Curr Drug Saf*. 2014;9(3):205-211.

62. Vermeeren A, Vuurman EFPM, Leufkens TRM, et al. Residual effects of low-dose sublingual zolpidem on highway driving performance the morning after middle-of-the-night use. *Sleep*. 2014;37(3):489-496. doi:10.5665/sleep.3482.

63. Bocca M-L, Marie S, Lelong-Boulouard V, et al. Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects. *Psychopharmacology (Berl)*. 2011;214(3):699-706. doi:10.1007/s00213-010-2075-5.

64. Gunja N. In the Zzz Zone: The Effects of Z-Drugs on Human Performance and Driving. *J Med Toxicol*. 2013;9(2):163-171. doi:10.1007/s13181-013-0294-y.

65. ICADTS Working Group. *Categorization System for Medicinal Drugs Affecting Driving Performance*.; 2007.

66. ICADTS. ICADTS Drug List - July 2007. 2007;(July):1-15. http://www.icadts.nl/reports/medicinaldrugs2.pdf.

67. Gjerde H, Strand MC, Morland J. Driving Under the Influence of Non-Alcohol Drugs--An Update Part I: Epidemiological Studies. *Forensic Sci Rev*. 2015;27(2):89-113.

68. Dassanayake T, Michie P, Carter G, Jones A. Effects of Benzodiazepines, Antidepressants and opoids on Driving: A Systematic Review and Meta-Analysis of Epidemiological and Experimental Evidence. *Drug Saf*. 2011;34(2):125-156.

69. Elvik R. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accid Anal Prev*. 2013;60:254-267. doi:10.1016/j.aap.2012.06.017.

70. Booth JN 3rd, Behring M, Cantor RS, et al. Zolpidem use and motor vehicle collisions in older drivers. *Sleep Med*. 2016;20:98-102. doi:10.1016/j.sleep.2015.12.004.

71. Yang Y-H, Lai J-N, Lee C-H, Wang J-D, Chen P-C. Increased risk of hospitalization related to motor vehicle accidents among people taking zolpidem: a case-crossover study. *J Epidemiol*. 2011;21(1):37-43.

72. Hansen RN, Boudreau DM, Ebel BE, Grossman DC, Sullivan SD. Sedative Hypnotic Medication Use and the Risk of Motor Vehicle Crash. *Am J Public Health*. 2015;105(8):e64-9. doi:10.2105/AJPH.2015.302723.

73. Orriols L, Philip P, Moore N, et al. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. *Clin Pharmacol Ther*. 2011;89(4):595-601. doi:10.1038/clpt.2011.3.

74. Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Mørland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med*. 2008;9(8):818-822. doi:10.1016/j.sleep.2007.11.011.

75. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet*. 1998;352(9137):1331-1336.

76. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review. *Accid Anal Prev*. 2016;96:255-270. doi:10.1016/j.aap.2016.08.001.

77. Verster JC, Roth T. Gender differences in highway driving performance after administration of sleep medication: a review of the literature. *Traffic Inj Prev*. 2012;13(3):286-292. doi:10.1080/15389588.2011.652751.

78. Kriikku P, Hurme H, Wilhelm L, et al. Sedative-hypnotics are widely abused by drivers apprehended for driving under the influence of drugs. *Ther Drug Monit*. 2015;37(3):339-346. doi:10.1097/FTD.0000000000000138.

79. Leslie WD, Morin SN. Osteoporosis epidemiology 2013: implications for diagnosis, risk assessment, and treatment. *Curr Opin Rheumatol*. 2014;26(4):440-446. doi:10.1097/BOR.0000000000000064.

80. Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. *Nat Rev Endocrinol*. 2014;10(10):592-602. doi:10.1038/nrendo.2014.125.

81. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int*. 2009;20(10):1633-1650. doi:10.1007/s00198-009-0920-3.

82. Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci*. 2007;62(10):1172-1181.

83. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009;169(21):1952-1960. doi:10.1001/archinternmed.2009.357.

84. Park H, Satoh H, Miki A, Urushihara H, Sawada Y. Medications associated with falls in older

people: systematic review of publications from a recent 5-year period. *Eur J Clin Pharmacol*. 2015;71(12):1429-1440. doi:10.1007/s00228-015-1955-3.

85. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Saf*. 2007;30(2):171-184.

86. Cumming R, Le Couteur D. Benzodiazepines and Risk of Hip Fractures in Older People - A Review of the Evidence. *CNS Drugs*. 2003;17(11):825-837.

87. Aronson J. Hypnosedatives. In: *Meyler's Side Effects of Psychiatric Drugs*. Elsevier; 2009:375-450. https://www-clinicalkey-com.uml.idm.oclc.org/#!/browse/book/3-s2.0-C20090017863.

88. Mets MAJ, Volkerts ER, Olivier B, Verster JC. Effect of hypnotic drugs on body balance and standing steadiness. *Sleep Med Rev*. 2010;14(4):259-267. doi:10.1016/j.smrv.2009.10.008.

89. Allain H, Bentué-Ferrer D, Polard E, Akwa Y, Patat A. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. *Drugs Aging*. 2005;22(9):749-765. doi:10.2165/00002512-200522090-00004.

90. Panneman MJM, Goettsch WG, Kramarz P, Herings RMC. The costs of benzodiazepine-associated hospital-treated fall Injuries in the EU: a Pharmo study. *Drugs Aging*. 2003;20(11):833-839.

91. Khong TP, De Vries F, Goldenberg JSB, et al. Potential impact of benzodiazepine use on the rate of hip fractures in five large European countries and the United States. *Calcif Tissue Int*. 2012;91(1):24-31. doi:10.1007/s00223-012-9603-8.

92. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: A meta-analysis. *Osteoporos Int*. 2014;25(1):105-120. doi:10.1007/s00198-013-2446-y.

93. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA*. 1989;262(23):3303-3307.

94. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med*. 1995;332(12):767-773. doi:10.1056/NEJM199503233321202.

95. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics and sedatives and risk of fractures: Effects of half-life. *Calcif Tissue Int*. 2008;82(1):34-43. doi:10.1007/s00223-007-9095-0.

96. Sgadari A, Lapane KL, Mor V, Landi F, Bernabei R, Gambassi G. Oxidative and nonoxidative benzodiazepines and the risk of femur fracture. The Systematic Assessment of Geriatric Drug Use Via Epidemiology Study Group. *J Clin Psychopharmacol*. 2000;20(2):234-239.

97. Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med*. 2004;164(14):1567-1572. doi:10.1001/archinte.164.14.1567.

98. Chang C-M, Wu EC-H, Chang I-S, Lin K-M. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. *Am J Geriatr Psychiatry*. 2008;16(8):686-692. doi:10.1097/JGP.0b013e31817c6a99.

99. Zint K, Haefeli W, Glynn R, Al E. Impact of drug interactions, dosage, duration of therapy on the risk of hip fracture associated with benzodiazepine use in older adults. *Pharmacoepidemiol Drug Saf*. 2010;19(12):1248-1255. doi:10.1002/pds.2031.Impact.

100. Skinner BW, Johnston E V, Saum LM. Benzodiazepine Initiation and Dose Escalation: A Risk

Factor for Inpatient Falls. *Ann Pharmacother*. November 2016. doi:10.1177/1060028016682530.

101. Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. *J Am Geriatr Soc*. 2000;48(6):682-685.

102. Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F. Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. *Arch Intern Med*. 1995;155(16):1801-1807.

103. Neutel CI, Hirdes JP, Maxwell CJ, Patten SB. New evidence on benzodiazepine use and falls: The time factor. *Age Ageing*. 1996;25(4):273-278. doi:10.1093/ageing/25.4.273.

104. Bartlett G, Abrahamowicz M, Grad R, Sylvestre M-P, Tamblyn R. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. *BMC Fam Pract*. 2009;10:1. doi:10.1186/1471-2296-10-1.

105. Park SM, Ryu J, Lee DR, Shin D, Yun JM, Lee J. Zolpidem use and risk of fractures: a systematic review and meta-analysis. *Osteoporos Int*. 2016;27(10):2935-2944. doi:10.1007/s00198-016-3605-8.

106. Finkle WD, Der JS, Greenland S, et al. Risk of Fractures Requiring Hospitalization After an Initial Prescription for Zolpidem, Alprazolam, Lorazepam, or Diazepam in Older Adults. *J Am Geriatr Soc*. 2011;59(10):1883-1890. doi:10.1111/j.1532.

107. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. *J Am Geriatr Soc*. 2001;49(12):1685-1690. doi:10.1046/j.1532-5415.2001.49280.x.

108. Kang D-Y, Park S, Rhee C-W, et al. Zolpidem use and risk of fracture in elderly insomnia patients. *J Prev Med Public Health*. 2012;45(4):219-226. doi:10.3961/jpmph.2012.45.4.219.

109. Day C. Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes. In: Rockville (MD); 2013.

110. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug Alcohol Depend*. 2012;125(1-2):8-18. doi:10.1016/j.drugalcdep.2012.07.004.

111. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract*. 2014;27(1):5-16. doi:10.1177/0897190013515001.

112. Horsfall JT, Sprague JE. The Pharmacology and Toxicology of the "Holy Trinity." *Basic Clin Pharmacol Toxicol*. 2016:1-5. doi:10.1111/bcpt.12655.

113. Saunders KW, Von Korff M, Campbell CI, et al. Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: prevalence and risk factors. *J Pain*. 2012;13(3):266-275. doi:10.1016/j.jpain.2011.11.004.

114. Mellbye A, Svendsen K, Borchgrevink PC, Skurtveit S, Fredheim OMS. Concomitant medication among persistent opioid users with chronic non-malignant pain. *Acta Anaesthesiol Scand*. 2012;56(10):1267-1276. doi:10.1111/j.1399-6576.2012.02766.x.

115. Skurtveit S, Furu K, Bramness J, Selmer R, Tverdal A. Benzodiazepines predict use of opioids--a follow-up study of 17,074 men and women. *Pain Med*. 2010;11(6):805-814. doi:10.1111/j.1526-4637.2010.00870.x.

116. Bramness JG, Kornor H. Benzodiazepine prescription for patients in opioid maintenance

treatment in Norway. *Drug Alcohol Depend*. 2007;90(2-3):203-209. doi:10.1016/j.drugalcdep.2007.03.008.

117. National Institute on Drug Abuse (NIDA). Overdose Death Rates. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Published 2017. Accessed February 2, 2017.

118. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686-688. doi:10.2105/AJPH.2016.303061.

119. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med*. 2015;49(4):493-501. doi:10.1016/j.amepre.2015.03.040.

120. Coben JH, Davis SM, Furbee PM, Sikora RD, Tillotson RD, Bossarte RM. Hospitalizations for Poisoning by Prescription Opioids, Sedatives, and Tranquilizers. *Am J Prev Med*. 2010;38(5):517-524. doi:10.1016/j.amepre.2010.01.022.

121. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ*. 2015;350:h2698.

122. Turner BJ, Liang Y. Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders. *J Gen Intern Med*. 2015;30(8):1081-1096. doi:10.1007/s11606-015-3199-4.

123. Canadian Institute for Health Information. Prescription Drug Abuse. https://www.cihi.ca/en/types-of-care/pharmaceutical-care-and-utilization/prescription-drug-abuse. Published 2017. Accessed January 5, 2017.

124. Buckley NA, McManus PR. Changes in Fatalities Due to Overdose of Anxiolytic and Sedative Drugs in the UK (1983-1999). *Drug Saf*. 2004;27(2):135-141. doi:10.2165/00002018-200427020-00004.

125. Liaw G-W, Hung D-Z, Chen W-K, Lin C-L, Lin I-C, Kao C-H. Relationship Between Acute Benzodiazepine Poisoning and Acute Pancreatitis Risk. *Medicine (Baltimore)*. 2015;94(52):e2376. doi:10.1097/MD.0000000000002376.

126. Lai SW, Lai HC, Lin CL, Liao KF. Zopiclone use associated with increased risk of acute pancreatitis: A case-control study in Taiwan. *Int J Clin Pract*. 2015;69(11):1275-1280. doi:10.1111/ijcp.12689.

127. Lai SW, Lin CL, Liao KF. Increased relative risk of acute pancreatitis in zolpidem users. *Psychopharmacology (Berl)*. 2015;232(12):2043-2048. doi:10.1007/s00213-014-3833-6.

128. Abed A, Minaiyan M, Safaei A, Taheri D. Effect of diazepam on severity of acute pancreatitis: possible involvement of peripheral benzodiazepine receptors. *ISRN Gastroenterol*. 2013;2013:484128. doi:10.1155/2013/484128.

129. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: a review. *Ochsner J*. 2015;15(1):45-51. http://www.ncbi.nlm.nih.gov/pubmed/25829880%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4365846.

130. Trivedi C, Pitchumoni C. Drug-induced pancreatitis: an Update. *J Clin Gastroenterol*. 2005;39(8):709-716.

131. Sanders RD, Godlee A, Fujimori T, et al. Benzodiazepine augmented gamma-amino-butyric acid signaling increases mortality from pneumonia in mice. *Crit Care Med*. 2013;41(7):1627-1636. doi:10.1097/CCM.0b013e31827c0c8d.

132. Sanders RD, Grover V, Goulding J, et al. Immune cell expression of GABAA receptors and the effects of diazepam on influenza infection. *J Neuroimmunol*. 2015;282:97-103. doi:10.1016/j.jneuroim.2015.04.001.

133. Galdiero F, Bentivoglio C, Nuzzo I, et al. Effects of benzodiazepines on immunodeficiency and resistance in mice. *Life Sci*. 1995;57(26):2413-2423.

134. Jirillo E, Maffione AB, Greco B, Cannuscio B, Calvello R, Covelli V. Triazolobenzodiazepines exert immunopotentiating activities on normal human peripheral blood lymphocytes. *Immunopharmacol Immunotoxicol*. 1993;15(2-3):307-319. doi:10.3109/08923979309026001.

135. Covelli V, Munno I, Decandia P, et al. Effects of benzodiazepines on the immune system. *Acta Neurol (Napoli)*. 1991;13(5):418-423.

136. Covelli V, Maffione AB, Nacci C, Tato E, Jirillo E. Stress, neuropsychiatric disorders and immunological effects exerted by benzodiazepines. *Immunopharmacol Immunotoxicol*. 1998;20(2):199-209. doi:10.3109/08923979809038539.

137. Nakafero G, Sanders RD, Nguyen-Van-Tam JS, Myles PR. The association between benzodiazepines and influenza-like illness-related pneumonia and mortality: a survival analysis using UK Primary Care data. *Pharmacoepidemiol Drug Saf*. 2016;25:1263-1273. doi:10.1002/pds.

138. Obiora E, Hubbard R, Sanders R. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: A nested case-control and survival analysis in a population-based cohort. *Thorax*. 2013;68:163-170. doi:10.1016/j.jemermed.2013.03.009.

139. Hak E, Bont J, Hoes AW, Verheij TJM. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Fam Pract*. 2005;22(4):375-380. doi:10.1093/fampra/cmi020.

140. Vergis EN, Brennen C, Wagener M, Muder R. Pneumonia in Long-term Care: A Prospective Case-Control Study of Risk Factors and Impact on Survival. *Arch Intern Med*. 2001;161:2378-2381.

141. Dublin S, Walker RL, Jackson ML, et al. Use of Opioids or Benzodiazepines and Risk of Pneumonia in Older Adults: A Population-Based Case-Control Study. *J Am Geriatr Soc*. 2011;59(10):1899-1907. doi:10.1111/j.1532-5415.2011.03586.x.Use.

142. van de Nadort C, Smeets HM, Bont J, Zuithoff NP a, Hak E, Verheij TJM. Prognosis of primary care patients aged 80 years and older with lower respiratory tract infection. *Br J Gen Pract*. 2009;59(561):e110-5. doi:10.3399/bjgp09X420239.

143. Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: Eszopiclone, ramelteon, zaleplon, and zolpidem. *J Clin Sleep Med*. 2009;5(4):377-383.

144. Roth T. Hypnotic use for insomnia management in chronic obstructive pulmonary disease. *Sleep Med*. 2009;10(1):19-25. doi:10.1016/j.sleep.2008.06.005.

145. Stege G, Vos PJE, van den Elshout FJJ, Richard Dekhuijzen PN, van de Ven MJT, Heijdra YF. Sleep, hypnotics and chronic obstructive pulmonary disease. *Respir Med*. 2008;102(6):801-814. doi:10.1016/j.rmed.2007.12.026.

146. Zhang XJ, Li QY, Wang Y, Xu HJ, Lin YN. The effect of non-benzodiazepine hypnotics on sleep

quality and severity in patients with OSA: a meta-analysis. *Sleep Breath*. 2014:1-9. doi:10.1007/s11325-014-0943-7.

147. Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane database Syst Rev*. 2015;(7):CD011090. doi:10.1002/14651858.CD011090.pub2.

148. Vozoris NT, Wang X, Fischer HD, et al. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J*. 2014;44:332-340. doi:10.1183/13993003.01967-2015.

149. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ*. 2014;348(jan30_2):g445. doi:10.1136/bmj.g445.

150. Chen S-J, Yeh C-M, Chao T-F, et al. The use of benzodiazepine receptor agonists and risk of respiratory failure in patients with chronic obstructive pulmonary disease: A nationwide population-based case-control study. *Sleep*. 2015;38(7):1045-1050. doi:10.5665/sleep.4808.

151. Chung W-S, Lai C-Y, Lin C-L, Kao C-H. Adverse Respiratory Events Associated With Hypnotics Use in Patients of Chronic Obstructive Pulmonary Disease. *Medicine (Baltimore)*. 2015;94(27):e1110. doi:10.1097/MD.0000000000001110.

152. Nakafero G, Sanders RD, Nguyen-Van-Tam JS, Myles PR. Association between benzodiazepine use and exacerbations and mortality in patients with asthma: a matched case-control and survival analysis using the United Kingdom Clinical Practice Research Datalink. *Pharmacoepidemiol Drug Saf*. 2015;24(8):793-802. doi:10.1002/pds.3799.

153. Rodriguez-Roisin R, Garcia-Aymerich J. Should we exercise caution with benzodiazepine use in patients with COPD? *Eur Respir J*. 2014;44(2):284-286. doi:10.1183/09031936.00071014.

154. Battaglia S, Bezzi M, Sferrazza Papa G.F. Are Benzodiazepines and Opioids really safe in patients with severe COPD? *Minerva Med*. 2014;105(6):1-7.

155. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane database Syst Rev*. 2016;10:CD007354. doi:10.1002/14651858.CD007354.pub3.

156. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *Biomed Res Int*. 2014;2014(Figure 1). doi:10.1155/2014/908915.

157. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive Effects of Long-Term Benzodiazepine Use: A Meta-Analysis. *CNS Drugs*. 2004;18(1):37-48. doi:10.2165/00023210-200418010-00004.

158. Pariente A, De Gage SB, Moore N, Bégaud B. The Benzodiazepine-Dementia Disorders Link: Current State of Knowledge. *CNS Drugs*. 2016;30(1):1-7. doi:10.1007/s40263-015-0305-4.

159. Billioti de Gage S, Pariente A, Bégaud B. Is there really a link between benzodiazepine use and the risk of dementia? *Expert Opin Drug Saf*. 2015;14(05):0. doi:10.1517/14740338.2015.1014796.

160. Islam MM, Iqbal U, Walther B, et al. Benzodiazepine Use and Risk of Dementia in the Elderly Population: A Systematic Review and Meta-Analysis. *Neuroepidemiology*. 2016:181-191. doi:10.1159/000454881.

161. Zhong G, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: A

meta-analysis. *PLoS One*. 2015;10(5):1-16. doi:10.1371/journal.pone.0127836.

162. Takada M, Fujimoto M, Hosomi K. Association between Benzodiazepine Use and Dementia: Data Mining of Different Medical Databases. *Int J Med Sci*. 2016;13(11):825-834. doi:10.7150/ijms.16185.

163. Chan T-T, Leung WC-Y, Li V, et al. Association between high cumulative dose of benzodiazepine in Chinese patients and risk of dementia: a preliminary retrospective case-control study. *Psychogeriatrics*. February 2017. doi:10.1111/psyg.12239.

164. Bietry FA, Pfeil AM, Reich O, Schwenkglenks M, Meier CR. Benzodiazepine Use and Risk of Developing Alzheimer's Disease: A Case-Control Study Based on Swiss Claims Data. *CNS Drugs*. January 2017. doi:10.1007/s40263-016-0404-x.

165. Gray SL, Dublin S, Yu O, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ*. 2016;352(feb02_4):i90. doi:10.1136/bmj.i90.

166. Chen PL, Lee WJ, Sun WZ, Oyang YJ, Fuh JL. Risk of Dementia in Patients with Insomnia and Long-term Use of Hypnotics: A Population-based Retrospective Cohort Study. *PLoS One*. 2012;7(11). doi:10.1371/journal.pone.0049113.

167. Shih H-I, Lin C-C, Tu Y-F, et al. An increased risk of reversible dementia may occur after zolpidem derivative use in the elderly population: a population-based case-control study. *Medicine (Baltimore)*. 2015;94(17):e809. doi:10.1097/MD.0000000000000809.

168. Bocti C, Roy-Desruisseaux J, Hudon C, Roberge P. Benzodiazepine and dementia: A time for reflection. *Maturitas*. 2013;75(2):105-106. doi:10.1016/j.maturitas.2013.03.001.

169. Barbui C, Gastaldon C, Cipriani A, Barbui C. Benzodiazepines and risk of dementia: true association or reverse causation? *Epidemiol Psychiatr Sci*. 2013;22(04):307-308. doi:10.1017/S2045796013000358.

170. Defrancesco M, Marksteiner J, Wolfgang Fleischhacker W, Blasko I. Use of benzodiazepines in Alzheimer's disease: A systematic review of literature. *Int J Neuropsychopharmacol*. 2015;18(10):1-11. doi:10.1093/ijnp/pyv055.

171. Tampi RR, Tampi DJ. Efficacy and Tolerability of Benzodiazepines for the Treatment of Behavioral and Psychological Symptoms of Dementia: A Systematic Review of Randomized Controlled Trials. *Am J Alzheimers Dis Other Demen*. 2014;29(7):565-574. doi:10.1177/1533317514524813.

172. Brambilla G, Carrozzino R, Martelli A. Genotoxicity and carcinogenicity studies of benzodiazepines. *Pharmacol Res*. 2007;56(6):443-458. doi:10.1016/j.phrs.2007.08.006.

173. Kao CH, Sun LM, Su KP, et al. Benzodiazepine use possibly increases cancer risk: A population-based retrospective cohort study in Taiwan. *J Clin Psychiatry*. 2012;73(4):555-560. doi:10.4088/JCP.11m07333.

174. Iqbal U, Nguyen P-A, Syed-Abdul S, et al. Is long-term use of benzodiazepine a risk for cancer? *Medicine (Baltimore)*. 2015;94(6):e483. doi:10.1097/MD.0000000000000483.

175. Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. Relationship of zolpidem and cancer risk: A Taiwanese population-based cohort study. *Mayo Clin Proc*. 2012;87(5):430-436. doi:10.1016/j.mayocp.2012.02.012.

176. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study - with comments. *BMJ Open*. 2012;2(1):e000850. doi:10.1136/bmjopen-2012-000850.

177. Kim H-B, Myung S-K, Park YC, Park B. Use of benzodiazepine and risk of cancer: A meta-analysis of observational studies. *Int J Cancer*. 2016;00(January):1-13. doi:10.1002/ijc.30443.

178. Harnod T, Lin CL, Sung FC, Kao CH. An association between benzodiazepine use and occurrence of benign brain tumors. *J Neurol Sci*. 2014;336(1-2):8-12. doi:10.1016/j.jns.2013.11.009.

179. Bradford-Hill A. The Enviroment and Disease: Association or Causation? *Proc R Soc Med*. 1965;58:295-300. doi:DOI: 10.1016/j.tourman.2009.12.005.

180. Shakir SAW, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. *Drug Saf*. 2002;25(6):467-471. doi:10.2165/00002018-200225060-00012.

181. WHO Collaborating Centre for Drug Statistics Methodology & Norweigan Institute of Public Health. *Guidelines for ATC Classification and DDD Assignment - 2017*.; 2017.

182. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2018. https://www.whocc.no/atc_ddd_index/. Published 2017. Accessed February 23, 2018.

183. Chauvin C, Madec F, Guillemot D, Sanders P. The crucial question of standardisation when measuring drug consumption. *Vet Res*. 2001;32(6):533-543. doi:10.1051/vetres:2001145.

184. Merlo J, Wessling A, Melander A. Comparison of dose standard units for drug utilisation studies. *Eur J Clin Pharmacol*. 1996;50(1-2):27-30.

185. Bandelow B, Zohar J, Hollander E, Kasper S, Moller H-J. World Federation of Societies of Biological Psychiatry (WfSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Psttraumatic Stress Disorders. *World J Biol Psychiatry*. 2008;9(4):248-312. doi:10.1080/15622970802465807.

186. Stein MB, Goin MK, H.Pollack M, Roy-Byrne P, Sareen J, Campbell-Sills L. Practice guideline for the Treatment of Patients With Panic Disorder (2nd ed.). *Am Psychiatr Assoc*. 2010;2:1-90. doi:10.1176/appi.books.9780890423905.154688.

187. Grimmsmann T, Himmel W. Discrepancies between prescribed and defined daily doses: A matter of patients or drug classes? *Eur J Clin Pharmacol*. 2011;67(8):847-854. doi:10.1007/s00228-011-1014-7.

188. Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry*. 2005;18(3):249-255. doi:10.1097/01.yco.0000165594.60434.84.

189. Ashton H. benzo.org.uk : Benzodiazepine Equivalence Table. http://www.benzo.org.uk/bzequiv.htm. Published 2007. Accessed February 3, 2017.

190. Shader RI, Greenblatt DJ. Can you provide a table of equivalences for benzodiazepines and other marketed benzodiazepine receptor agonists? *J Clin Psychopharmacol*. 1997;17(4):331.

191. Brett J, Murnion B. Management of benzodiazepine misuse and dependence. *Aust Prescr*. 2015;38(5):152-155. doi:10.18773/austprescr.2015.055.

192. Strand MC, Mørland J, Slørdal L, et al. Conversion factors for assessment of driving impairment after exposure to multiple benzodiazepines/z-hypnotics or opioids. *Forensic Sci Int*. 2017;281(February 2016):29-36. doi:10.1016/j.forsciint.2017.10.022.

193. Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: The use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliat Med*. 2011;25(7):725-732. doi:10.1177/0269216311398300.

194. Busse J, Guyatt G, Carrasco A, Akl E, Agoritsas T. *The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain*. Hamilton, ON,; 2017. doi:10.13140/RG.2.2.34863.33448.

195. Nosè M, Tansella M, Thornicroft G, et al. Is the Defined Daily Dose system a reliable tool for standardizing antipsychotic dosages? *Int Clin Psychopharmacol*. 2008;23(5):287-290. doi:10.1097/YIC.0b013e328303ac75.

196. Sweileh WM, Odeh JB, Shraim NY, Zyoud SH, Sawalha AF, Al-Jabi SW. Evaluation of Defined Daily Dose, percentage of British National Formulary maximum and chlorpromazine equivalents in antipsychotic drug utilization. *Saudi Pharm J*. 2014;22(2):127-132. doi:10.1016/j.jsps.2013.03.003.

197. Berman E, Eyal S, Marom E. Trends in utilization of benzodiazepine and Z-drugs in Israel. *Pharmacoepidemiol Drug Saf*. 2017;(September):1-6. doi:10.1002/pds.4338.

198. De Visser SJ, Van Der Post JP, De Waal PP, Cornet F, Cohen AF, Van Gerven JMA. Biomarkers for the effects of benzodiazepines in healthy volunteers. *Br J Clin Pharmacol*. 2003;55(1):39-50. doi:10.1046/j.1365-2125.2002.t01-10-01714.x.

Chapter 3 –Utilisation of Benzodiazepines and Z-Drugs in Manitoban Adults (2001-2016)

***Disclaimer*:** This section is an adapted version of the accepted manuscript:

Brandt J, Alessi-Severini S, Singer A, Leong C, Novel Measures of Benzodiazepine and Z-Drug Utilization Trends in a Canadian Provincial Adult Population (2001-2016). *J Popul Ther Clin Pharmacol.* 26(1): 1-17. 2019. DOI: 10.22374/1710-6222.26.1.2

Student contribution: *conceptualised topic, conducted data analysis and interpretation, wrote first draft and final version. Student was corresponding author to editor and peer-reviewers.*

3.1) Introduction

Benzodiazepines (BZD) and Z-Drugs (i.e zopiclone, eszopiclone, zolpidem, zaleplon) persist as commonly used central nervous system depressant medications for the treatment of anxiety disorders and insomnia, respectively.[1] Their popularity among patients and clinicians is primarily owed to their effectiveness and rapid onset in producing anxiolysis compared to other agents such as antidepressants which typically require weeks to months before perceived benefit. Unfortunately, this rapid effectiveness is often limited by tolerance and dependence with repeated dosing, risk of psychomotor impaired accidents (motor vehicle accidents, falls) and potential misuse (use other than as prescribed or diversion).[2–4] For these reasons, clinical practice guidelines universally recommend short-term use (4-12 weeks maximum) or as needed use as an adjunct to other agents such as antidepressants as a means to optimally balance the benefit-risk ratio.[5–10] Furthermore, use of psychosocial interventions or alternative pharmacotherapy is widely advocated as first-line treatment options over BZD and Z-Drug use, especially for older adults.[11]

Beyond this well-established body of evidence, emerging literature has raised additional concerns that BZD and Z-Drugs may be causal contributors to increased rates of infection,

dementia, pancreatitis and respiratory disease exacerbations.[12–16] Currently, the total body of evidence is either insufficient and/or too conflicting to substantiate any of these associations.[17] Nonetheless, this research adds to the existent and long-standing controversies and concerns regarding usage of this medication class. For these reasons, observational studies evaluating utilisation patterns over time remain highly relevant for informing health policy or professional practice. Furthermore, as morbidity and mortality risk is substantially increased with combination BZD-opioid use, benzodiazepine utilisation studies can provide additional information for public health use in nations experiencing opioid epidemics.[18,19]

Observational studies in the past decade on BZD, both in North America and abroad, have found that concerning or questionable patterns of use persist in different patient populations despite the long-standing conservative approach advocated by practice guidelines.[20–25] This drug utilisation study (part of a larger project) sought to update past utilisation work on benzodiazepines and Z-Drugs in the province of Manitoba, Canada as well as to examine utilisation patterns by different indicators that went unexplored by the previous study.[26] As Manitoba is the province located most geographically central within Canada and has a stable, yet diverse population, the results of this study may be partially generalizable to other provinces.

The primary study objectives were to determine and evaluate trends, measured annually, from 2001 to 2016 for the following outcome measures (defined in methods):

i) *Consumption* by drug class, individual agent and age-sex category

ii*) Pharmacologic exposure* by drug class and age-sex category

iii) *Dose intensity* by drug class, individual agent and age-sex category

iv) *Prevalence* of 'any' use by drug class and age-sex category

3.2) Methods

3.2.1) *Study Design, Data Source and Data Validity*

This drug utilisation study used routinely collected administrative prescription drug dispensation data, entered by community pharmacy personnel into the Drug Program Information Network (DPIN) from April 1st 2001 to March 31st 2016. DPIN is maintained and operated by the Provincial Drug Programs department of Manitoba Health. Patient level data elements are de-identified by a confidential algorithmic process which scrambles patients' Personal Health Information Number (PHIN) prior to transmission and further data cleaning by the Manitoba Centre for Health Policy (MCHP) at the University of Manitoba.[27] The DPIN database has been previously validated.[28]

The Manitoba Population Health Insurance Registry was also used for this study. This registry was used to determine the number of all adult individuals registered by Manitoba Health in the province for each fiscal year as well as to ascertain their date of birth and biological sex. The registry does not comprehensively account for the indigenous population in remote areas, federal employees or very new residents. However, it has been shown repeatedly to closely approximate alternative population data sources such as the Canadian government census.[29]

3.2.2) *Data Description, Exclusion and Analytic Preparation*

All outpatient prescription claims for adults (≥18 years) from April 1st 2001 to March 31st 2016 for benzodiazepines and Z-Drugs were extracted for the study. DPIN prescription drug claims (i.e individual line-level observations) include information on de-identified PHIN, date of drug dispensed, drug product, strength, dosage form, metric quantity dispensed and day supply. The date variable for each dispensation was categorised by fiscal year (April 1 – March 31st) for the purposes of aggregate annual calculations. The DPIN and registry datasets were linked by

scrambled PHIN and fiscal year. New variables were generated on each line-level observation for total dispensed milligrams (equation 1), daily dose (equation 2) and Diazepam Milligram Equivalent (DME) daily dose (equation 3).

$$(1)\ \ Quantity\ x\ Dosage\ Strength = Total\ Prescription\ Milligrams$$

$$(2)\ \ \frac{Total\ Prescription\ Milligrams}{Day\ Supply} = Daily\ Dose$$

$$(3)\ Daily\ Dose\ x\ Conversion\ Factor = DME\ Daily\ Dose$$

Observations were excluded if any of the data fields mentioned above were missing. Exclusions also occurred if either the days supply or quantity dispensed was '0'. This was because it was questionable that a true dispensation took place and because it would result in errors in the calculation of other generated variables. Furthermore, observations were excluded where the quantity dispensed exceeded 1000 oral units (i.e tablets) with a corresponding day supply of 30 days or less. This was because these claims were not only incredulous but more likely also attributed to pharmacy data entry error. Removal of observations using these criteria would be expected to make the results more conservative in their estimates and so were deemed to be acceptable to exclude these claims.

Health registry data provided dates of birth and biological sex for the majority of the Manitoba adult population (>98%). Using the registry, the total adult population as well as the populations for male and females in the distinct age ranges 18-65 and 65+ were calculated for each fiscal year to serve as the denominator for outcome measures.

3.2.3) *Outcome Measures*

Consumption was calculated for each drug on the basis of their assigned Anatomical Therapeutic Chemical (ATC) classification codes and Defined Daily Dose (DDD) values as per the World Health Organizations Collaborating Centre for Drug Statistics Methodology (Table

3.1).[30] Consumption was measured and reported as DDD/1000 persons/day. The DME conversions were derived from work conducted by Dr. Ashton (table 3.1).[31,32] These equivalency sources appeared to us as the most prominent in the literature to date (though this is debatable).[23,33] *Dose intensity*, measured as mean daily dose per year, was calculated in original milligrams and then converted to DME for each drug and by class (DME/day on a weighted basis by proportional use of each drug per year). Estimated annual *pharmacologic exposure*, measured by DME-DDD/1000 inhabitants per day, while similar to our calculation of consumption, accounts for relative differences in potency of agents to aid in interpretation and standardised comparison of utilisation to other nations or geographic regions.[33] This measure is more interpretable because it represents the approximate number of daily doses equal to 10 mg of diazepam rather than the distinct DDD values of all agents pooled together into a class estimate.[33] Lastly, *prevalence* was measured as the percent proportion of the total registry population in a given year who received at least one dispensation of a benzodiazepine or Z-Drug, regardless of dose or duration.

Table 3.1 – ATC, DDD and DME conversion ratios for Benzodiazepines and Z-Drugs used in Manitoba, Canada (2001-2016)[32]

Drug	ATC code	DDD	Equivalence to 10 mg Diazepam
Alprazolam	N05BA12	1 mg	0.5 mg
Bromazepam	N05BA08	10 mg	5 mg
Chlordiazepoxide	N05BA02	30 mg	25 mg
Clobazam	N05BA09	20 mg	20 mg
Clonazepam	N03AE1	8 mg	0.5 mg
Clorazepate	N05BA05	20 mg	15 mg
Diazepam	N05BA01	10 mg	10 mg
Flurazepam	N05CD01	30 mg	30 mg
Lorazepam	N05BA06	2.5 mg	1 mg
Oxazepam	N05BA04	50 mg	20 mg
Nitrazepam	N05CD02	5 mg	10 mg
Temazepam	N05CD07	20 mg	20 mg
Triazolam	N05CD05	0.25 mg	0.5 mg
Zaleplon	N05CF03	10 mg	20 mg
Zolpidem	N05CF02	10 mg	20 mg
Zopiclone	N04CF01	7.5 mg	15 mg

3.2.4) *Statistical Techniques*

Trends for consumption, pharmacologic exposure and prevalence (all being dependent on population count data) were statistically evaluated using Poisson regression in a generalised linear model. Dose intensity (being independent of population count data) was evaluated using bi-variate linear regression. Sub-analyses were conducted by age-sex stratification (18-64, 65+). Statistical rates of change were determined and reported at 95% confidence intervals. Three sensitivity analyses were undertaken on dose intensity and pharmacologic exposure by applying different

DME conversion values from alternative sources,[34,35] or by modification of the original source given the values of the 'outlier' BZD; clonazepam.[32] All programming, data manipulation and analysis was conducted using Base SAS v9.4©.

3.3) Results

12,407,898 dispensations (73.8% BZD, 26.2% Z-Drug) were available for 394,151 patients from April 1st 2001 to March 31st 2016. No claims were excluded on the basis of missing data fields. Only 1,568 claims (<0.01%) were excluded for being spurious (i.e '0' day/quantity supply or incredibly high dispensed quantity to day-supply ratio) thus bringing the final analyzable dataset to 12,406,330 dispensations for 394,126 patients over the 15-year period. Annualized aggregated data in tabulated form, from which the following results are derived, is available in Appendix 2

3.3.1) Utilisation by Drug Class

Table 3.2 displays the statistical results on the primary outcome measures for the overall study population unstratified by age or sex grouping and according to drug class. Figures 3.1 to 3.4 visually depict the trends for these measures.

Table 3.2 – Absolute and Relative Changes in Utilisation Measures for BZD & Z-Drugs in Manitoban Adults (2001-2016)

Parameter	Z-Drug	BZD	Combined (BZD + Z-Drug)
Consumption (DDD/1000 Persons/Day)	↑ 8.2 (2001) to 28.6 (2016)	NS; 31.2 (2001) to 30.3 (2016)	↑ 39.4 (2001) to 58.9 (2016)
Pharmacologic Exposure (DME-DDD/1000 Persons/Day)	↑ 4.1 (2001) to 14.3 (2016)	NS; 69.8 (2001) to 82.2 (2016)	NS; 73.9 (2001) to 96.5 (2016)
Dose Intensity (DME/Day)	↑ 5.0 (2001) to 5.43 (2016)	↑ 17.1 (2001) to 20.1 (2016)	NS; 15.1 (2001) to 14.4 (2016)
Prevalence (% Proportion of Manitoban Adults)	↑ 2.0% in 2001 to 4.8% in 2016.	↓ 9.3% in 2001 to 8.1% in 2016.	NS; 9.2% (2001) to 11.7% (2016)

NS - Not statistically significant

All measures of utilisation increased for Z-Drugs (~99% prescriptions were for zopiclone). In contrast, only dose intensity increased for BZD and prevalence dropped. However, despite these differences, when BZD and Z-Drugs were pooled together only the consumption trend remained significant. This is because the proportional differences in use and DME potency between Z-Drugs and BZD resulted in the negation of the other utilisation measures. For example, while the dose intensity increased for both BZD and Z-Drugs separately, the increasing prevalence of Z-Drug use, decreasing prevalence of BZD use and lower DME based dose for Z-Drugs cancelled out any significant trend for combined dose intensity. In particular, the decline in consumption and pharmacologic exposure that occurred for BZD from 2011 onward, is at least partially explained by a previous audit-feedback intervention study aimed to reduce inappropriate BZD prescribing around this time period.[36]

Figure 3.1 – Consumption Trends for Benzodiazepines and Z-Drugs in Manitoban Adults

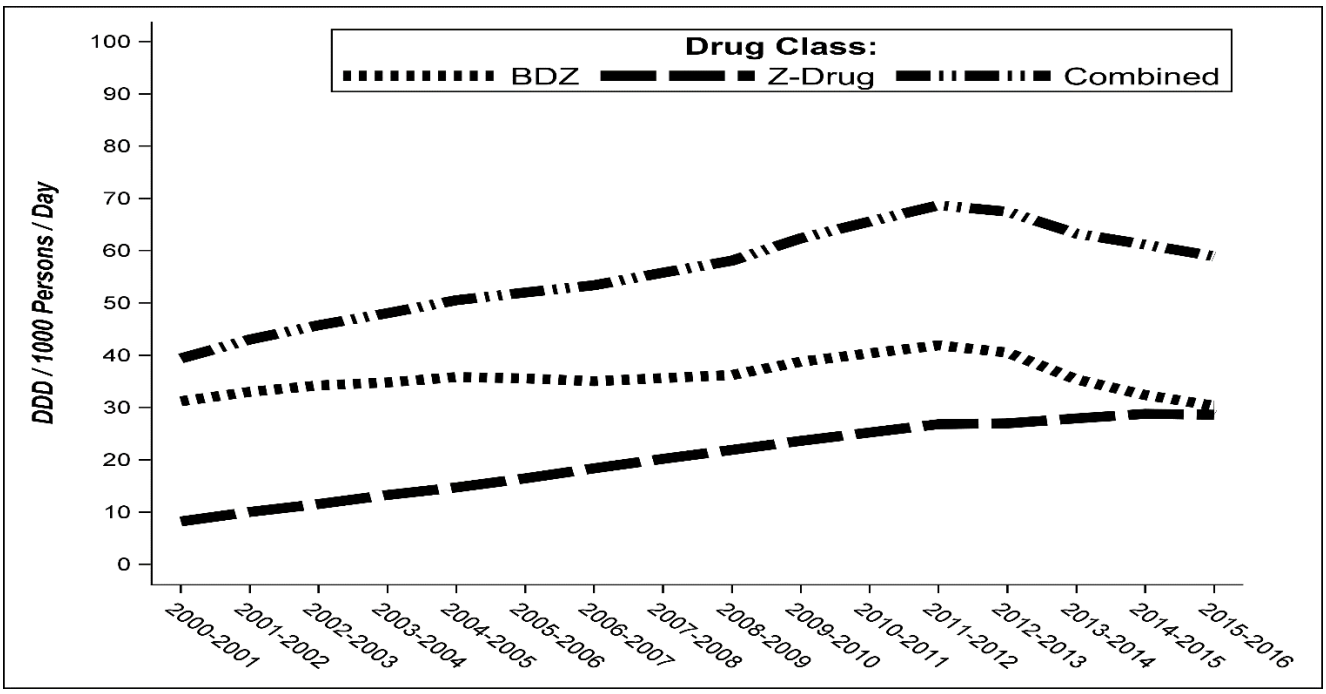


Figure 3.2 – Pharmacologic Exposure Trends for Benzodiazepines and Z-Drugs in Manitoban Adults

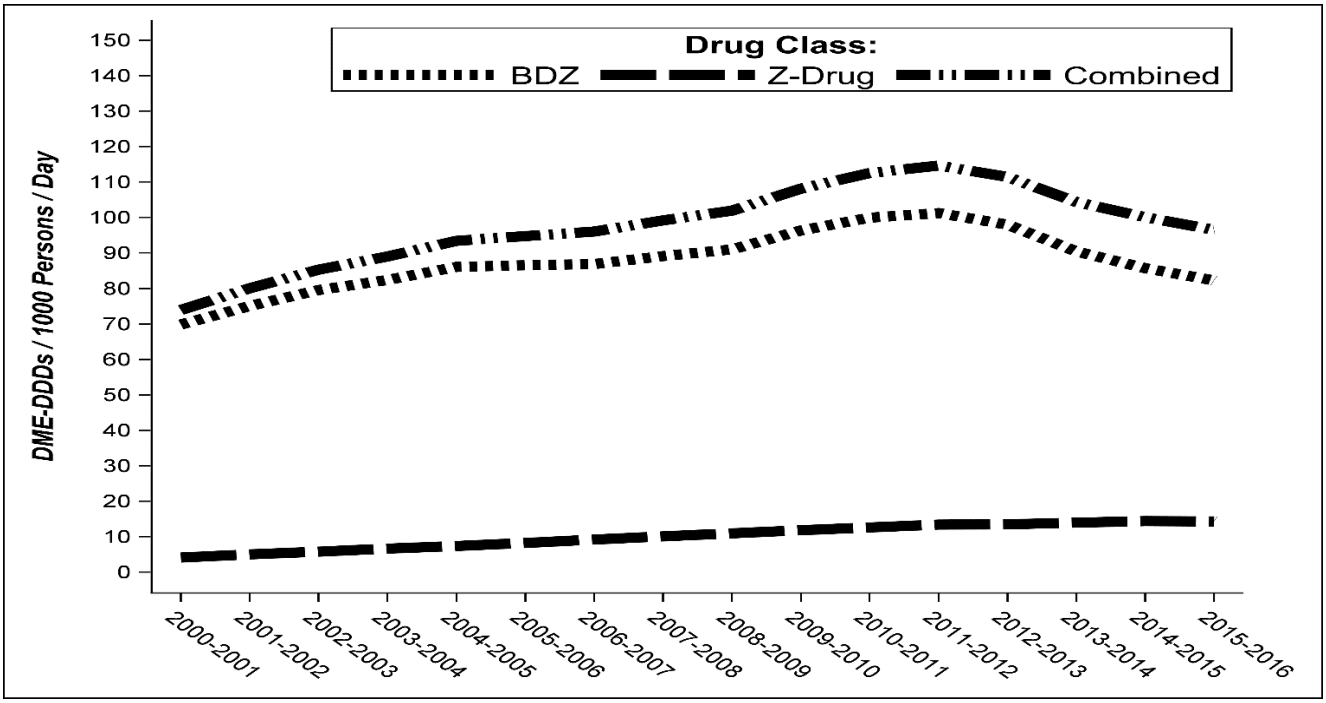


Figure 3.3 – Dose Intensity Trends for Benzodiazepines and Z-Drugs in Manitoban Adults

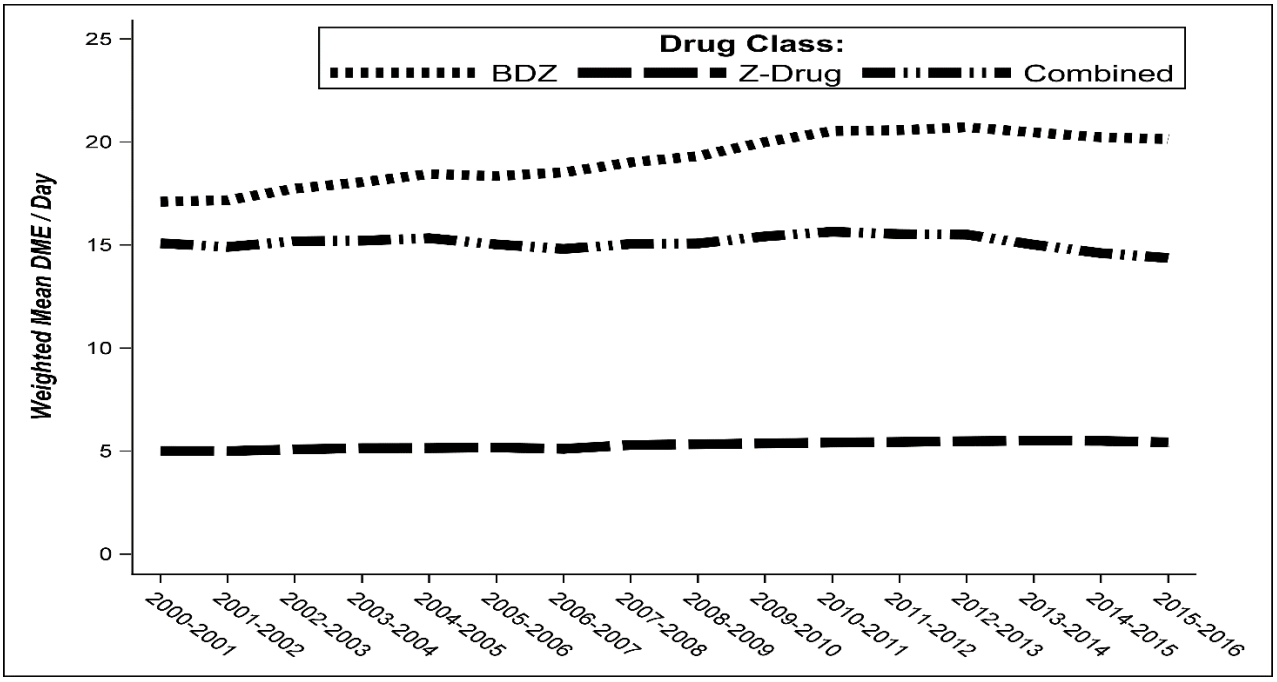
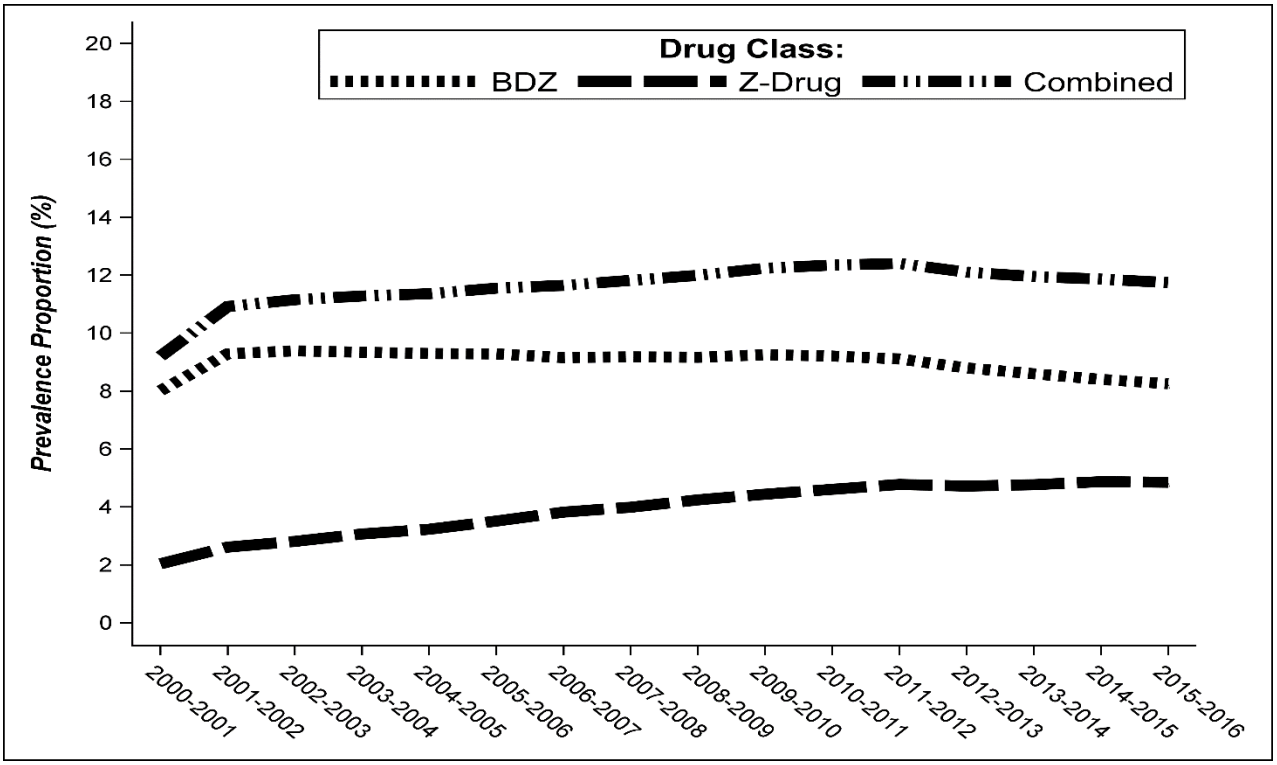


Figure 3.4 – Prevalence Proportion Trends for Benzodiazepines and Z-Drugs in Manitoban Adults



3.3.2) Utilisation by Age-Sex Category

Regression model trend results for the age-sex categories on the main outcome measures are presented in Table 3.3.

Table 3.3 - Absolute and Relative Changes in Utilisation Measures for Benzodiazepines and Z-Drugs (combined) by Age-Sex category

Parameter	Male, 18-64	Female, 18-64	Male, 65+	Female, 65+
Consumption (DDD/1000 Persons/Day)	↑ 22.8 (2001) to 39.0 (2016)	↑ 36.0 (2001) to 56.4 (2016)	↑ 63.6 (2001) to 84.7 (2016)	↑ 98.5 (2001) to 123.9 (2016)
Pharmacologic Exposure (DME-DDD/1000 Persons/Day)	↑ 38.5 (2001) to 64.0 (2016)	↑ 59.9 (2001) to 93.4 (2016)	↑ 79.0 (2001) to 109.8 (2016)	↑ 124.8 (2001) to 163.2 (2016)
Dose Intensity (DME/Day)	NS; 16.1 (2001) to 16.3 (2016)	↑ 13.9 (2001) to 14.8 (2016)	↑ 9.7 (2001) to 11.2 (2016)	↑ 8.62 (2001) to 10.0 (2016)
Prevalence (% Proportion of Manitoban Adults)	↑ 5.0% (2001) to 7.4% (2016)	↑ 9.4% (2001) to 12.3% (2016)	NS; 13.0% (2001) to 15.3% (2016)	NS; 22.4% (2001) to 24.5% (2016)

NS – Not statistically significant

Figures 3.5 to 3.8, on the following pages, depict the trends over time for these same outcome measures, stratified by age and sex category.

Notably, consumption and pharmacologic exposure for BZD+Z-Drugs combined increased over the study period for all age groups. Dose intensity, measured by DME, increased more for the 65+ population relative to younger adults but remained lower overall, as would be expected based on known physiologic and pharmacokinetic changes that occur with aging, necessitating lower average doses. The reverse pattern was observed for prevalence, wherein the rate of change showed a statistically significant increase in adults under 65 despite that prevalence remained consistently higher each year for older adults, particularly older females.

Figure 3.5 - Consumption Trends for Benzodiazepines and Z-Drugs by Age-Sex Category

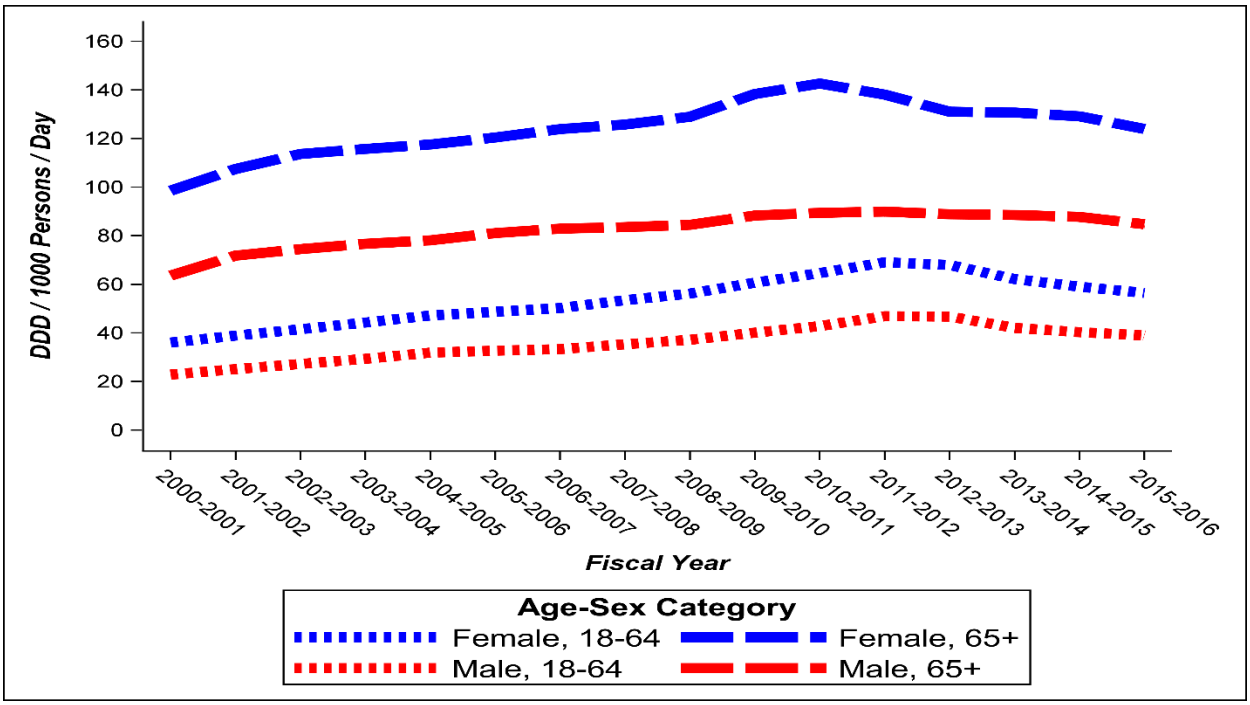


Figure 3.6 – Pharmacologic Exposure Trends for Benzodiazepines and Z-Drugs by Age-Sex Category

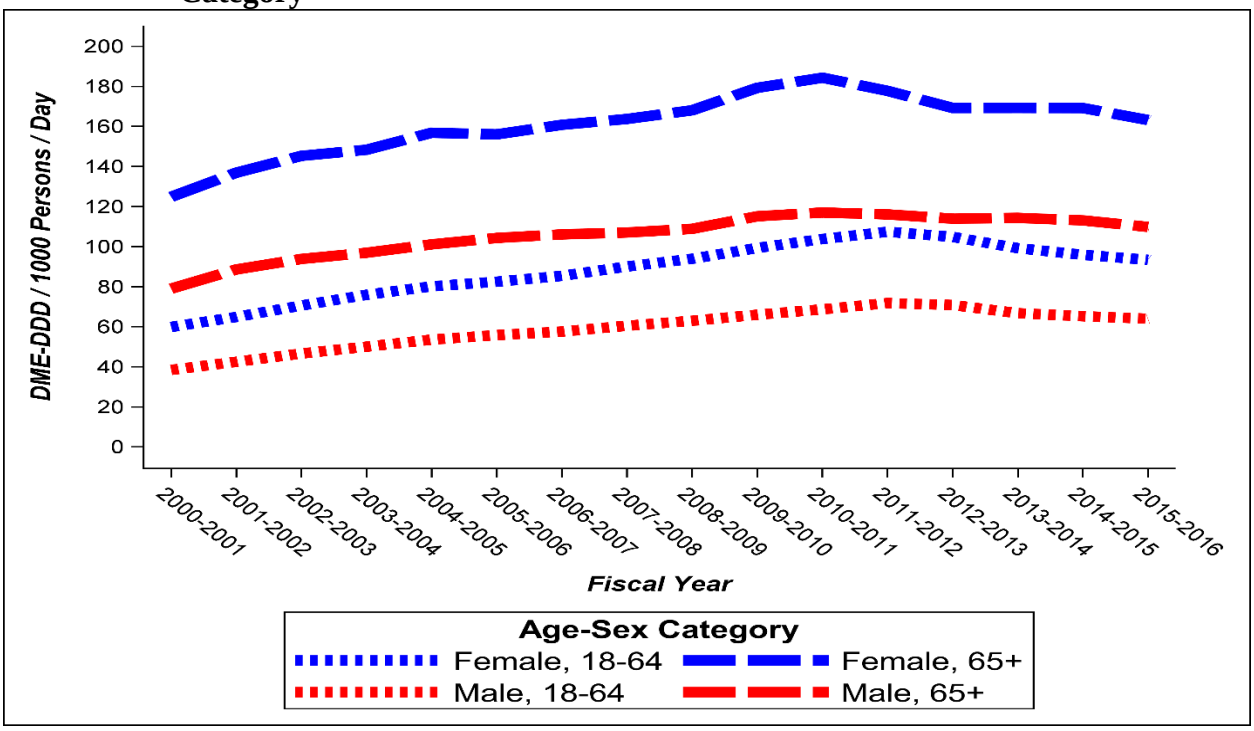


Figure 3.7 – Dose Intensity Trends for Benzodiazepines and Z-Drugs by Age-Sex Category

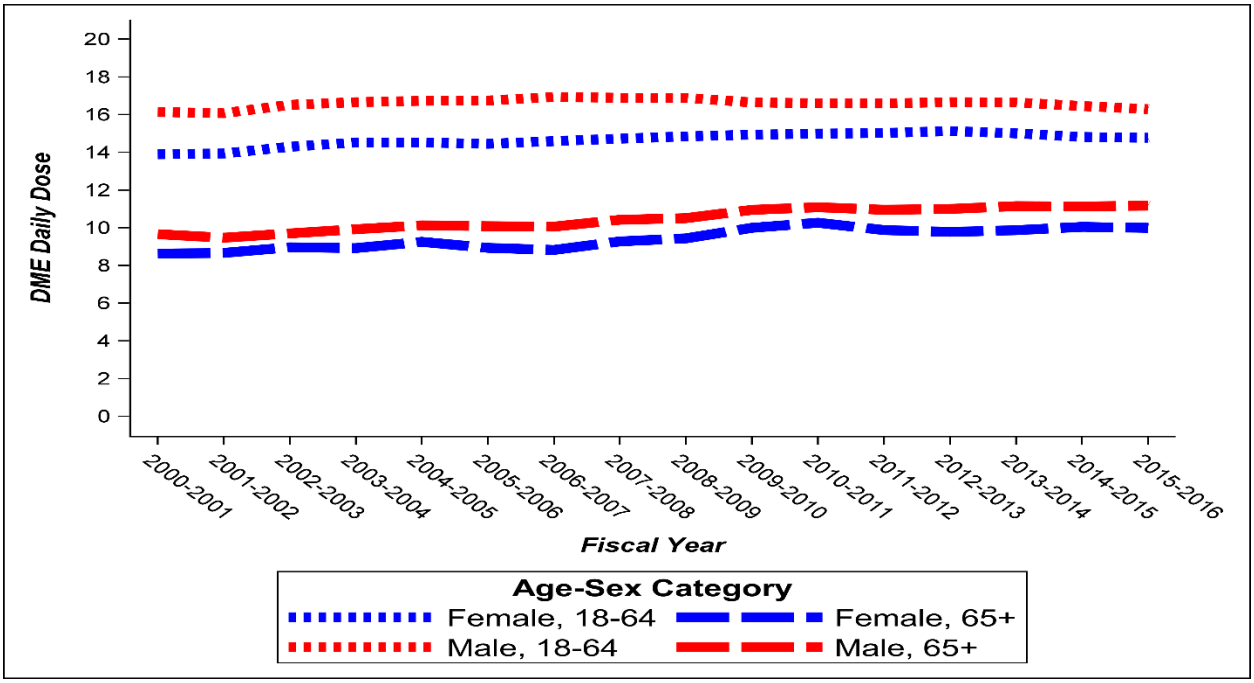
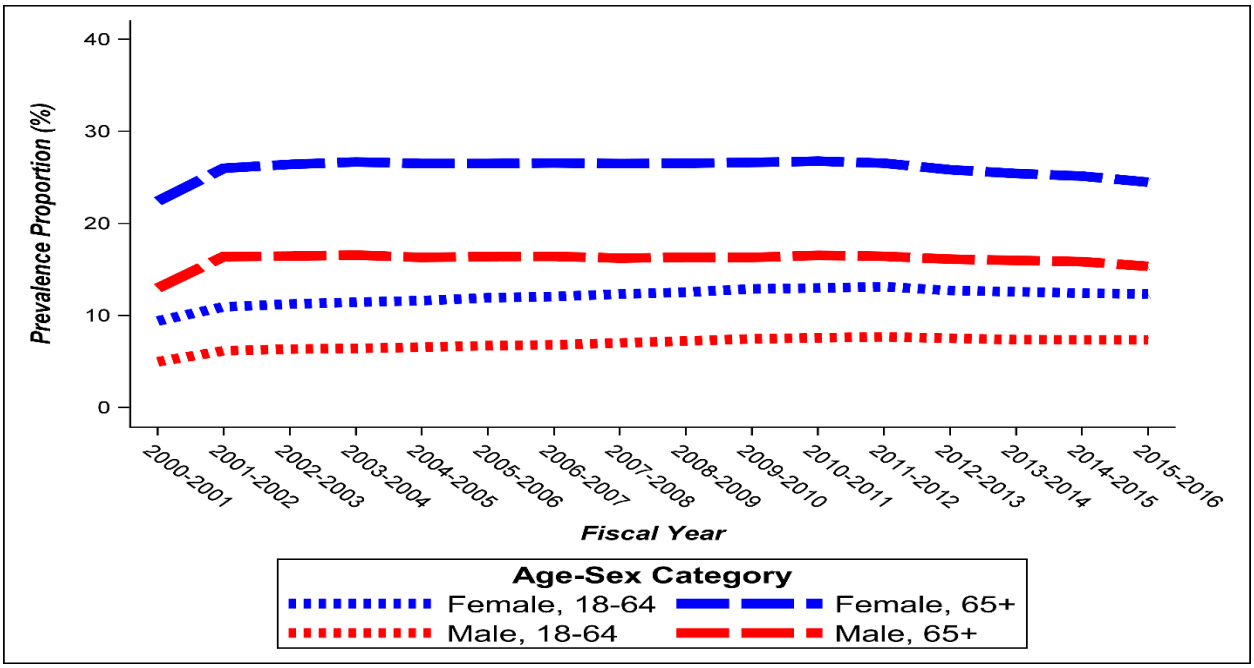


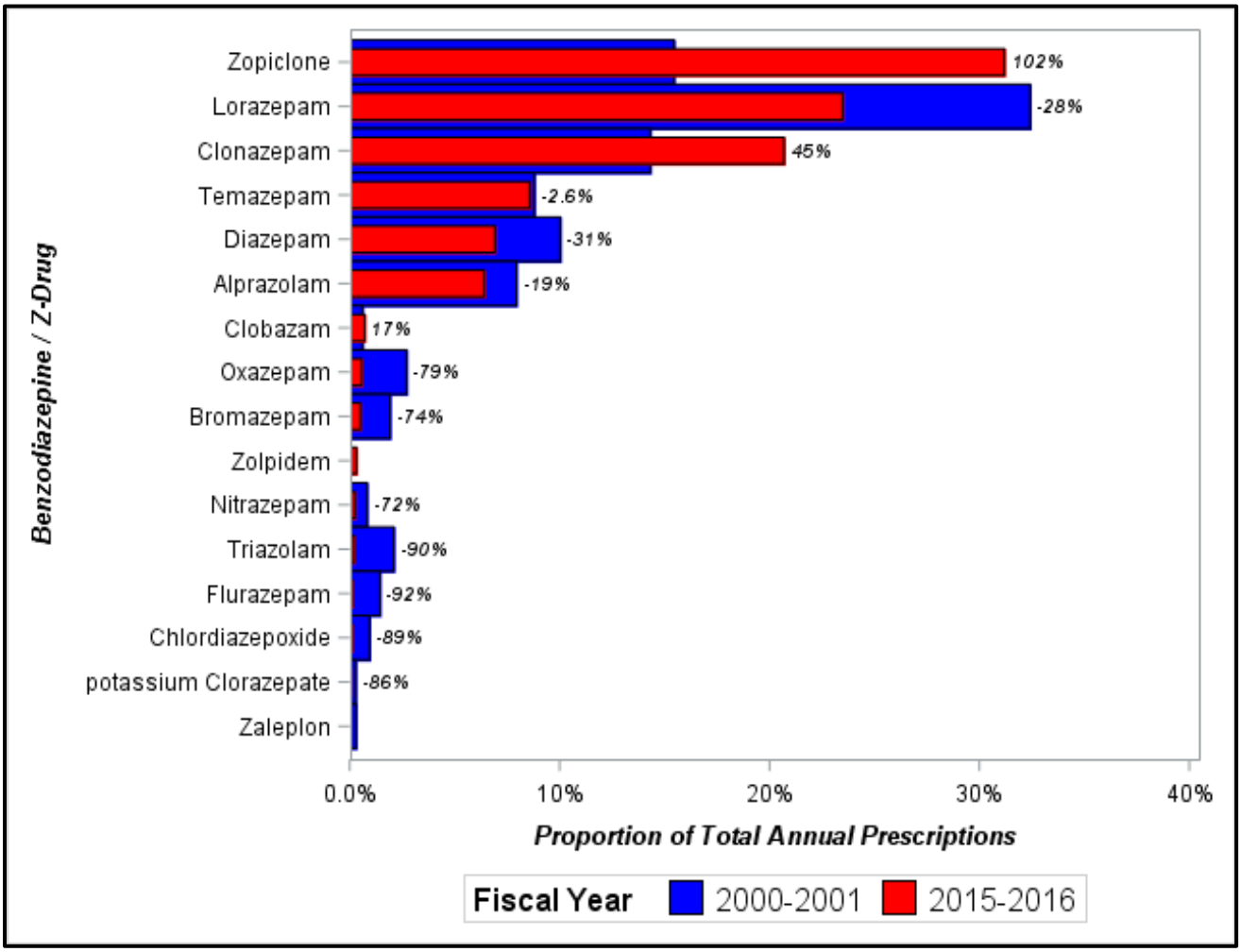
Figure 3.8 – Prevalence Proportion Trends for Benzodiazepines and Z-Drugs by Age-Sex Category



3.3.3) Utilisation by Agent

Figure 3.9 compares the proportional representation of annual prescriptions by agent in the first and last year of the study. This was calculated by dividing the total number of prescriptions for a particular drug in that year by the total number of BZD/Z-Drug prescriptions in that same year.

Figure 3.9 – Proportion of Annual Prescriptions in First and Last Year of Study by BZD



**Percentage at end of horizontal bar for each drug represents the relative change in number of prescriptions from start of study to the end of the study*

Analysis of dose intensity trends by individual agent, in their respective milligram potencies, revealed statistically significant increases in daily doses for zopiclone, temazepam, triazolam, alprazolam, oxazepam and diazepam over the study period. Chlordiazepoxide, clobazam and clonazepam saw statistically significant decreases in daily dose. All other agents had non-significant changes in dose intensity at an alpha of 0.05. The agent that saw the greatest change in average dose over time was alprazolam, rising 34.7% from 0.98 mg/day (2001) to 1.32 mg/day (2016).

Consumption trends (DDD/1000-person days) by individual agent revealed statistically significant increases (% increase per year at $p < 0.05$) for zopiclone (7.4%), alprazolam (4.4%), temazepam (3.4%), clonazepam (2.9%) and clobazam (1.1%). Statistically significant decreases (% reduction per year at $p < 0.05$) were observed for flurazepam (13.2%), chlordiazepoxide (12.5%) triazolam (12.5%), potassium clorazepate (9.0%), oxazepam (7.5%), bromazepam (5.8%), nitrazepam (4.4%), diazepam (2.1%) and lorazepam (0.3%). Zolpidem and zaleplon were not analysed individually due to their limited representation and incomplete market availability over the study duration.

3.3.4) *Sensitivity Analysis for DME-based Utilisation Measures*

Equivalency values for each alternative published source used in the sensitivity analysis are provided below in Table 3.4.

Table 3.4 – DME Conversion Source Values Used in Sensitivity Analysis

Drug	Ashton[32]	Ashton (modified)	Shader & Greenblatt[35]	Alessi-Severini et al.[34]
Alprazolam	0.5 mg	0.5 mg	1 mg	1 mg
Bromazepam	5 mg	5 mg	N/A	10 mg
Chlordiazepoxide	25 mg	25 mg	50 mg	20 mg
Clobazam	20 mg	20 mg	N/A[1]	20 mg
Clonazepam	0.5 mg	**1 mg**	0.5 mg	0.5 mg
Potassium Clorazepate	15 mg	15 mg	15 mg	N/A[1]
Diazepam	10 mg	10 mg	10 mg	10 mg
Flurazepam	30 mg	30 mg	30 mg	30 mg
Lorazepam	1 mg	1 mg	2 mg	2 mg
Oxazepam	20 mg	20 mg	30 mg	20 mg
Nitrazepam	10 mg	10 mg	10 mg	10 mg
Temazepam	20 mg	20 mg	30 mg	30 mg
Triazolam	0.5 mg	0.5 mg	0.25 mg	0.25 mg
Zaleplon	20 mg	20 mg	N/A[1]	20 mg
Zolpidem	20 mg	20 mg	10 mg	NA[1]
Zopiclone	15 mg	15 mg	N/A[1]	7.5 mg

[1]In absence of available value, Ashton value was used

Detailed results for the sensitivity analysis are provided in Table 3.5 on the following pages. Overall, substitution of DME conversion values from the three differing sources did not result in significant change in trends for dose intensity or pharmacologic exposure for Z-Drugs or BZD when assessed separately. However, when they were combined, discrepant trends emerged. For individual agents, some equivalency values differed by two-fold or more and this would dramatically impact class-based DME estimates if such agents constituted a large portion of the annual prescription share.

Notably, average daily dose in DME remained significantly higher for clonazepam compared to other agents, thus prompting an additional *post-hoc* sensitivity analysis wherein its

conversion value was changed from 1 mg = 20 DME to 1 mg = 10 DME. This 'modified' Ashton scale, with all other BZD conversions being held constant, constituted the third sensitivity analysis. However, while the statistical significance of the trends did not change, the daily dose intensity dropped by a range of 1-3 DME for each year of the study for both BZD and combined BZD with Z-Drugs.

Table 3.5 - Sensitivity Analysis Results on DME-Based Indicators of Utilization

Source	Parameter	Z-Drug	BDZ	Combined (BDZ + Z-Drug)
Ashton (main results)[32]	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	↑ 4.1 (2001) to 14.3 (2016)	NS; 69.8 (2001) to 82.2 (2016)	NS; 73.9 (2001) to 96.5 (2016)
	Dose Intensity (DME/Day)	↑ 5.0 (2001) to 5.43 (2016)	↑ 17.1 (2001) to 20.1 (2016)	NS ; 15.1 (2001) to 14.4 (2016)
Clonazepam conversion change (Modified Ashton)	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	↑ 4.1 (2001) to 14.3 (2016)	NS; 60.0 (2001) to 65.4 (2016)	NS; 64.1 (2001) to 79.7 (2016)
	Dose Intensity (DME/Day)	↑ 5.0 (2001) to 5.43 (2016)	↑ 14.7 (2001) to 16.0 (2016)	NS; 13.1 (2001) to 11.9 (2016)

Source	Parameter	Z-Drug	BDZ	Combined (BDZ + Z-Drug)
Alessi-Severini et al.[34]	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	↑ 8.13 (2001) to 28.4 (2016)	NS; 51.4 (2001) to 61.9 (2016)	↑ 59.5 (2001) to 90.3 (2016)
	Dose Intensity (DME/Day)	↑ 9.9 (2001) to 10.8 (2016)	↑ 12.6 (2001) to 15.2 (2016)	↑ 12.4 (2001) to 13.4 (2016)
Shader et al.[35]	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	↑ 8.2 (2001) to 28.6 (2016)	NS ; 51.1 (2001) to 62.0 (2016)	↑ 59.3 (2001) to 90.5 (2016)
	Dose Intensity (DME/Day)	↑ 10.0 (2001) to 10.9 (2016)	↑ 12.5 (2001) to 15.2 (2016)	↑ 12.1 (2001) to 13.5 (2016)

NS – Not statistically significant

3.4) Discussion

3.4.1) Findings and Implications

This study provides updated information on utilisation of BZD and Z-Drugs in a large Canadian population. The presented data and trends provide valuable information that may be of use to prescribers, pharmacists and healthcare authorities in Manitoba to guide efforts to improve usage of BZD and Z-Drugs. This remains an important ongoing endeavor because of the delicately complex balance between benefits and risks inherent to use of these medications, as well as the differing opinions expressed among health professionals on their place in therapy.[37–39]

Overall, the annual prevalence of combined BZD+Z-Drug use amongst adults (ranging between 9-12%) was similar to the various national estimates for prevalence of use.[40,41] However, comparison of average consumption estimates for all of Canada, taken from the 2017 technical report of the International Narcotics Control Board (INCB) for the years 2014-2016, revealed that average Manitoba consumption of BZD (not including Z-Drugs) over this 3-year period was lower than the total Canadian estimate at 32.7 and 55.3 DDD/1000 person days, respectively.[42] However, this comparison should be viewed cautiously given the relative differences and underlying assumptions between these data sources. Namely that one uses pharmacy dispensing records and the other uses international manufacture and import/export reporting records.

The higher prevalence, consumption and pharmacologic exposure in the 65+ population and particularly females, is a finding that has been repeatedly encountered in pharmacoepidemiologic studies.[43] While this was not surprising, the vulnerability of this population to the cognitive and psychomotor impairing effects of these drugs is an ongoing concern. Furthermore, the increase in dose intensity over the study period in this population was unexpected and, while the magnitude of absolute increase in DME/day is debatable in terms of its

clinical significance, the fact that the dose intensity increased as opposed to remaining stable or decreasing is problematic in and of itself.

The increased utilisation of Z-Drugs (almost completely zopiclone) and decline of BZD use is in accordance with past observations in Manitoba[26] and elsewhere.[44–47] However, widespread substitution of BZD use with Z-Drug use, while often considered the 'lesser of two evils' in terms of safety, is neither devoid of substantial risk nor clearly superior in effectiveness.[48–50] Additionally, the increase in all measures of Z-Drug usage may indicate a rise in the burden of insomnia and related sleep disorders in the Manitoba population over the 15-year study period. Observed increases in dose intensity or consumption of common hypnotic benzodiazepines such as temazepam and triazolam lend further support to this hypothesis. These trends may be explained, but not definitively confirmed, by factors such as pharmacologic tolerance with longer use, population aging[51] and increased widespread use of various sleep-disrupting, mobile technologies.[52] As newer, seemingly safer pharmacotherapies for insomnia, such as orexin-1 antagonists (i.e suvorexant) and melatonin receptor agonists (i.e ramelteon), continue to become available and gain evidence-based recognition as potential alternative first-line treatments, the use of BZD and Z-Drugs may decline in the years that follow.[53] Until then, a focus on non-pharmacologic treatment modalities combined with deprescribing intervention knowledge would be expected to be useful to improve quality of life and prevent harm in at-risk users.[54]

The usage of particular BZDs merit discussion. First, the use of alprazolam is higher now than in the early 2000s (though it peaked in the period from 2011-2013) despite its reputation for overdose and misuse potential relative to other BZDs.[55,56] The slight reduction in its use after 2013 is likely not coincidental with the timing of the IMPRxOVE study in Manitoba, which aimed to

reduce potentially inappropriate BZD use.[36] Nevertheless, return to the level of alprazolam utilisation predating the 2010's could be viewed as a continued goal worth pursuing.

While lorazepam has easily maintained its position as the most frequently used BZD, it was gradually supplanted by zopiclone (when the drug classes were combined) with respect to the overall annual prescription share. Clonazepam use continued to rise over the study period, albeit not in terms of dose intensity. Similar observations of rising clonazepam use were made in two recent studies.[47,57] In the neighbouring Canadian province of Ontario, Davies et al. reported a gradual increase in prevalence of clonazepam use by ~70% from 1998 to 2013 in the 65+ population.[57] These authors speculate that the perception of superiority of clonazepam over other BZD amongst prescribers, resulting in its increase in use, is owed to its favorable pharmacokinetic profile (long half-life with no active metabolites) and clinical trial evidence supporting its use as a monotherapy or adjunctive treatment for certain anxiety disorders, even with long-term use.[58,59] Kurko et al., in a Finnish population register study, observed that, contrary to the other BZD, long-term use of clonazepam increased in the elderly population.[47]

By contrast, other long-acting BZD such as diazepam, chlordiazepoxide and flurazepam saw sustained decreases in their utilisation. Furthermore, this pattern of reduction in use was not limited to the long-acting agents, as any agent that was infrequently used in 2000 became even less so by 2016. If this trend continues, it appears that total BZD use will essentially be consolidated in the use of only 7 agents; zopiclone, lorazepam, clonazepam, temazepam, diazepam, alprazolam and clobazam. Indeed, these 7 agents are already representative of the various indications and pharmacokinetic properties needed to individualize therapy for patients in clinical practice, thus arguably limiting the need for other BZDs. This shift towards the

simplification of BZD use in Manitoba via elimination of older BZD could be perceived as an improvement indicative of progressive practice change over time.

This study was unique insofar as it explored BZD and Z-Drug utilisation trends by DME based indicators; dose intensity and pharmacologic exposure. While the sensitivity analysis demonstrated the volatility of these indicators in terms of their annual point estimates, the overall trends remained stable in terms of which measures statistically increased or decreased. Importantly, the calculated values for pharmacologic exposure (DME-DDD) were consistently and markedly higher than the WHO standard consumption method (DDD). This suggests that the traditional reliance on the latter method may underestimate meaningful population use of BZD and Z-Drugs. This distinction would be important in understanding how the magnitude of population exposure could be correlated with population harm outcomes such as overdoses or motor-vehicle accidents. While prone to ecological fallacy and confounding, in the absence of linkage of individual level data and longitudinal follow-up, this method may be of some practical use for adoption in ongoing pharmacovigilance monitoring (especially when used in tandem with prescription opioid data) if it is shown to positively correlate with important harm outcomes.

3.4.2) *Strengths & Limitations*

This study had some important strengths and limitations which should be recognized when interpreting the results. In terms of strengths, the DPIN database provides an almost complete and highly accurate account of dispensed prescriptions in the province of Manitoba. The use of multiple indicators and sub-analyses offered a nearly complete interpretation of aggregated BZD and Z-Drug use in Manitoba over the past 15 years. Lastly, a sensitivity analysis, using various DME conversion sources, ensured the validity of the utilisation trends by confirmation of their

consistency and directionality, in spite of differences between sources in the determination of annual point estimates.

In terms of limitations, duration of use and individual patient characteristics beyond age and sex were not assessed and so this limits the ability to make more targeted inferences relevant to clinical practice decision-making. Furthermore, as these medications are frequently taken on an as needed ('prn') basis, it was impossible to know which dispensing observations were characterised by as needed use and which ones were dosed on a regular basis. Therefore, the misclassification, especially in the determination of dose intensity is possible. However, it would be expected that this misclassification would be non-differential over time and therefore less likely to produce false positive trends. Though, this too is under the assumption that the proportion of 'prn' to 'regular' dosed prescriptions remained stable over time. Lastly, as with any drug utilisation study relying on administrative prescription claims, dispensation data ultimately represents an overestimate of medication consumption.

3.5) Conclusion

This study has important conclusions both provincially within Manitoba in terms of clinical practice and beyond its borders in terms of drug utilisation research. In regards to the former, utilization of BZD gradually increased until the 2011-2013 period before declining. This recent decline may be attributable to both the provincial wide audit and feedback study during this period as well as the clinical culture of recent years emphasizing deprescribing. To this point, the continued reduction in use of older, long-acting BZD, witnessed in this study, may be perceived as an improvement in prescribing practice. Though, further improvement may be sought by focusing on reducing the use of the 'problem' BZD alprazolam and ensuring the increasing reliance on clonazepam as a BZD of choice is appropriate and justified. Another matter of potential concern

is the fact that Z-Drug use in the Manitoba population remains high. Although, utilization may be stabilising given data from the most recent years. Non-pharmacologic treatment modalities or safer pharmacologic options should continue to be emphasized in the treatment of sleep disorders. In terms of drug utilisation research for BZD and Z-Drugs, DME based measurements, while somewhat unstable, may aid in the interpretation of the extent and intensity of pharmacologic exposure in patient populations. However, DME based sources and values for particular agents (i.e clonazepam) should be further refined and validated to improve future measurement of population benzodiazepine exposure.

Chapter 3 References

1. Starcevic V. The reappraisal of benzodiazepines in the treatment of anxiety and related disorders. *Expert Rev Neurother*. 2014;14(11):1275-1286. doi:10.1586/14737175.2014.963057.

2. Lader M. Benzodiazepine harm: How can it be reduced? *Br J Clin Pharmacol*. 2014;77(2):295-301. doi:10.1111/j.1365-2125.2012.04418.x.

3. Khong TP, De Vries F, Goldenberg JSB, et al. Potential impact of benzodiazepine use on the rate of hip fractures in five large European countries and the United States. *Calcif Tissue Int*. 2012;91(1):24-31. doi:10.1007/s00223-012-9603-8.

4. Becker WC, Fiellin DA, Desai RA. Non-medical use, abuse and dependence on sedatives and tranquilizers among U.S. adults: Psychiatric and socio-demographic correlates. *Drug Alcohol Depend*. 2007;90(2-3):280-287. doi:10.1016/j.drugalcdep.2007.04.009.

5. Lingford-Hughes A, Welch S, Peters L, Nutt D. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *J Psychopharmacol*. 2012;26(7):899-952. doi:10.1177/0269881112444324.

6. Bandelow B, Zohar J, Hollander E, Kasper S, Moller H-J. World Federation of Societies of Biological Psychiatry (WfSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Psttraumatic Stress Disorders. *World J Biol Psychiatry*. 2008;9(4):248-312. doi:10.1080/15622970802465807.

7. Sateia MJ, Buysse D, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin sleep Med JCSM Off Publ Am Acad Sleep Med*. December 2016.

8. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175.

9. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.

10. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-439. doi:10.1177/0269881114525674.

11. American Geriatrics Society Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246. doi:10.1111/jgs.13702.

12. Ickowicz S, Hayashi K, Dong H, et al. Benzodiazepine use as an independent risk factor for HIV infection in a Canadian setting. *Drug Alcohol Depend*. 2015;155:190-194. doi:10.1016/j.drugalcdep.2015.07.017.

13. Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: Eszopiclone, ramelteon, zaleplon, and zolpidem. *J Clin Sleep Med*. 2009;5(4):377-383.

14. Zhong G, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: A meta-analysis. *PLoS One*. 2015;10(5):1-16. doi:10.1371/journal.pone.0127836.

15. Liaw G-W, Hung D-Z, Chen W-K, Lin C-L, Lin I-C, Kao C-H. Relationship Between Acute Benzodiazepine Poisoning and Acute Pancreatitis Risk. *Medicine (Baltimore)*. 2015;94(52):e2376. doi:10.1097/MD.0000000000002376.

16. Vozoris NT, Wang X, Fischer HD, et al. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J*. 2014;44:332-340. doi:10.1183/13993003.01967-2015.

17. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017;17(4):493-507. doi:10.1007/s40268-017-0207-7.

18. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract*. 2014;27(1):5-16. doi:10.1177/0897190013515001.

19. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002−2014. *Am J Prev Med*. 2016;51(2):1-10. doi:10.1016/j.amepre.2016.02.014.

20. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-142. doi:10.1001/jamapsychiatry.2014.1763.

21. Sanyal C, Asbridge M, Kisely S, Sketris I, Andreou P. The utilization of antidepressants and benzodiazepines among people with major depression in Canada. *Can J Psychiatry*. 2011;56(11):667-676. doi:10.1177/070674371105601105.

22. Berman E, Eyal S, Marom E. Trends in utilization of benzodiazepine and Z-drugs in Israel. *Pharmacoepidemiol Drug Saf*. 2017;(September):1-6. doi:10.1002/pds.4338.

23. Islam MM, Conigrave KM, Day CA, Nguyen Y, Haber PS. Twenty-year trends in benzodiazepine dispensing in the Australian population. *Intern Med J*. 2014;44(1):57-64.

doi:10.1111/imj.12315.

24. Murphy KD, Sahm LJ, McCarthy S, Byrne S. Benzodiazepine prescribing guideline adherence and misuse potential in Irish minors. *Int J Clin Pharm*. 2015;37(5):749-752. doi:10.1007/s11096-015-0138-8.

25. Tjagvad C, Clausen T, Handal M, Skurtveit S. Benzodiazepine prescription for patients in treatment for drug use disorders: a nationwide cohort study in Denmark, 2000-2010. *BMC Psychiatry*. 2016;16:168. doi:10.1186/s12888-016-0881-y.

26. Alessi-Severini S, Bolton JM, Enns MW, et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. *C open*. 2014;2(4):E208-16. doi:10.9778/cmajo.20130076.

27. Univeristy of Manitoba. Manitoba Centre for Health Policy. Departmental Webpage. http://umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/. Published 2017. Accessed November 6, 2017.

28. Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. *Ann Pharmacother*. 1998;32(11):1152-1157. doi:10.1345/aph.18117.

29. Manitoba Centre for Health Policy. Population Estimates and Comparison of Data Sources. Concept Dictionary. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1203. Published 2009. Accessed April 30, 2018.

30. WHO Collaborating Centre for Drug Statistics Methodology & Norweigan Institute of Public Health. *Guidelines for ATC Classification and DDD Assignment - 2017*.; 2017.

31. Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry*. 2005;18(3):249-255. doi:10.1097/01.yco.0000165594.60434.84.

32. Ashton H. benzo.org.uk : Benzodiazepine Equivalence Table. http://www.benzo.org.uk/bzequiv.htm. Published 2007. Accessed February 3, 2017.

33. Brandt J, Alkkabanni W, Alessi-severini S, Leong C. Translating Benzodiazepine Utilization Data into Meaningful Population Exposure : Integration of Two Metrics for Improved Reporting. *Clin Drug Investig*. 2018. doi:10.1007/s40261-018-0648-y.

34. Alessi-severini S, Bolton JM, Enns MW. Sustained Use of Benzodiazepines and Escalation to High Doses in a Canadian Population. *Psychiatr Serv*. 2016;67(9):1012-1018. doi:10.1176/appi.ps.201500380.

35. Shader RI, Greenblatt DJ. Can you provide a table of equivalences for benzodiazepines and other marketed benzodiazepine receptor agonists? *J Clin Psychopharmacol*. 1997;17(4):331.

36. Chateau D, Enns M, Ekuma O, et al. *Evaluation of the Manitoba IMPRxOVE Program*. Winnipeg, MB; 2015. http://mchp-appserv.cpe.umanitoba.ca/concept//ImproveRx_report_website.pdf.

37. Moore N, Pariente A, Bégaud B. Why are benzodiazepines not yet controlled substances? *JAMA Psychiatry*. 2015;72(2):110-111. doi:10.1001/jamapsychiatry.2014.2190.

38. El-Guebaly N, Sareen J, Stein MB. Are There Guidelines for the Responsible Prescription of Benzodiazepines? *Can J Psychiatry*. 2010;55(11):709-714.

39. Lembke A, Papac J, Humphreys K. Our Other Prescription Drug Problem. *N Engl J Med*. 2018;378(8):693-694. doi:10.1056/NEJMp1715050.

40. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine Use, Misuse, and Harm at the Population Level in Canada: A Comprehensive Narrative Review of Data and Developments Since 1995. *Clin Drug Investig*. 2016;36(7):519-530. doi:10.1007/s40261-016-0397-8.

41. Canadian Centre on Substance Abuse. *Prescription Sedatives (Canadian Drug Summary)*.; 2015.

42. International Narcotics Control Board (INCB). *Techncal Report on Psychotropic Substances - Statistics for 2016*. New York, NY: United Nations; 2018. https://www.incb.org/documents/Psychotropics/technical-publications/2017/Technical_Publication_2017_English_04042018.pdf.

43. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

44. Hausken AM, Furu K, Skurtveit S, Engeland A, Bramness JG. Starting insomnia treatment: The use of benzodiazepines versus z-hypnotics. A prescription database study of predictors. *Eur J Clin Pharmacol*. 2009;65(3):295-301. doi:10.1007/s00228-008-0565-8.

45. Esposito E, Barbui C, Patten SB. Patterns of benzodiazepine use in a Canadian population sample. *Epidemiol Psichiatr Soc*. 2009;18(3):248-254.

46. Lader M. Benzodiazepines revisited-will we ever learn? *Addiction*. 2011;106(12):2086-2109. doi:10.1111/j.1360-0443.2011.03563.x.

47. Kurko T, Saastamoinen LK, Tuulio-Henriksson A, et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf*. 2018;(October 2017):3-6. doi:10.1002/pds.4551.

48. Curreen M, Lidmila J. Zopiclone: Is there cause for concern in addiction services and general practice? *Int J Risk Saf Med*. 2014;26(4):183-189. doi:10.3233/JRS-140633.

49. Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *Bmj*. 2012;345(dec17 6):e8343-e8343. doi:10.1136/bmj.e8343.

50. Siriwardena AN, Qureshi MZ, Dyas J V., Middleton H, Orner R. Maqic bullets for insomnia? Patients' use and experiences of newer (Z drugs) versus older (benzodiazepine) hypnotics for sleep problems in primary care. *Br J Gen Pract*. 2008;58(551):417-422. doi:10.3399/bjgp08X299290.

51. Ancoli-Israel S. Sleep and its disorders in aging populations. *Sleep Med*. 2009;10(SUPPL. 1):S7-S11. doi:10.1016/j.sleep.2009.07.004.

52. Fossum IN, Nordnes LT, Storemark SS, Bjorvatn B, Pallesen S. The association between use of electronic media in bed before going to sleep and insomnia symptoms, daytime sleepiness, morningness, and chronotype. *Behav Sleep Med*. 2014;12(5):343-357. doi:10.1080/15402002.2013.819468.

53. Schroeck JL, Ford J, Conway EL, et al. Review of Safety and Efficacy of Sleep Medicines in Older Adults. *Clin Ther*. 2016;38(11):2340-2372. doi:10.1016/j.clinthera.2016.09.010.

54. Ng BJ, Couteur DG Le, Hilmer SN. Deprescribing Benzodiazepines in Older Patients : Impact of Interventions Targeting Physicians , Pharmacists , and Patients. *Drugs Aging*. 2018. doi:10.1007/s40266-018-0544-4.

55. Ait-Daoud N, Hamby AS, Sharma S, Blevins D. A Review of Alprazolam Use, Misuse, and Withdrawal. *J Addict Med*. 2018;12(1):4-10. doi:10.1097/ADM.0000000000000350.

56. Darke S, Torok M, Duflou J. Circumstances and toxicology of sudden or unnatural deaths involving alprazolam. *Drug Alcohol Depend*. 2014;138(1):61-66. doi:10.1016/j.drugalcdep.2014.01.023.

57. Davies SJC, Jacob B, Rudoler D, Zaheer J, de Oliveira C, Kurdyak P. Benzodiazepine prescription in Ontario residents aged 65 and over: a population-based study from 1998 to 2013. *Ther Adv Psychopharmacol*. 2018;8(3):99-114. doi:10.1177/https.

58. Nardi AE, Freire RC, Mochcovitch MD, et al. A randomized, naturalistic, parallel-group study for the long-term treatment of panic disorder with clonazepam or paroxetine. *J Clin Psychopharmacol*. 2012;32(1):120-126. doi:10.1097/JCP.0b013e31823fe4bd.

59. Nardi AE, Machado S, Almada LF, et al. Clonazepam for the treatment of panic disorder. *Curr Drug Targets*. 2013;14(3):353-364.

Chapter 4 – Evaluation of Benzodiazepine and Z-Drug Use Among Adults with Anxiety and Insomnia in Manitoba: *15-Year Retrospective Cohort Study (2001-2016)*

***Disclaimer*:** This section is an adapted version of the submitted manuscript for journal publication:

Brandt J, Alessi-Severini S, Chateau D, Leong C, Evaluation of Benzodiazepine and Z-Drug Use Duration among Adults with Anxiety and Sleep Disorders in Primary Care. *Epidemiology and Psychiatric Sciences* (submitted)

Student contribution: *conceptualised topic, conducted data analysis and interpretation, wrote first draft and final version. Student was corresponding author to editor and peer-reviewers.*

4.1) Introduction

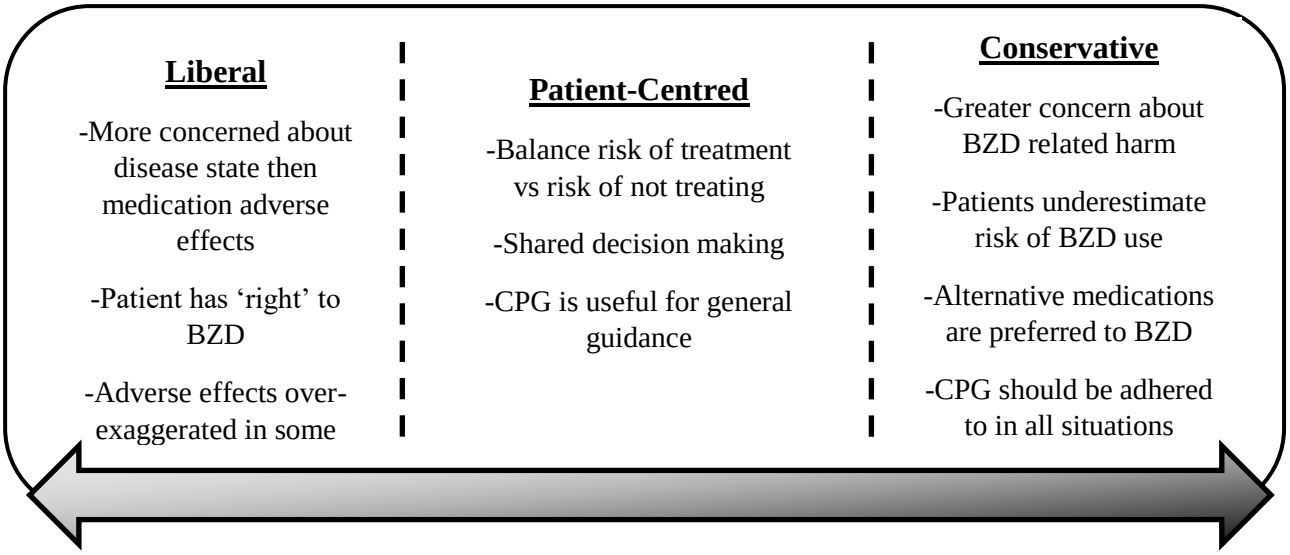
4.1.1) Background

Prescription benzodiazepine and Z-Drug (BZD) use is frequently subject to differences of opinion between individual clinicians and broader controversy among the larger medical communty.[1–7] The advent of these agents began in the late 1950's with the introduction of chlordiazepoxide and diazepam.[8] In the years that followed, BZDs rapidly replaced the inferior, non-specific pharmacological agents of greater toxicity that psychiatry had relied on up until then (i.e barbiturates, chloral hydrate, bromides etc.).[8] Due to their greater safety profile of BZDs, treatment that was once more restricted to the more severely mentally ill became more widely available to the "worried-well"; patients with comparably minor psychiatric illnesses who could now be treated pharmacologically by general practitioners.[8]

Nonetheless, the controversy surrounding these agents became prominent in the 1970's and 1980's, with widespread publicity regarding emerging issues of physical dependence and chemical withdrawal, culminating in anti-BZD campaigns and tighter regulatory controls.[8,9] Over

decades, this controversy and lack of consensus has been sustained by a number of factors. On the one hand, long-standing safety concerns such as psychomotor impaired accidents (i.e falls and motor-vehicle accidents) and dependency have been cited to support arguments for conservative use or discontinuation efforts.[10–12] Contrarian arguments for more liberal, relativist use often invoke the long-standing track record of BZD as rapidly effective anxiolytics and hypnotics.[13] Proponents of this prescribing perspective maintain that withholding or limiting BZD use is frequently impractical within patient-provider relationships and, more often than not, increases psychiatric symptom burden and patient distress which is not always counter-balanced by the avoided harm that may have otherwise resulted.[14] Nevertheless, a patient-centered approach which carefully takes into consideration the risks associated with both a conservative and liberal prescribing philosophy is likely to yield the best clinical results (Figure 4.1).[15] The complexity of factors that influence BZD prescribing decisions within the patient-provider dyad is discussed extensively elsewhere, is beyond the scope of this article and cannot be fully communicated by Figure 4.1, which only offers a simplistic conceptualization applicable to clinicians.[5,16,17]

Figure 4.1 – Benzodiazepine Prescribing Philosophy Spectrum



Clinical Practice Guidelines (CPG), in efforts to properly balance these perspectives along the spectrum, have attempted to provide general direction to practitioners and pharmacists on how these medications should be managed according to the best available evidence.[18–22] However, CPGs themselves usually tend to err closer to the conservative end of the prescribing spectrum when making pronouncements on general use duration (Figure 4.1). Population wide prescribing practice evaluations to determine the extent of adherence to CPG recommendations, with respect to duration of use, have only been rarely conducted.[23]

4.1.2) Objectives and Rationale

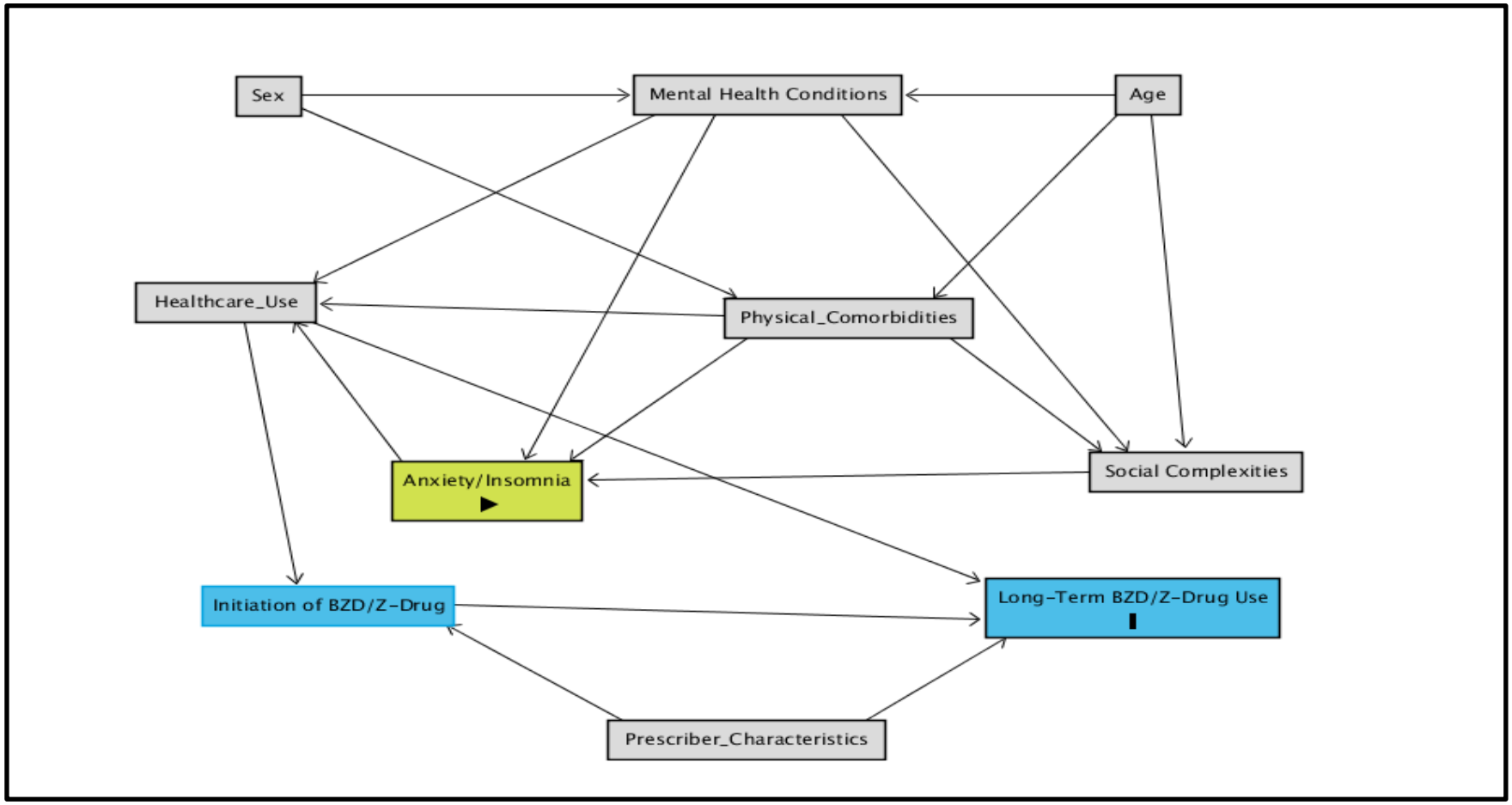
i) Quantify the proportion of patients becoming long-term BZD users after their initial prescription.

This study sought to evaluate the BZD / Z-Drug treatment duration among a large, sample of adult, incident users against guideline recommendations. Because individual patient encounters are subject to practitioner professional judgment, it is not expected that all patients fit nicely into the ideal world of CPGs formed by academic medicine. However, population level assessment could reasonably determine the extent of disparity between real-world prescribing and the recommended prescribing advocated by CPGs. Discovery of major discrepancies between the 'real' (i.e observational results of this study) and the 'ideal' (CPG recommendations) would suggest that either one or both require systematic change to coordinate healthcare efforts to further optimize health outcomes with respect to BZD use.

ii) Determine which factors are predictive of progression to long-term BZD use in the Manitoba adult patient population

Beyond quantification of CPG adherence, exploration of factors associated with short-term and long-term use of these agents was undertaken as a means to understand patient and provider characteristics. Characterization of differences between short-term and long-term BZD use has been the focus of many previous studies (see section 2.1.2). However, this topic is far from exhausted especially given the fact that many individual studies are questionable in regards to their external validity beyond their respective study populations. Therefore, this study may either generate hypotheses about previously unidentified factors associated with certain BZD use patterns or provide further supporting evidence for factors previously identified in the literature. A conceptual framework in the form of a Directed Acyclic Graph (DAG) is presented in Figure 4.2.[24] Discernment of factors associated with different patterns of use is expected to provide important contextual information to aid future practitioner' prescribing decisions. Furthermore, knowledge of factors that contribute towards higher risk use patterns may assist in various knowledge translation efforts to optimize population level use via timely prevention strategies.[25] For example, development, validation and implementation of a BZD clinical risk prediction tool, not dissimilar to the Opioid Risk Tool (ORT) may improve benzodiazepine prescribing.[26]

Figure 4.2 – Directed Acyclic Graph Showing Associations and Causal Links to Long-Term BZD/Z-Drug Use



Legend

→ = Association/Link between Variables
Yellow = Assumed Necessary Precondition
Blue = Variables Directly Observable for Causation
Gray = Adjusted Independent Variable

4.2) Methods

4.2.1) Study Design and Data Sources

This study was a retrospective, new-user, longitudinal cohort study which used routinely collected administrative healthcare data pertaining to prescription drug dispensations, outpatient physician claims and hospitalization discharge abstracts. Although these were the primary data sources utilised, other datasets were used minimally as they related to important independent variables (i.e social data, patient demographics etc.). All data used (except for Federal government census data) was extracted from the Manitoba Centre for Health Policy's (MCHP) Population Research Data Repository (PRDR); details of which are displayed in Table 4.1. Merging of the various data sources was facilitated via linkage of unique de-identified Personal Health Information Numbers (PHIN). The PHINs are scrambled through a confidential algorithmic process by the department of Information Management and Analytics of the Manitoba Health, Seniors and Active Living (MHSAL) branch of the provincial government before this data is transmitted securely to MCHP for research purposes. All data was manipulated and analyzed using Base SAS v9.4©.

Table 4.1 –Raw Data Sources and Relevant Corresponding Data Elements

Database	Date Range of Data	Relevant Data Elements
Drug Program Information Network (DPIN)	Apr. 1/2000 – Mar. 31/2016	Prescriptions for benzodiazepines (ATC codes N03AE, N05BA, N05CD), Z-Drugs (N05CF), Antidepressants, Antipsychotics, Mood stabilisers, Lithium and Opioids drug, dosage strength, dosage type, metric quantity dispensed, day supply, date of dispensation
Manitoba Health Insurance Registry	Apr. 1/1996 – Mar. 31/2016	Birth date/age of patient; sex; location of residence, marital status, date of Manitoba Health coverage, date of coverage end, reason for coverage end (i.e death, emigration etc.)
Medical Claims (Physician Billings)	Apr. 1/1996 – Mar. 31/2016	Services - type of physician (e.g., psychiatrist); dates of services, specific diagnoses (ICD-9 or ICD-10 equivalent)
Hospital Separations Abstracts	Apr. 1/1996 – Mar. 31/2016	Diagnoses (ICD-9 or ICD-10 equivalent), length of stay, admission dates, discharge dates,
Provider Registry/Physician Master File	Apr. 1/1996 – Mar. 31/2016	Physician Age, Sex, Specialty
Social Allowances Management Information Network (SAMIN)	Apr. 1/2001– Mar. 31/2013	Receipt of income assistance
Canadian Government Census	2001, 2006, 2011, 2016	Geographic area-based income (income quintile)

4.2.2) Cohort Inclusion/Exclusion Criteria

Eligible patients were those ≥18 years old with at least 1 prescription dispensation with no preceding dispensations from April 1, 2000 to March 31, 2001 (to avoid prevalent user bias). A minimum 1-year of follow-up from the first prescription as determined by their insurance registry coverage was also required for cohort inclusion.

Eligibility was also based on diagnostic criteria for common anxiety related disorders and/or insomnia based on ICD-9-CM or ICD-10-CA claims, either at outpatient physician visits

or hospitalizations, occurring within a 5-year period prior to the first prescription. The ICD diagnostic criteria chosen are a combination of the definitions from two sources. The first is from a recent report by the Canadian Public Health Association on mental health surveillance [27] which recommends the range of ICD codes to be considered for Mood/Anxiety disorder research. The second source is from the MCHP concept dictionary which listed the various past-case definitions employed in previous research within Manitoba for mood and anxiety disorders.[28–30] Most of the authors cited from this source used similar case-definitions (i.e 1 hospital code or 3 ambulatory codes) and so there was limited rationale to justify straying from already validated case-finding algorithms. As would be expected, there is strong overlap between the ICD codes chosen for the case definition from both sources (Table 4.2). However, because the ICD diagnostic range in this study was more specific to mood and anxiety disorders, the look-back period was set at 5-years to increase the sample size, especially as BZD use for alternative indications was minimized by exclusion criteria thereby improving the expected specificity. Lastly, because reliance on ICD codes is expected (and has been previously shown) to underestimate capture of sleep disorder cases, in addition we also accepted receipt of a Z-Drug as being 'diagnostic' for insomnia as they are indicated solely for this purpose.[31]

Table 4.2 – International Classification for Disease Coding for Mood/Anxiety/Sleep Disorders (Cohort Inclusion)

	Source 1 - CPHA	**Source 2 - MCHP**	**Study Algorithm**
ICD Codes	<u>All Mental Health Disorders:</u> 9-CM: 290-319 10-CA: F00-F99	Mood Disorders: Anxiety Disorders: 300 (ICD-9-CM) or F40-F42	<u>Mood disorders</u>: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) <u>Anxiety disorders:</u> 300 (ICD-9-CM) or F40-F43 (ICD-10-CA) <u>Sleep disorders</u>: 307, 780 or F51, G47 ICD-10-CA)
Case Definition	≥1 hospitalization or outpatient medical claim within 1 year	≥1 hospitalization or ≥1-3 outpatient medical claims within 3-5 years*	≥1 hospitalization or ≥3 outpatient medical claims within 5 years**

**Range of similar definitions between studies from 2000 to 2016*

***The decision to use a 5-year pre-exposure window was based on the fact that all patients received a BZD, which itself increases specificity for anxiety/sleep disorder diagnoses.*

To reduce confounding, we established cohort exclusion criteria that otherwise may have justified long-term use of BZDs in clinical scenarios beyond the scope of general guideline recommendations for anxiety and sleep. Namely, patients were excluded if they had at least one ICD code for a seizure disorder or a cancer or if there was placement in the Manitoba palliative care drug program at any point in the 5 years preceding their first prescription for a BZD (Table 4.3). Where patients became palliative only after ≥1 year after the initial BZD dispensation, their ongoing use of BZD was censored beginning from the date of their placement, but all use prior to their palliation status was retained.

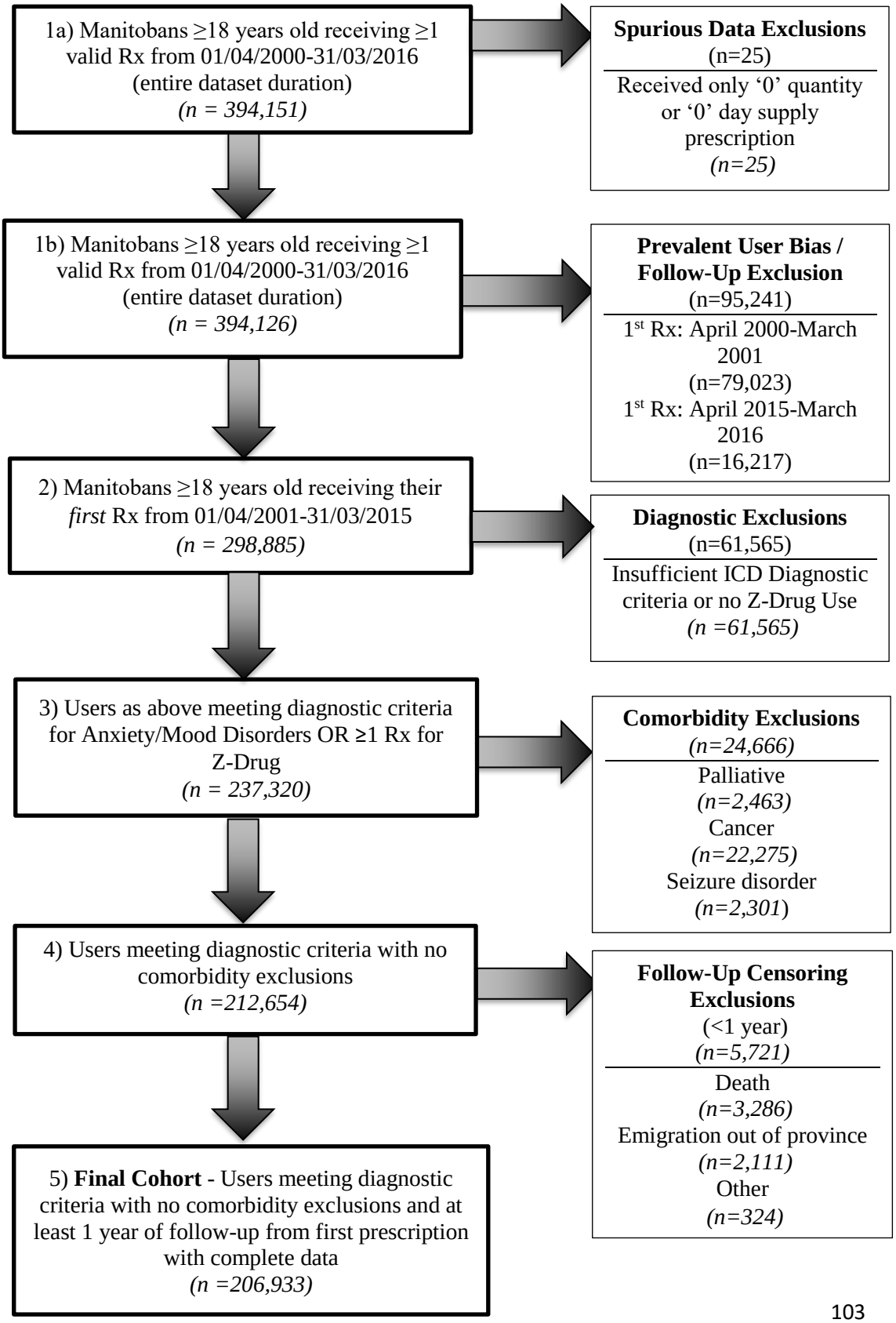
Table 4.3 – International Classification for Disease Coding Algorithms for Epilepsy, Cancer and Palliation (Cohort Exclusion)

	Seizure Disorders	**Cancer and other Neoplasms**	**Palliation**
ICD Codes	9-CM: 345 10-CA: G40	9-CM: 140-165, 170-176,179-195, 200-208 10-CA: C00-C99	N/A*
Case Definition	≥1 hospitalization or ≥3 outpatient medical claim within 5 years before index date	≥1 hospitalization or ≥3 outpatient medical claims within 5 years before index date	Carrier code indicating palliative drug program enrollment in DPIN

**While ICD codes do exist for palliation, the DPIN carrier code '04' is expected to be a reliable indicator of when patients become ill enough that community use of medication is required for symptom management.*

In terms of seizure disorders, clobazam use was excluded entirely from the evaluated drug claims because it is approved only as an adjunctive agent for epilepsy in Canada and so would not be expected to be used in the context we are interested in.

Figure 4.3 – Construction of Cohort by Inclusion/Exclusion Criteria

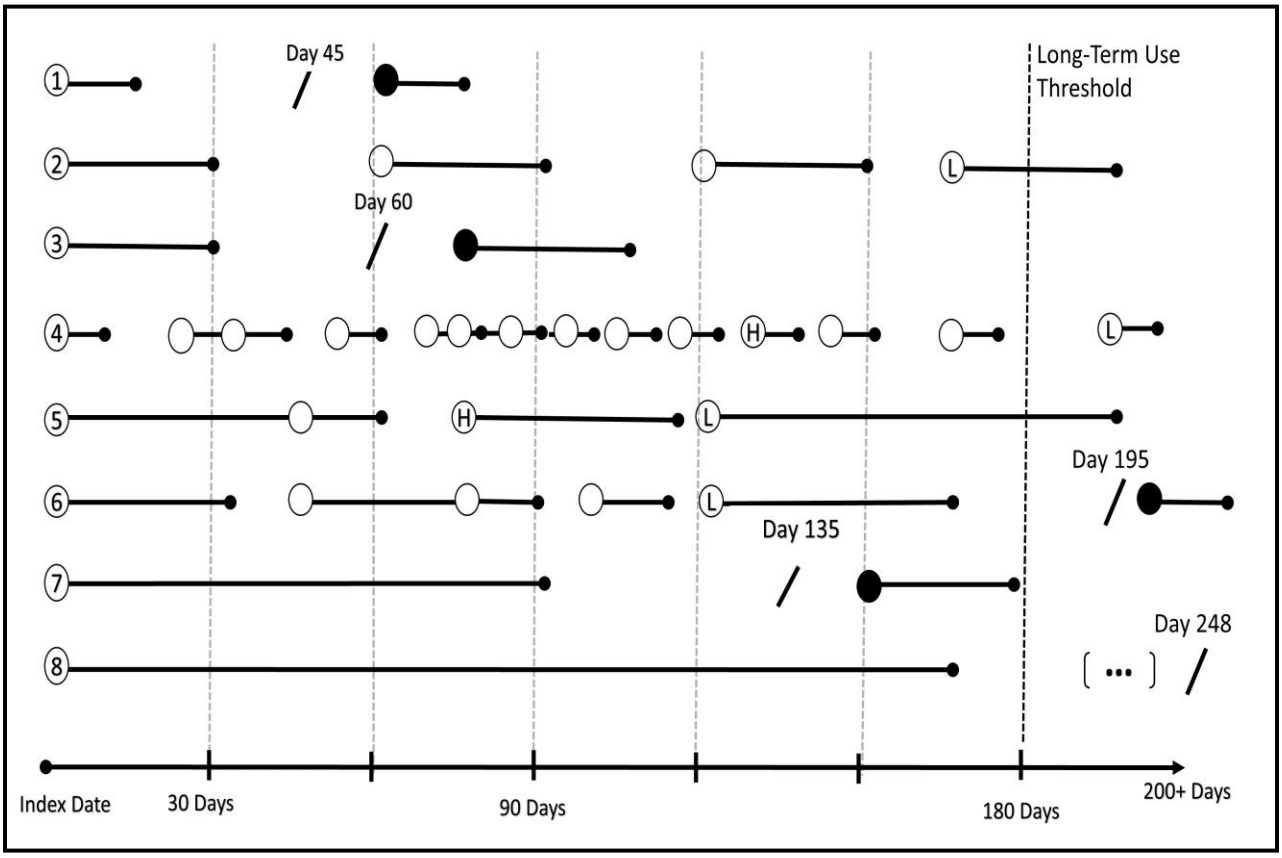


4.2.3) Main Outcome Measures

Patients were followed, from the date of their first prescription, forward in time. BZD 'use episodes' were determined according to consecutive prescription overlap based on dispensation dates and coded day supply. The allowable gap between prescriptions was the greater of either 30 days or 50% of the last prescription day supply after the end-date (dispensation date + day-supply) of the prior prescription. This gap was chosen because we believed it was an acceptable compromise in the absence of prescription use directions because it allowed for clinically significant, but persistent, 'as needed' BZD use while excluding infrequent 'as needed' prescription fills as contributing to 'use episodes'. Examples of BZD use episodes are depicted visually in Figure 4.4 and explained by the accompanying legend on the following page. Episode end dates were the date of the last prescription plus day-supply where use became disqualified according to the allowable gap rule. To account for immeasurable time bias, hospitalization time was assumed to be continuation of BZD use given that in-patient drug use data was unavailable.[32]

Patients were able to have multiple use episodes over the entire study duration; first episode duration and average episode duration were recorded for each user. If patients only had one use episode both of these values were the same. Patients were allowed to switch BZDs without it interrupting their 'use episodes'. As all independent variables (next section) were only measured before or at the time of the first prescription (index date), the logistic regression model (section 4.2.5) was only applied to the first episode use duration, lest significant misclassification occur in the prediction of 'average user duration' due to unaccounted, time-varying, measures.

Figure 4.4 – Determination of Cohort Individuals' BZD Episodic Use Duration



Legend

= Initial Prescription at Start of Use Episode
(# denotes distinct individuals)

= Prescription During Use Episode

= Hospitalization (BZD use assumed to continue)

= Last prescription at end of use episode
(end date is end of prescription day supply)

= Lapse date (episode expiration)*

= Prescription after lapse date
(not part of use episode)

**Lapse date determined as the greater of either 30 days or 50% of the previous prescription day supply*

Long-term use episodes were defined *a priori* as a minimum use duration of 180 days. This was selected on the basis of a concluding recommendation from a previous systematic review of similar studies.[33] This duration is longer than CPG duration recommendations and is of sufficient length, with repeated dosing, for physical dependence to arise in many users.[34]

4.2.4) Independent Variables

Variables used for statistical prediction of long-term use and their associated definitions are provided in Tables 4.4 and 4.5. Variables were conceptually categorized into two groups relating to either characteristics of the patient (Table 4.4) or characteristics of the first clinical encounter preceding initiation of BZD use (Table 4.5). The reader is referred to section 2.1.2 and Figure 4.2 for the purposive reasoning (building from work of previous studies) justifying their inclusion in this study. The majority of variables were assessed at baseline; either within 1-year before the index date, at the index date or up to 6-months past the index date (for psychotropic or opioid prescriptions). For the latter time window, prescription medication use within the early baseline period after BZD use commenced may have influenced future BZD use. For example, an antidepressant started 2 weeks after the first BZD prescription may have been intended, in some situations, as a pharmacotherapy replacement (with the BZD to be discontinued) after the latency period was observed for the former. Where possible, variable definitions were copied exactly or modified from previously validated research measures derived from MCHP data.

During the regression modelling stage, the CCI, RUB, and concurrent prescription use variables were transformed into reduced groups to improve interpretability of the model while minimizing the loss of context. This was done because of violations of distribution at certain levels of the *a priori* variable definition. For example, those who had no healthcare usage (RUB=0) had higher odds-ratios for long-term use than those with low or low-moderate use (RUB=1 or 2) but

less than those with high use (RUB=4 or 5). Furthermore, those who received no opioid prescriptions at baseline had higher odds ratios than those who had received one opioid prescription but lower odds than those who had received two or more prescriptions.

Table 4.4 – Independent 'Patient' Variables for Prediction of Long-Term BZD Use

Baseline Patient Characteristics	**Definition (Variable Type)**	**Measurement Period**
Age	*3 age groups; 18-44, 45-64, 65+ (Ordinal)*	*Index Date*
Sex	*Male or Female (Dichotomous Categorical)*	*Index Date*
Region	*Urban; Winnipeg or Brandon postal-codes Rural; Any other Manitoba postal-code (Dichotomous Categorical)*	*Census Period closest in time to the index date*
Socioeconomic Status	*SEFI-2 score*[35] *(Ordinal Scale)*	*Census Period closest in time to the index date*
Income Assistance	*Record of income assistance (Dichotomous Categorical)*	*Up to 1-year before the Index Date*
Marriage Record	*Record of Marriage (Dichotomous Categorical)*	*Entire available registry period up to the Index Date*
Residential Mobility (i.e frequent mover)	*Average of 1 move every 3 years from beginning of registry coverage to index date (Dichotomous)*	*Entire available registry period up to the Index Date*
Comorbidity Burden	*Charlson Comorbidity Index*[36] *(CCI) Score; 0, 1, 2+ (Ordinal Scale)*	*Up to 1-year before the Index Date*
Healthcare Resource Use	*Johns Hopkins Adjusted Clinical Groups Resource*[37] *Utilization Band (RUB); 1 (Ordinal Scale)*	*Up to 1-year before the Index Date*
Prescription Psychotropic Use (non-BZD)	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*
Prescription Opioid Use	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*

Table 4.5 - Independent 'First-Prescription' Variables for Prediction of Long-Term BZD Use

Characteristics of First Consultation and Subsequent Prescription	Definition	Measurement Period
Fiscal Year Period	*Fiscal year of first prescription Assigned to 3 five-year intervals; 2001-2005, 2006-2010, 2011-2015 (Ordinal)*	*Index Date*
Prescriber	*10 Years or More (Dichotomous)*	*Index Date*
Sex of Prescriber	*Male or Female (Dichotomous)*	*Index Date*
Prescriber Specialty	*General Practitioner, Psychiatry or Other (Categorical)*	*Index Date*

4.2.5) Logistic Regression Model Construction

Reporting criteria developed by Bagley et al. were followed in the approach to logistic regression modelling.[38] A summary detailing the approach towards each criterion is presented in Appendix 3 (Table A3.1).

Univariate analysis was performed first in the form of simple logistic regression. Variables were retained if they were considered essential (i.e sex, age), significant in replicated literature or if the p-value was < 0.25.[39] Odds ratios (both crude and adjusted) were calculated with 95% confidence intervals.

For ordered categorical or continuous variables, odds-ratios and β-coefficients were compared between different models to determine if the assumption of linearity was violated. Likelihood-ratio tests were conducted to confirm which form the variables should take to optimize model prediction and fit ($\alpha = 0.05$). This distinction is represented in the form of the following two equations where X (in this case) represents the *same* variable but in different forms.[40]

$$(1)\ y = \beta_0 + \beta X\ (grouped\ linear\ model)$$

$$(2)\ y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3\ (full\ categorical\ model)$$

Note that, for the full categorical model, the values of X will be either 0 or 1 and so for every level of scale there will be a different β that will apply in calculating the predicted for each observation.

Multicollinearity and effect-measure modification (i.e interaction effects) were assessed when it was suspected that variables were either correlated or non-independent. In order to perform these diagnostics, the binary dependent variable was first substituted for a linear variable (first-episode duration in days) to conduct a multiple *linear* regression. Specifically, collinearity was determined to be a model threat if any correlation coefficient in the independent variable correlation matrix was $\geq |0.8|$ or if any variance inflation factor was unreasonably high ($\geq$10) while the corresponding tolerance factor was miniscule ($\leq$0.1).[41]

The multi-variable model was constructed using a stepwise addition/subtraction method to determine the most parsimonious model for prediction of long-term BZD use. Differences between models in their maximum log-likelihood estimation, likelihood ratios and other goodness-of-fit test statistics enabled model discrimination.[42]

To handle missing data, an 'available case-analysis' approach was employed for each co-variate in simple logistic regression given the fact that missing data was rare and expected to be missing-at-random thus limiting statistical bias of calculated variance.[43] For the multiple logistic regression, 'complete case-analysis' was used because the extent of missing data was too small to justify the need for multiple imputation procedures. The only variable with significant missing data was that of 'prescriber type' (~38,000 missing observations or 17.5% of final sample).

4.2.6) Quantitative Bias Analyses

To assess the robustness of the primary outcome, 6 sensitivity analyses were conducted to determine how the proportion of long-term use changed under differing parameter assumptions.[44] The threshold duration for long-term use was adjusted to values ranging from 60 days to 365 days. Additionally, the episode lapse criteria (i.e 'gap rule') was changed from the maximum of either 30 days or 50% of the previous dispensed day supply to 1) the greater of either 60 days or 50% of the previous dispensed day supply or 2) a 90-day gap from the end date of the previous prescription. While the analysis was not exhaustive for every conceivable combination of these two parameters, the selected values were chosen because they were judged to be representative of how peers in the scientific community may have defined or measured 'long-term use' of BZD.

4.3) Results

4.3.1) Episodic BZD/Z-Drug Use (Main Outcomes)

Overall, the 206,933 cohort members had 931,271 BZD/Z-Drug use-episodes over the 15-year study duration, accounting for a total of 337,341 person-years of BZD/Z-Drug use based upon our use-duration measurement method (Figure 4.4). Over the study period, cohort individuals had a median of 3 and average of 4.5 (95% CI 4.48-4.52) BZD/Z-Drug use episodes, respectively. First-episodes of use were of a mean duration of 87 days (IQR = 10-30 days). For all use-episodes, the average use duration (mean of all individuals mean episode durations) was 164 days (IQR = 15-111 days). Evaluation of long-term use revealed that only 4.51%-9.64% of patients used a BZD for 180-days or longer in their 'first' episode of use. However, the proportion of long-term users increased considerably after averaging for all episodes for each user (range: 15.6%-35.1%). The detailed results for sensitivity analyses on the proportion of long-term use by measurement and operational definition are presented in Table 4.6.

Table 4.6 – Proportion of Long-Term BZD/Z-Drug Use by Differing Parameters and Duration Thresholds

Scenario*	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Cohort
A1**	First-Use Episode ≥ 180 days	30 days or 50% of previous Day Supply	9,327	4.51%
A2	First-Use Episode ≥ 90 days	30 days or 50% of previous Day Supply	13,745	6.64%
A3	First-Use Episode ≥ 60 days	30 days or 50% of previous Day Supply	19,948	9.64%
A4	First-Use Episode ≥ 180 days	60 Days or 50% of previous Day Supply	13,050	6.31%
A5	First-Use Episode ≥ 180 days	90 Days	16,831	8.13%
A6	First-Use Episode ≥ 270 days	90 Days	15,214	7.35%
A7	First-Use Episode ≥ 365 days	90 Days	14,219	6.87%
B1	Mean Episode Duration ≥ 180 days	30 days or 50% of previous Day Supply	38,853	18.78%
B2	Mean Episode Duration ≥ 90 days	30 days or 50% of previous Day Supply	58,442	28.24%
B3	Mean Episode Duration ≥ 60 days	30 days or 50% of previous Day Supply	72,639	35.10%
B4	Mean Episode Duration ≥ 180 days	60 Days or 50% of previous Day Supply	44,593	21.55%
B5	Mean Episode Duration ≥ 180 days	90 Days	50,142	24.23%
B6	User Mean Episode Duration ≥ 270 days	90 Days	39,395	19.04%
B7	User Mean Episode Duration ≥ 365 days	90 Days	32,200	15.56%

*A=First Episode Scenario; B=Mean Episode Duration Scenario

**Primary Scenario Used for Logistic Regression

To evaluate treatment duration for insomnia, a separate *post-hoc* analysis was performed on only Z-Drugs (*n*=110,663). This was done to mitigate confounding from concurrent BZD use and to get a more specific estimate for insomnia treatment duration. The same primary outcomes measures, with sensitivity analysis results, are provided in Table A3.2.

4.3.2) Factors Predicting Long-term First Episode Use

Simple bivariate logistic regression was first performed to calculate crude odds-ratios and slope coefficients. From there, the full, main-effects logistic regression model was generated to evaluate how the odds ratios were adjusted in the presence of other predictors. Both the crude and adjusted odds ratios are presented for BZD+Z-Drugs in Table 4.7. Generally speaking, the statistical magnitude of the odds-ratios decreased as the long-term use definition became shorter in duration.

Significantly important interaction effects included age category*sex and residential mobility*income assistance. The former was handled by combining both age and sex into a single variable (3 x 2 = 6 categories). Other statistically significant interactions of limited importance which were ultimately excluded from the final models were: CCI score*RUB, SEFI*income assistance and SEFI*residential mobility. After multiple models were constructed, the best fitting and most appropriate main-effects multiple logistic regression model and the best fitting interaction-effects multiple logistic regression model were selected (Table 4.8). The Receiver Operator Curve (ROC) generated from the data of the slightly superior, interaction effects model is depicted in Figure 4.5. However, another ROC for model 1 would appear identical as the explanatory power between the two is not practically distinguishable.

Table 4.7 – Statistical Associations between Predictor Variables and Long-term Use of BZD/Z-Drugs

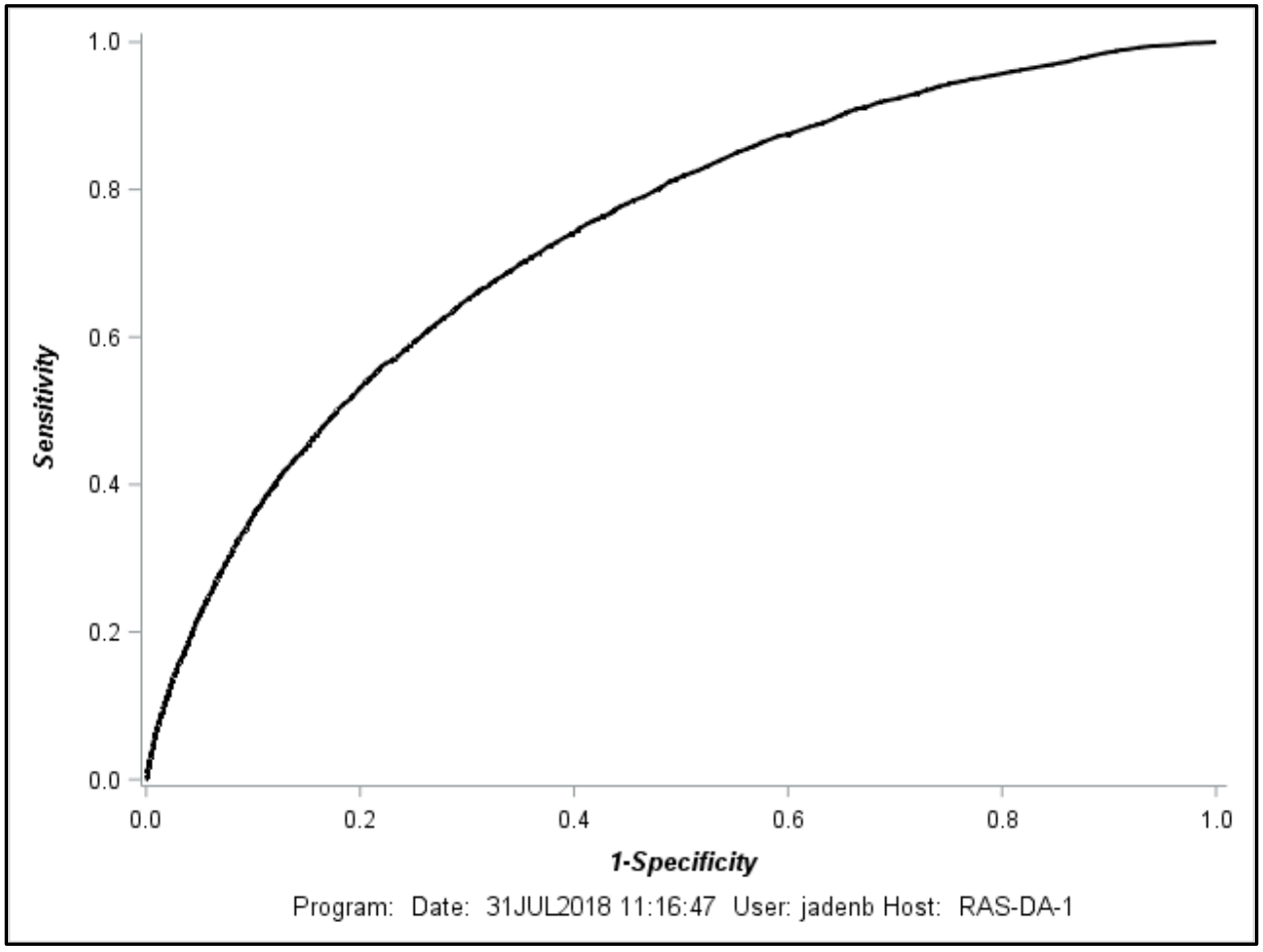
Independent Variable		***Use Duration***					
		≥180 Days		***≥90 Days***		***≥60 Days***	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Male		1.41 (1.35-1.47)	1.33 (1.27-1.39)	1.40 (1.35-1.45)	1.34 (1.29-1.40)	1.30 (1.26-1.34)	1.27 (1.23-1.31)
Age	*18-44*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.82 (1.73-1.92)	2.24 (2.11-2.38)	1.77 (1.70-1.85)	2.00 (1.91-2.10)	1.81 (1.75-1.86)	1.89 (1.82-1.97)
	65+	4.06 (3.86-4.28)	5.15 (4.81-5.52)	3.56 (3.41-3.72)	4.11 (3.88-4.36)	3.34 (3.22-3.47)	3.52 (3.36-3.70)
Rural Residence		1.07 (1.02-1.11)	1.10 (1.04-1.15)	0.97 (0.93-1.00)	0.97 (0.94-1.02)	0.90 (0.87-0.92)	0.92 (0.88-0.95)
High Residential Mobility		1.52 (1.45-1.60)	1.14 (1.08-1.21)	1.35 (1.29-1.40)	1.06 (1.01-1.11)	1.14 (1.10-1.18)	1.01 (0.97-1.06)
Income Assistance		1.46 (1.37-1.55)	1.68 (1.55-1.81)	1.14 (1.08-1.21)	1.35 (1.26-1.45)	0.88 (0.84-0.93)	1.12 (1.06-1.20)
SEFI-2 Score	*<-1*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.08 (1.00-1.15)	0.99 (0.92-1.07)	0.96 (0.91-1.02)	0.91 (0.86-0.97)	0.90 (0.87-0.95)	0.89 (0.85-0.94)
	0 to 1	1.16 (1.07-1.24)	1.02 (0.94-1.10)	0.98 (0.93-1.04)	0.92 (0.87-0.98)	0.87 (0.83-0.91)	0.89 (0.84-0.94)
	>1	1 (0.92-1.09)	0.93 (0.84-1.03)	0.78 (0.73-0.84)	0.80 (0.74-0.87)	0.63 (0.59-0.67)	0.73 (0.68-0.78)
Married		0.91 (0.87-0.95)	0.79 (0.76-0.83)	1.01 (0.98-1.05)	0.89 (0.85-0.92)	1.13 (1.10-1.16)	0.95 (0.92-0.99)
Opioid Use		1.19 (1.14-1.27)	1.16 (1.11-1.22)	1.08 (1.04-1.12)	1.09 (1.05-1.14)	0.99 (0.96-1.02)	1.05 (1.01-1.09)

Independent Variable		***Use Duration***					
		≥180 Days		***≥90 Days***		***≥60 Days***	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Psychotropic Rx Use (non-BZD)		1.82 (1.75-1.90)	1.93 (1.83-2.02)	1.62 (1.56-1.67)	1.75 (1.69-1.83)	1.34 (1.30-1.38)	1.49 (1.44-1.54)
Charlson Comorbidity Index Score	*0*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.44 (1.36-1.51)	1.11 (1.04-1.17)	1.33 (1.27-1.39)	1.08 (1.02-1.13)	1.24 (1.19-1.29)	1.04 (1.00-1.08)
	2+	2.96 (2.79-3.15)	1.43 (1.32-1.55)	2.41 (2.29-2.54)	1.33 (1.24-1.42)	2.01 (1.92-2.11)	1.23 (1.15-1.31)
Resource Utilization Band	*0-3*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4	1.84 (1.73-1.95)	1.15 (1.07-1.23)	1.58 (1.50-1.66)	1.08 (1.01-1.14)	1.37 (1.31-1.43)	1.00 (0.94-1.05)
	5	3.48 (3.24-3.73)	1.46 (1.33-1.60)	2.73 (2.56-2.92)	1.31 (1.20-1.42)	2.21 (2.08-2.35)	1.17 (1.09-1.27)
Male Prescriber of First Prescription		1.07 (1.02-1.12)	1.03 (0.98-1.09)	1.07 (1.02-1.11)	1.04 (0.99-1.09)	1.01 (0.98-1.05)	0.98 (0.94-1.02)
Prescriber Age ≥50 Years		1.08 (1.03-1.12)	0.98 (0.94-1.03)	1.08 (1.04-1.12)	0.99 (0.95-1.03)	1.15 (1.11-1.18)	1.08 (1.04-1.11)
Type of Prescriber of First Prescription	*GP*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	Psychiatrist	2.06 (1.89-2.25)	2.11 (1.93-2.32)	1.85 (1.72-2.00)	1.89 (1.75-2.05)	1.54 (1.44-1.65	1.63 (1.51-1.75)
	Other	1.09 (0.98-1.21)	0.92 (0.82-1.03)	1.07 (0.98-1.17)	0.92 (0.84-1.01)	1.16 (1.07-1.24)	1.03 (0.96-1.11)
Period of First Prescription	*2001-2006*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	2006-2011	1.66 (1.58-1.75)	1.74 (1.64-1.85)	1.58 (1.51-1.65)	1.65 (1.57-1.7)	1.41 (1.36-1.46)	1.48 (1.42-1.54)
	2011-2015	2.93 (2.78-3.08)	2.99 (2.80-3.18)	2.59 (2.48-2.71)	2.71 (2.57-2.8)	1.97 (1.90-2.05)	2.07 (1.98-2.16)

Table 4.8 – Goodness of Fit for Final Logistic Regression Models Predicting Long-Term Use of BZD/Z-Drugs

Model	Model Type	Independent Variables	Likelihood Ratio (higher is better)	C-statistic	Hosmer-Lemeshow Chi-Square Statistic
1	Main-Effects	9 Variables; Age-Sex Category, Period of First Rx, Psychotropic Use, Opioid Use, Income Assistance, Marriage, RUB CCI Score, Residential Mobility	6932 ($p < 0.001$)	0.738	10.78 ($p = 0.215$)
2	Main-Effects + Interaction Effects	10 Variables: All from Model 1 + Residential Mobility*Income Assistance	6945 ($p < 0.001$)	0.739	11.02 ($p = 0.20$)

Figure 4.5 – Receiver Operator Curve for Final Logistic Regression Model



4.4) Discussion

4.4.1) Adherence to CPG Recommendations

Quantification of CPG adherence in general practice remains important to identify areas in need of knowledge translation or continuous quality improvement efforts.[45] Contrary to past rhetoric about an epidemic of inappropriate BZD use[cite], the present study demonstrates that 'first-episode' use appears to be overwhelmingly in accordance with general guideline recommendations in regards to usage duration. Only 4.5% of the main cohort and 7.4% of the Z-Drug cohort were 'long-term' first-episode users according to the best available evidence-based

consensus definition (180 days).[33] Of the five other case-definitions of long-term use (all of which had greater latitude in their parameterization), none resulted in a classification of users exceeding 10% for the main cohort. In general, restricting the analysis to Z-Drug use showed that the frequency of long-term use was higher than that of the main cohort. This may be due to the common and persistent clinical perception among prescribers that these agents are 'safer' than BZD, having a lower propensity for dependency problems. However, strictly in terms of CPG recommendations, the duration of use advocated for Z-Drugs in the treatment of primary insomnia is often shorter (range of ≤4-6 weeks) than that allowed for benzodiazepines in anxiety states (See Appendix Table A1.2). Therefore, these results suggest potentially greater room for practice improvement in the area of sleep medicine.

The proportion of patients who met criteria for 'long-term/chronic' use after accounting for all of their use-episodes was approximately 3.5 times higher than the proportion of patients meeting criteria after only their first episode of use. These results indicate that repeated episodes of BZD/Z-Drug use are associated with progression to longer-term use episodes. Though, the majority of repeat users still only take BZD/Z-Drugs for intermittent, short-term periods. Furthermore, confounding variables such as age and accrued comorbidity over time suggest a legitimate requirement for future longer-term use in some patients. Nonetheless, these results support the observed difficulty in deprescribing once the BZD "train has left the station too many times" because of the complex ethical tension and differences in values between practitioners and patients in terms of how these medications are managed (in addition to the obvious issues of physical dependency).[5,17] Lastly, other clinical considerations such as fear of patient withdrawal,

patient dissatisfaction or interference with another practitioners prescribing decisions likely undermine potential deprescribing efforts that are becoming popularised in the medical literature.[5]

4.4.2) Factors Predicting Long-Term Use of BZD/Z-Drugs

Logistic regression modelling provided valuable insight in characterising a patient population at comparably higher likelihood of long-term 'first episode' BZD/Z-Drug use. Older age, male sex, psychiatrist as prescriber, receipt of income assistance, higher than average healthcare use (RUB), poor physical health (CCI), frequent relocation of home residence, prescription opioid or psychotropic use and receipt of first prescription after 2006 were all predictive of long-term use. These findings were also replicated in the post-hoc analysis restricted to Z-Drug users.

Basic demographic variables have been repeatedly observed to be associated with longer-term BZD/Z-Drug use; older age and female sex being the most frequent characteristics identified from previous studies.[46–57] In contrast to the prevailing literature, but in agreement with a few other studies, we found although females have greater representation in all patterns of BZD use, being male was more specifically predictive of long-term use.[58–60] As with almost all of the previously published studies, older age was strongly associated with long-term BZD/Z-Drug use.[46,48–54,57,59–63] Indeed, this variable was the most robust predictor of long-term use of BZD/Z-Drugs.

With the exception of SEFI, the other socioeconomic variables were modest predictors of long-term use. Income assistance in the year prior to the first prescription was particularly associated with long-term use. There exists other supporting evidence that government financial assistance for disabled or otherwise non-working persons is a factor associated with long-term BZD use.[49,56] When income assistance occurred in conjunction with frequent residence relocation

in the years preceding the first prescription, the odds of long-term use were further compounded. In this case, the need for government financial assistance paired with frequent moving may indicate general instability in a patient's life circumstances. This in turn would explain the continued use of BZD/Z-Drugs, in some patients, as coping medications to diminish external life stressors. Nonetheless, somewhat contradictory to this finding was the absence of any significant trend between SEFI-2 scores and long-term use. Oddly, those patients who were most deprived (SEFI-2 score >1) were slightly less likely to use BZD/Z-Drugs long-term than the least deprived patients. And while SEFI interacted slightly with both income assistance and residential mobility, there was no perceivable trend that offered explanation to reconcile these findings.

Significant associations for marriage and residence geography were observed only for the 180-day threshold, thus making these findings less robust than the other social variables. Rural residence may have a small effect on longer-term BZD/Z-Drug use perhaps because of the relative unavailability of timely scheduled follow-up which may necessitate prescriptions of greater quantity or for longer periods. Another study which also found rural adults to be at higher odds of inappropriate BZD use determined that rural prescribers may be less well-equipped to manage inappropriate BZD prescribing.[64]

Marriage appeared to be somewhat preventive for progression to long-term use and this may fit within the prior explanation about social or general life stability, as positive relationships are known to reduce certain life stressors and improve manageability of mental health.[65] The reverse has also been observed in other studies wherein divorced or widowed patients were statistically more likely to become long-term users.[51,56] Unfortunately, as marriage record data is

subject to major differential misclassification in the general Manitoba adult population (younger couples less likely to register as married), this finding is subject to doubt.

When measured, healthcare consumption and/or the presence of various physical illnesses have been consistent predictors of long-term BZD/Z-Drug use.[48,50,51,60,66] In the present study, as both the CCI and Johns-Hopkins RUB increased, so did the odds of longer-term use. While there was some limited interaction between these two variables, both were independent enough from each other to warrant inclusion of both in the final model. Importantly, both indices have been shown to perform differently in predicting various outcomes; the CCI being better for mortality and the RUB for healthcare utilization.[67,68] We speculate that the positive relationship between these two indices and long-term use may be partially explained by unmeasured 'health' anxiety or associated mental health issues arising secondary to the physical comorbidities. Investigation of this link in future studies may better inform clinicians on the appropriate and inappropriate prescribing of BZD/Z-Drugs for such 'atypical' anxiety states.

A sub-analysis of the higher CCI scores in the long-term user groups shows that this relationship was mainly driven by cardiovascular diseases, diabetes and dementia (though nearly all diagnoses had statistically significant differences). Proportions for these particular diagnoses were 2 to 5 times higher in the long-term user group, with the greatest difference existing for dementia (long-term; 8.5% vs short-term; 1.5%). While these findings are not particularly surprising given the relatively higher proportion of older adults in the long-term user group, the greater degree of BZD/Z-Drug exposure among those patients with dementia is alarming given the causal controversy between dementia and BZD use (see section 2.2.7). This concern is echoed by a previous European study that found higher prevalence rates of long-term use of BZD in

community dwelling elderly with Alzheimer's disease.[55] The higher frequency of cardiovascular diseases in the long-term user group can be partially explained by the higher proportion of disease prevalence in males.[69]

In alignment with previous studies, prescriptions for a psychotropic agent (antidepressant, mood stabiliser, antipsychotic or stimulant) or an opioid during the baseline period was modestly predictive for future long-term use.[49,52,56,58,60] Those having received a non-BZD prescription agent for a psychiatric disorder could reasonably be expected to have had greater disease severity on average than those BZD/Z-Drug users who did not receive such treatment early on. Furthermore, certain antidepressants, namely SSRIs, may stimulate a greater need for a BZD due to their adverse pharmacology resulting in what has been termed "anxiety/jitteriness syndrome".[70] Therefore, undetected angiogenic effects of other psychotropic medications may, in some cases, result in perpetual, but otherwise unwarranted, BZD use.

The only prescriber characteristic predictive of long-term BZD/Z-Drug use was being a psychiatrist. As psychiatrists are expected to see more mentally ill patients of higher disease severity than general practitioners, it is not surprising that patients who received their first BZD/Z-Drug from these prescribers would also be more likely to require longer term treatment with these agents. This conclusion has also been reached by other observational studies assessing long-term use patterns of BZD/Z-Drugs.[46,59,60]

The most surprising finding that is indicative of a significant trend in use of BZD/Z-Drugs in Manitoba over the past 15 years was the time period of first prescription. This trend, showing that as the date of the first prescription became more recent the odds of long-term use increased, is contrary to what may be expected from cumulative knowledge on BZD/Z-Drugs and the long-

standing emphasis on short-term use advised in the general clinical literature.[6,71–73] Nevertheless, this trend may be partially explained by changes in the clinical selection of BZD/Z-Drugs over the course of the 15-year study period (see section 3.3.3) and the corresponding evidence for the popularity of certain agents. In particular, increases in zopiclone and clonazepam over this period have been well noted in previous studies in the Manitoba population.[47,54] In regards to zopiclone, the relative absence of preferred alternative first-line pharmacotherapies in the Manitoba prescriptive armamentarium may have resulted in this agent being frequently defaulted to by many prescribers to treat insomnia. Furthermore, a perception of lesser risk (compared to BZD) coupled with increases in population prevalence of insomnia over time (due to various factors such as population aging, increased technological screen time etc.) may account for why the incidence of long-term use has increased. Lastly, increasing clonazepam usage is interesting in the matter of long-term use insofar as this is the only BZD that has an evidence-based track record for being effective as long-term monotherapy (specifically for PD).[74,75]

4.4.3) Study Strengths and Limitations

This study has a number of strengths that bolster scientific confidence in the results. This study used administrative data sources that were near complete in their coverage of the study population's prescription drug dispensations and healthcare contact. Rigorous application of cohort inclusion and exclusion criteria in a carefully designed incident user longitudinal design limited confounding and bias to the most reasonable extent possible. Multiple sensitivity analyses on the main outcome measure, the duration of BZD/Z-Drug use measurement method and the association between the independent and dependent variables for two cohorts reduced quantitative bias to ensure high-level confidence in the results.

Nonetheless, despite the strengths in the methodological choices and conduct of the study, a number of important limitations should be acknowledged. Firstly, administrative data is prone to some unmeasured misclassification of many variables. For instance, diagnostic criteria for cohort case inclusion and exclusion will differ in their true sensitivity and specificity, regardless of prior validation or case definitions. Hospitalization time was especially likely to be misclassified in terms of user-time because of the absence of drug use data for in-patient stays. Secondly, non-pharmacological interventions such as psychological therapy are not accounted for in administrative data and so it was impossible to determine which patients underwent such treatment before, during or after receiving BZD. Lastly, a number of variables went unexplored. Additional factors that may have provided greater predictive power included the type of BZD first prescribed (and who prescribed it as an interaction term), ethnicity, educational attainment and multiple pharmacy use.

4.5) Conclusion

Although prescribing of BZD/Z-Drugs is mostly in accordance with CPG in the Manitoba population, the odds of long-term BZD use has increased in Manitoba over the past 15 years. For many patients, the likelihood of long-term episodic BZD/Z-Drug use increases each time a BZD/Z-Drug is re-initiated after a sustained period without use. Patients who are male, of older age, are socially or financially deprived, have poor physical health, use opioids or other psychotropic agents and are frequent consumers of healthcare resources are more likely to use BZD/Z-Drugs long-term after their first prescription.

Chapter 4 - References

1. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry*. 2005;66 Suppl 2(suppl 2):28-33.
2. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry*. 2013;28(1):7-20. doi:10.1016/j.eurpsy.2011.11.003.
3. Kroll DS, Nieva HR, Barsky AJ, Linder JA. Benzodiazepines are Prescribed More Frequently to Patients Already at Risk for Benzodiazepine-Related Adverse Events in Primary Care. *J Gen Intern Med*. 2016;31(9):1027-1034. doi:10.1007/s11606-016-3740-0.
4. Smith A, Tett S. Improving the use of benzodiazepines-Is it possible? A non-systematic review of interventions tried in the last 20 years. *BMC Health Serv Res*. 2010;10(1):321. doi:10.1186/1472-6963-10-321.
5. Sirdifield C, Anthierens S, Creupelandt H, Chipchase SY, Christiaens T, Siriwardena AN. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC Fam Pract*. 2013;14:191. doi:10.1186/1471-2296-14-191.
6. Moore N, Pariente A, Bégaud B. Why are benzodiazepines not yet controlled substances? *JAMA Psychiatry*. 2015;72(2):110-111. doi:10.1001/jamapsychiatry.2014.2190.
7. Dobscha SK. Prescription Opioids and Benzodiazepines: Moving Beyond "Just Say No." *Pain Med (United States)*. 2013;14(10):1447-1449. doi:10.1111/pme.12237.
8. López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. *J Anxiety Disord*. 2011;25(4):554-562. doi:10.1016/j.janxdis.2011.01.002.
9. Weintraub M. Consequences of the 1989 New York State Triplicate Benzodiazepine Prescription Regulations. *JAMA J Am Med Assoc*. 1991;266(17):2392. doi:10.1001/jama.1991.03470170080028.
10. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23(1):19-34. doi:10.2165/0023210-200923010-00002.
11. Zhong G, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: A meta-analysis. *PLoS One*. 2015;10(5):1-16. doi:10.1371/journal.pone.0127836.
12. Kim H-B, Myung S-K, Park YC, Park B. Use of benzodiazepine and risk of cancer: A meta-analysis of observational studies. *Int J Cancer*. 2016;00(January):1-13. doi:10.1002/ijc.30443.
13. El-Guebaly N, Sareen J, Stein MB. Are There Guidelines for the Responsible Prescription of Benzodiazepines? *Can J Psychiatry*. 2010;55(11):709-714.
14. Bendtsen P, Hensing G, McKenzie L, Stridsman AK. Prescribing benzodiazepines - A critical incident study of a physician dilemma. *Soc Sci Med*. 1999;49(4):459-467. doi:10.1016/S0277-9536(99)00133-1.
15. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. *Expert Opin Drug Saf*. 2014;13(7):919-934. doi:10.1517/14740338.2014.925444.

16. Hoffmann F. Benefits and risks of benzodiazepines and Z-drugs: comparison of perceptions of GPs and community pharmacists in Germany. *Ger Med Sci*. 2013;11:1-7. doi:10.3205/000178.

17. Sirdifield C, Chipchase SY, Owen S, Siriwardena AN. A Systematic Review and Meta-Synthesis of Patients' Experiences and Perceptions of Seeking and Using Benzodiazepines and Z-Drugs: Towards Safer Prescribing. *Patient*. 2016:1-15. doi:10.1007/s40271-016-0182-z.

18. Bandelow B, Zohar J, Hollander E, Kasper S, Moller H-J. World Federation of Societies of Biological Psychiatry (WfSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Psttraumatic Stress Disorders. *World J Biol Psychiatry*. 2008;9(4):248-312. doi:10.1080/15622970802465807.

19. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-439. doi:10.1177/0269881114525674.

20. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol*. 2010;24(11):1577-1601. doi:10.1177/0269881110379307.

21. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.

22. National Institute for Clinical Excellence. *Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia*.; 2004. https://www.nice.org.uk/guidance/ta77/resources/guidance-on-the-use-of-zaleplon-zolpidem-and-zopiclone-for-the-shortterm-management-of-insomnia-2294763557317.

23. Murphy KD, Sahm LJ, McCarthy S, Byrne S. Benzodiazepine prescribing guideline adherence and misuse potential in Irish minors. *Int J Clin Pharm*. 2015;37(5):749-752. doi:10.1007/s11096-015-0138-8.

24. Textor J, Van Der Zander B, Gilthorpe MS, Likiewicz M, Ellison GTH. Robust causal inference using Directed Acyclic Graphs: the R package "dagitty." *Int J Epidemiol*. 2016;45(6):1887-1894. doi:10.1093/ije/dyw341.

25. Pollmann AS, Murphy AL, Bergman JC, Gardner DM. Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review. *BMC Pharmacol Toxicol*. 2015;16:19. doi:10.1186/s40360-015-0019-8.

26. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6(6):432-442. doi:10.1111/j.1526-4637.2005.00072.x.

27. Public Health Agency of Canada. Government of Canada. *Report from the Canadian Chronic Disease Surveillance System: Mood and Anxiety Disorders in Canada*.; 2016. http://healthycanadians.gc.ca/publications/diseases-conditions-maladies-affections/mental-illness-2015-maladies-mentales/index-eng.php.

28. Manitoba Centre for Health Policy, Department of Community Health Sciences U of M. Concept: Mood and Anxiety Disorders - Measuring Prevalence. http://mchp-

appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1391#a_references. Published 2015. Accessed February 21, 2017.

29. MCHP. University of Manitoba - Manitoba Centre for Health Policy - Concept: Depression - Defining in Administrative Data. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1180. Published 2014. Accessed July 11, 2018.

30. MCHP. University of Manitoba - Manitoba Centre for Health Policy - Glossary: Anxiety /Anxiety States. http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=102267. Published 2010. Accessed July 11, 2018.

31. Chung K-F, Yeung W-F, Ho FY-Y, Yung K-P, Yu Y-M, Kwok C-W. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). *Sleep Med*. 2015;16(4):477-482. doi:10.1016/j.sleep.2014.10.018.

32. Palmaro A, Boucherie Q, Dupouy J, Micallef J, Lapeyre-Mestre M. Immeasurable time bias due to hospitalization in medico-administrative databases: which impact for pharmacoepidemiological studies? *Pharmacoepidemiol Drug Saf*. 2017;26(5):544-553. doi:10.1002/pds.4193.

33. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

34. Lader M. Benzodiazepine harm: How can it be reduced? *Br J Clin Pharmacol*. 2014;77(2):295-301. doi:10.1111/j.1365-2125.2012.04418.x.

35. Chateau D, Metge C, Prior H, Soodeen RA. Learning from the census: The socio-economic factor index (SEFI) and health outcomes in Manitoba. *Can J Public Heal*. 2012;103(SUPPL.2). doi:10.2307/41995685.

36. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433.

37. Reid R, MacWilliam L, Noralou Roos MP, Bogdanovic B, Charlyn Black B. *Measuring Morbidity in Populations : Performance of the Johns Hopkins Adjusted Clinical Group (ACG) Case - Mix Adjustment System in Manitoba*.; 1999.

38. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol*. 2001;54(10):979-985. doi:10.1016/S0895-4356(01)00372-9.

39. Sperandei S. Understanding logistic regression analysis. *Biochem Medica*. 2014;24(1):12-18. doi:10.11613/BM.2014.003.

40. Li A. A Tutorial on PROC LOGISTIC. In: *MWSUG 2013 Conference Proceedings*. Columbus, OH; 2013:1-19.

41. Schreiber-Gregory DN. *Multicollinearity : What Is It , Why Should We Care , and How Can It Be Controlled ?*; 2017. https://analytics.ncsu.edu/sesug/2017/SESUG2017_Paper-160_Final_PDF.pdf.

42. Rasouliyan L, Miller DP. The Logic and Logistics of Logistic Regression. In: *Western Users of SAS Software 2006*. Irvine, CA; 2006:1-14. https://www.lexjansen.com/wuss/2006/analytics/ANL-Rasouliyan.pdf.

43. Bennett D. How can I deal with missing data in my study? *Aust New Zeal J public …*. 2001;25(5):464-469. http://onlinelibrary.wiley.com/doi/10.1111/j.1467-842X.2001.tb00294.x/abstract.

44. Lash TL, Fox MP, Maclehose RF, Maldonado G, Mccandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985. doi:10.1093/ije/dyu149.

45. Vander Schaaf EB, Seashore CJ, Randolph GD. Translating Clinical Guidelines Into Practice: Challenges and Opportunities in a Dynamic Health Care Environment. *N C Med J*. 2015;76(4):230-234. doi:10.18043/ncm.76.4.230.

46. Simon GE, VonKorff M, Barlow W, Pabiniak C, Wagner E. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *J Clin Epidemiol*. 1996;49(9):1067-1073. doi:10.1016/0895-4356(96)00139-4.

47. Alessi-Severini S, Bolton JM, Enns MW, et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. *C open*. 2014;2(4):E208-16. doi:10.9778/cmajo.20130076.

48. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: Examining the impact of increasing research and guideline cautions against long-term use. *Health Policy (New York)*. 2010;97(2-3):122-129. doi:10.1016/j.healthpol.2010.03.008.

49. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-1011. doi:http://dx.doi.org/10.1176/appi.ps.54.7.1006.

50. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BHC. Determinants of chronic benzodiazepine use in the elderly: A longitudinal study. *Br J Clin Pharmacol*. 2008;65(4):593-599. doi:10.1111/j.1365-2125.2007.03060.x.

51. Jorm AF, Grayson DA, Creasey H, Waite L, Broe GA. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health*. 2000;24(1):7-10. doi:10.1111/j.1467-842X.2000.tb00715.x.

52. Sakshaug S, Handal M, Hjellvik V, et al. Long-term Use of Z-Hypnotics and Co-Medication with Benzodiazepines and Opioids. *Basic Clin Pharmacol Toxicol*. 2016. doi:10.1111/bcpt.12684.

53. Kurko T, Saastamoinen LK, Tuulio-Henriksson A, et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf*. 2018;(October 2017):3-6. doi:10.1002/pds.4551.

54. Alessi-severini S, Bolton JM, Enns MW. Sustained Use of Benzodiazepines and Escalation to High Doses in a Canadian Population. *Psychiatr Serv*. 2016;67(9):1012-1018. doi:10.1176/appi.ps.201500380.

55. Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. Long-term use of benzodiazepines and related drugs among community-dwelling individuals with and without Alzheimer's disease. *Int Clin Psychopharmacol*. 2015;30(4):202-208. doi:http://dx.doi.org/10.1097/YIC.0000000000000080.

56. Anderson ABT et al. Long-term use of zopiclone, zolpidem and zaleplon among Danish elderly and the association with sociodemographic factors and use of other drugs. *Pharmacoepidemiol Drug Saf*. 2011;20:378-385. doi:10.1002/pds.

57. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-142. doi:10.1001/jamapsychiatry.2014.1763.

58. Fride Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. *Scand J Prim Health Care*. 2015;33(4):252-259. doi:10.3109/02813432.2015.1117282.

59. Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *Eur J Clin Pharmacol*. 2012;68(3):311-319. doi:10.1007/s00228-011-1124-2.

60. Fang SY, Chen CY, Chang IS, Wu ECH, Chang CM, Lin KM. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: A population-based study. *Drug Alcohol Depend*. 2009;104(1-2):140-146. doi:10.1016/j.drugalcdep.2009.04.017.

61. Isacson D. Long-term benzodiazepine use: Factors of importance and the development of individual use patterns over time - A 13-year follow-up in a Swedish community. *Soc Sci Med*. 1997;44(12):1871-1880. doi:10.1016/S0277-9536(96)00296-1.

62. van Hulten R, Teeuw KB, Bakker A, Leufkens HG. Initial 3-month usage characteristics predict long-term use of benzodiazepines: an 8-year follow-up. *Eur J Clin Pharmacol*. 2003;58:689-694. doi:10.1007/s00228-002-0548-0.

63. Egan M, Moride Y, Wolfson C, Monette J. Long term continuous use of benzodiazepines by older adults in Quebec: Prevalence, incidence and risk factors. *J Am Geriatr Soc*. 2000;48(7):811-816. http://sfx.nelliportaali.fi.libproxy.helsinki.fi/sfxlcl3?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&genre=article&sid=ProQ:ProQ:psycinfo&atitle=Long+term+continuous+use+of+benzodiazepines+by+older+adults+in+Quebec:+Prevalence%252.

64. Mattos MK, Sereika SM, Naples JG, Albert SM. Differences in Benzodiazepine Receptor Agonist Use in Rural and Urban Older Adults. *Drugs - Real World Outcomes*. 2016;3(3):289-296. doi:10.1007/s40801-016-0080-7.

65. Scott KM, Wells JE, Angermeyer M, et al. Gender and the relationship between marital status and first onset of mood, anxiety and substance use disorders. *Psychol Med*. 2010;40(9):1495-1505. doi:10.1017/S0033291709991942.

66. Manthey L, Van Veen T, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: The Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol*. 2011;71(2):263-272. doi:10.1111/j.1365-2125.2010.03818.x.

67. Zielinski A, Kronogard M, Lenhoff H, Halling A. Validation of ACG Case-mix for equitable resource allocation in Swedish primary health care. *BMC Public Health*. 2009;9:347. doi:10.1186/1471-2458-9-347.

68. Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M, Lacaille D. A systematic review identifies valid comorbidity indices derived from administrative health data. *J Clin Epidemiol*. 2015;68(1):3-14. doi:10.1016/j.jclinepi.2014.09.010.

69. Spence JD, Pilote L. Importance of sex and gender in atherosclerosis and cardiovascular disease. *Atherosclerosis*. 2015;241(1):208-210. doi:10.1016/j.atherosclerosis.2015.04.806.

70. Sinclair LI, Christmas DM, Hood SD, et al. Antidepressant-induced jitteriness/anxiety syndrome: Systematic review. *Br J Psychiatry*. 2009;194(6):483-490. doi:10.1192/bjp.bp.107.048371.

71. Lader M. Benzodiazepines revisited-will we ever learn? *Addiction*. 2011;106(12):2086-2109. doi:10.1111/j.1360-0443.2011.03563.x.

72. Stevens JC, Pollack MH. Benzodiazepines in clinical practice: Consideration of their long-term use and alternative agents. *J Clin Psychiatry*. 2005;66(SUPPL. 2):21-27.

73. Janhsen K, Roser P, Hoffmann K. The problems of long-term treatment with benzodiazepines and related substances. *Dtsch Arztebl Int*. 2015;112(1-2):1-7. doi:10.3238/arztebl.2015.0001.

74. Nardi AE, Freire RC, Mochcovitch MD, et al. A randomized, naturalistic, parallel-group study for the long-term treatment of panic disorder with clonazepam or paroxetine. *J Clin Psychopharmacol*. 2012;32(1):120-126. doi:10.1097/JCP.0b013e31823fe4bd.

75. Worthington JJ 3rd, Pollack MH, Otto MW, McLean RY, Moroz G, Rosenbaum JF. Long-term experience with clonazepam in patients with a primary diagnosis of panic disorder. *Psychopharmacol Bull*. 1998;34(2):199-205.

Chapter 5 – Global Discussion and Conclusions

5.1) General Overview

At this stage, we return to the original research questions to guide an overview of the thesis work as a whole (section 1.2):

I) What is already known about the pharmacoepidemiology of benzodiazepines and Z-Drugs in terms of different patterns of use?

Population based usage patterns of BZD/Z-Drugs have been determined globally, nationally and provincially.[1–3] While particular regional utilization patterns are somewhat limited in their generalizability, certain consistent findings contribute to a broader understanding of how these medications are used and by whom. Prevalence of use remains highest in the older adult population and in females especially.[4] Older, long-acting BZDs such as flurazepam, diazepam and chlordiazepoxide (among others) have fallen out of favor while Z-Drugs, clonazepam and intermediate or short-acting BZDs continue to remain popular. Concurrent use of BZDs and opioids remains a safety concern in many jurisdictions.[5] Long-term use of BZD/Z-Drugs does not appear to result in dose escalation overtime for the majority of patients.[6,7] However, higher dose use, abuse and misuse is more frequent among younger persons (especially males) with social complexities.[2,6,7]

II) What is the evidence for each of the various major adverse health outcomes from benzodiazepine / Z-Drug use reported on in the literature?

The evidence for certain safety considerations is incontrovertible for some adverse events and debatable for others. Falls leading to fractures and motor vehicle accidents, both of which result from cognitive and psychomotor impairment, have been well established to the point of

being irrefutable.[8] In contrast, the evidence for emerging harm associations such as dementia, infections, cancer, pancreatitis and respiratory disease state exacerbation is speculative, conflicting and ultimately yet to be proven.[8]

III) What are the relative advantages or disadvantages of each of the various prescription-based methods for measuring the utilization of benzodiazepines / Z-Drugs in large patient populations?

Standard measures of drug utilization such as prevalence, incidence and DDDs are useful to determine and evaluate trends associated with the use of benzodiazepines. Where prevalence and incidence are standard epidemiologic measures that deal with persons and person-time, DDD based measurements offer estimates of total population drug consumption.[9] Although DDD is a standard international unit, the changing preferences of BZDs in regions over time and the variation in the availability of BZDs between countries limits the interpretability of drug utilization study results. Fortunately, the DME, a unit developed on the basis of BZD pharmacologic potency, though imperfect, accounts for the approximate intensity of BZD use in a population.[10,11] The DME-DDD, an integrated metric, retains the DDD as a standard unit while further adjusting for BZD potency to improve the reporting of population pharmacologic exposure (dose intensity & consumption) by offering superior interpretability for comparisons across time and place.[12]

IV) How has the utilization of benzodiazepines / Z-Drugs changed in the Manitoba adult population over the past 15 years?

BZD use saw a gradual increase in total consumption from 2001 to 2011/2012. After 2012, there was a relative decline in consumption and overall pharmacologic exposure to this drug class (Chapter 3). This is largely explained by the provincial wide audit-feedback study, IMRxOVE,

which targeted potentially inappropriate prescribing of these agents.[13] Nevertheless, dose intensity for BZD increased over the 15-year period, explained primarily by increasing clonazepam usage (BZD of higher DME potency). In regards to Z-Drugs (>99% zopiclone), all measures of utilization including consumption, pharmacologic exposure, dose intensity and prevalence increased steadily over the study period (Chapter 3). However, the rate of increase slowed in the last few years of the study perhaps signaling a stabilization of population usage for the future.

V) What factors are associated with the progression to long-term benzodiazepine use in the Manitoba adult population with anxiety and sleep disorders?

Adult patients with anxiety or insomnia who are male, older, socially or financially deprived, have high residential mobility, use opioids or other psychotropic agents, frequently come in contact with the healthcare system and who are of poor physical health, are more likely to use BZD/Z-Drugs long-term after their first prescription (Chapter 4). Additionally, receipt of the first prescription in recent years (post-2006) was associated with increasing odds of long-term 'first-episode' use (Chapter 4).

VI) How does the average duration of benzodiazepine / Z-Drug use in the Manitoba adult population with anxiety and insomnia compare with common recommendations from clinical practice guidelines?

Duration of BZD/Z-Drug use in the Manitoba population is overwhelmingly in accordance with CPG's early on in a patient's treatment course; ~5-10% of users are treated beyond recommended treatment duration for their first episode of use (Chapter 4). On the other hand, repeated treatment courses of BZD/Z-Drug use lead to longer average durations of use overall;

~15.5-35% of patients had treatment courses (median = 3) of average duration that exceeded those advised by CPGs (Chapter 4).

5.2) Conclusions and Future Directions

This thesis work offers important contributions to the subject of BZD pharmacoepidemiology. It is clear that, even after more than 50 years since their introduction to clinical practice, the record is not yet complete on the safety of BZDs. The controversy regarding general patterns of their use will inevitably persist into the foreseeable future, especially given their wide usage and emerging harm associations. In the meantime, as drug utilisation data on BZDs become more routinely evaluated in different parts of the world, superior estimation of pharmacologic exposure, using the simple, proposed DME-DDD methodology, would be expected to improve population use monitoring for the purpose of clinical audit, policy making and knowledge translation of results.

In regards to the Manitoba population, while Z-Drug use and clonazepam use has increased from 2001-2016 (at the expense of other BZD agents), the clinical use of these agents, in terms of dose and patient use duration, is largely in accordance with CPGs. Nevertheless, a number of patient and prescription characteristics may reasonably predict the likelihood of patients becoming long-term users after their first prescription. As many of the results of studies examining long-term use patterns remain somewhat contradictory or non-generalizable, a second systematic review of the available original studies on long-term use should be conducted. This would be expected to more broadly inform clinical practice and prescribing decisions beyond the borders of particular studies.

Chapter 5 References

1. International Narcotics Control Board (INCB). *Techncal Report on Psychotropic Substances - Statistics for 2016*. New York, NY: United Nations; 2018. https://www.incb.org/documents/Psychotropics/technical-publications/2017/Technical_Publication_2017_English_04042018.pdf.

2. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine Use, Misuse, and Harm at the Population Level in Canada: A Comprehensive Narrative Review of Data and Developments Since 1995. *Clin Drug Investig*. 2016;36(7):519-530. doi:10.1007/s40261-016-0397-8.

3. Alessi-Severini S, Bolton JM, Enns MW, et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. *C open*. 2014;2(4):E208-16. doi:10.9778/cmajo.20130076.

4. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

5. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002−2014. *Am J Prev Med*. 2016;51(2):1-10. doi:10.1016/j.amepre.2016.02.014.

6. Alessi-severini S, Bolton JM, Enns MW. Sustained Use of Benzodiazepines and Escalation to High Doses in a Canadian Population. *Psychiatr Serv*. 2016;67(9):1012-1018. doi:10.1176/appi.ps.201500380.

7. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-1011. doi:http://dx.doi.org/10.1176/appi.ps.54.7.1006.

8. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017;17(4):493-507. doi:10.1007/s40268-017-0207-7.

9. Lewandowski CM, Co-investigator N, Lewandowski CM. *World Health Organization. Guidelines for ATC Classification and DDD Assignment 2016*. Vol 1.; 2015. doi:10.1017/CBO9781107415324.004.

10. Ashton H. benzo.org.uk : Benzodiazepine Equivalence Table. http://www.benzo.org.uk/bzequiv.htm. Published 2007. Accessed February 3, 2017.

11. Islam MM, Conigrave KM, Day CA, Nguyen Y, Haber PS. Twenty-year trends in benzodiazepine dispensing in the Australian population. *Intern Med J*. 2014;44(1):57-64. doi:10.1111/imj.12315.

12. Brandt J, Alkkabanni W, Alessi-severini S, Leong C. Translating Benzodiazepine Utilization Data into Meaningful Population Exposure : Integration of Two Metrics for Improved Reporting. *Clin Drug Investig*. 2018. doi:10.1007/s40261-018-0648-y.

13. Chateau D, Enns M, Ekuma O, et al. *Evaluation of the Manitoba IMPRxOVE Program*. Winnipeg, MB; 2015. http://mchp-appserv.cpe.umanitoba.ca/concept//ImproveRx_report_website.pdf.

Appendices

Appendix 1 – Comparison of Clinical Practice Guideline Recommendations for Benzodiazepine and Z-Drug Use

Table A1.1 – Clinical Practice Guidelines Recommendations for Benzodiazepine use in Anxiety Disorders

Practice Guideline	CAGIG[1] (2014)	APA[2] (2009,2004)	NICE[3] (2011, 2013)	WFSBP[4] (2012)	IPAP[5] (2010)	BAP[6] (2014)
Indications Covered	GAD, PD, SAD, PTSD, OCD	PD (2009), PTSD (2004)	GAD, PD (2011) SAD (2013)	GAD, PD, SAD, PTSD, OCD	GAD	GAD, PD, SAD, PTSD, OCD
Treatment Recommendation Evidence Grading/Coding System* ***MA=Meta-analysis RCT=Randomized Controlled Trial**	**Recommendation Grades:** **1** – Large/multiple RCT or MA+ Clinical support for efficacy and safety **2** – Small uncontrolled trial + Clinical support for efficacy and safety **3** – Anecdotal evidence or expert opinion + Clinical support for efficacy and Safety	**Recommendation Grades:** [**I**]-Substantial Clinical Confidence [**II**]-Moderate Clinical Confidence [**III**]-Only on the basis of individual circumstances	**no formal rating/grading assigned directly to recommendations in the guideline.** However, very rigorous and transparent assessment of all examined clinical trials and studies from which recommendations were derived.	**Recommendation Grades:** **1**-Full evidence from Controlled studies AND strong benefit/risk ratio **2**- Same as 1 AND moderate benefit/risk ratio **3**-Limited positive evidence from controlled studies **4**-Uncontrolled studies/Case reports/Expert opinion **5**-Inconsistent results	**Recommendation Grades:** **1**-More than one placebo RCT of ≥30 subjects **2**-One placebo RCT of ≥30 subjects **3**-One or more RCT of <30 subjects **4**-Case reports or open label trials **5**-Consensus reports or expert opinion	**Recommendation Grades**: **A**-MA or placebo RCT **B**- non-Placebo RCT or extrapolated from A **C**- non-experimental descriptive studies or extrapolated from B **D**- Consensus or expert opinion **S**-Standard care

Practice Guideline	**CAGIG (2014)**	**APA (2009,2004)**	**NICE (2011, 2013)**	**WFSBP (2012)**	**IPAP (2010)**	**BAP (2014)**
Indications Covered	GAD, PD, SAD, PTSD, OCD	PD (2009), PTSD (2004)	GAD, PD (2011) SAD (2013)	GAD, PD, SAD, PTSD, OCD	GAD	GAD, PD, SAD, PTSD, OCD
Pharmacologic Therapy Recommendations for Benzodiazepines (recommendation grade)	2nd line maintenance treatment – SAD, PD, GAD (**1**) Not recommended – OCD (**2**) PTSD (**2**, **3**) Temporary co-prescription for some patients beginning AD (**1**)	PD – Appropriate for Maintenance Monotherapy in patients without comorbid depression or Substance Abuse [**I**] Adjunct to anti-depressant for rapid response or breakthrough somatic symptoms [**II**] PTSD – Not currently recommended as monotherapy. May be useful adjunct in select patients for sleep and anxiety [**III**]	1.2.25 - "Do not offer a BDZ for the treatment of GAD in primary or secondary care except as a short-term measure during crises" 1.4.7- "BDZs are associated with inferior outcomes in the long term and should not be prescribed for the treatment of individuals with PD." 1.6.2- "Do not routinely offer anticonvulsants, tricyclic AD, BZD or antipsychotic medication to treat SAD in adults."	2nd line maintenance treatment -PAD **(2)** , GAD **(2)** 3rd line maintenance treatment – SAD **(3)** Not recommended – OCD, PTSD, Comorbid MD **(ungraded)** Temporary co-prescription for some patients beginning Anti-depressants **(ungraded)**	2nd line maintenance treatment-GAD (**1**) If intolerance to 2 AD trials may switch to BZD for maintenance (**5**) For GAD with PD a BZD is a reasonable 1st line choice (**1**) For augmentation if only partial response to first line monotherapy (**5**) Temporary co-prescription for beginning Anti-depressants (**ungraded**)	Adjunctive or acute phase use (**A**) – SAD, PD, GAD Maintenance treatment only if multiple prior failed treatment approaches– SAD (**D**), PD (**S**), GAD (**S**) PD-Consider combining BDZ with CBT as this approach is superior to BDZ alone (**A**)

Practice Guideline	**CAGIG (2014)**	**APA (2009,2004)**	**NICE (2011, 2013)**	**WFSBP (2012)**	**IPAP (2010)**	**BAP (2014)**
Indications Covered	GAD, PD, SAD, PTSD, OCD	PD (2009), PTSD (2004)	GAD, PD (2011) SAD (2013)	GAD, PD, SAD, PTSD, OCD	GAD	GAD, PD, SAD, PTSD, OCD
Specific Duration of Use and Dosing Recommendations for BZD in Pharmacotherapy (recommendation grade)	PD **- <8 weeks** including tapering period starting from initiation of AD (**1**) GAD- **"Short term**" or temporary use whenever possible (**ungraded**)	PD – **4-6 weeks** from initiation of AD (**ungraded**) PD – Regular dosing preferred over "prn" dosing [**II**]	**2-4-week** period cited as appropriate for initial phase of pharmacotherapy (**ungraded**)	All indications- Used "prn" only for short term distress **(ungraded)** All Indications- Used for first few weeks of Antidepressant treatment **(ungraded)** GAD-Only for long-term use when other drug and non-drug treatments have failed **(ungraded)**	**2-3 week** period cited as appropriate for initial phase of pharmacotherapy **(ungraded)** Adequate maintenance trial cited as Diazepam milligram equivalent of 40 mg/day **for 3-4 weeks (ungraded)** Data too limited for certainty of efficacy in continued long-term treatment of BZD in GAD **(ungraded)**	PD- Use for a "**few weeks"** to manage initial side effects of AD (i.e increased anxiety) (**D**) SAD, PD, GAD - acute phase use implicitly defined as <**12 weeks (A**)

Practice Guideline	**CAGIG (2014)**	**APA (2009,2004)**	**NICE (2011, 2013)**	**WFSBP (2012)**	**IPAP (2010)**	**BAP (2014)**
Indications Covered	GAD, PD, SAD, PTSD, OCD	PD (2009), PTSD (2004)	GAD, PD (2011) SAD (2013)	GAD, PD, SAD, PTSD, OCD	GAD	GAD, PD, SAD, PTSD, OCD
Harm Reduction Recommendations Specific to BZD (recommendation grade)	Caution and careful monitoring of use in elderly, cognitively impaired or those with substance abuse issues (**ungraded)** GAD- Adjunctive CBT may assist patients in facilitating dose tapering to discontinuation **(ungraded)**	Warn patients about additive effects of alcohol and in operating machinery or driving [**I**] Caution and monitoring of use in elderly, cognitively impaired or those with substance abuse issues [**I**] Discontinuation should be a gradual tapering of dose over 2-4 months at rates ≤10% of original dose per week. [**I**] CBT may also be helpful. [**I**]	Refers reader to British National Formulary (BNF) for prescribing management of benzodiazepines BNF states: "BZD withdrawal should be flexible and carried out at a reduction rate that is tolerable for the patient. The rate should depend on the initial dose of BZD, duration of use, and the clinical response. Short-term users of BZDs can usually taper off within 2–4 weeks. However, long-term users should be withdrawn over a much longer period of several months or more."	Generally, exclude or treat carefully those with substance use disorders. **(ungraded)** BDZ are not preferable in elderly due to cognitive impairment and risk of paradoxical excitatory reactions **(ungraded)** Caution use in breastfeeding and monitor infant for somnolence **(ungraded)**	Avoid or caution use in aggressiveness or impulsivity as these traits can be worsened by BZD (**4**) Avoid in patients with alcohol problems unless for detoxification (**ungraded**) Hostility or suspected Substance or BZD abuse should warrant dose reduction or tapering to discontinuation (**ungraded**) Use is generally not advisable in elderly, pregnant or breastfeeding (**ungraded**)	BZD may cause excess sedation and cognitive impairment in short-term and long-term use but it is difficult to determine those at risk of long-term use (**D**) GAD, PD, SAD – Recommendations for all pharmacologic maintenance treatment include: warning patients about abrupt discontinuation syndrome (**S**) and when stopping treatment reduce dose gradually over time (**A**) with a minimum tapering period of 12 weeks in the absence of other evidence (**D**)

Table A1.2 – Clinical Practice Guideline Recommendations for Benzodiazepines and Z-Drugs Use in Insomnia

Practice Guideline	**ACP[7] (2016)**	**AASM[8] (2016)**	**NICE[9] (2004)**	**BAP[10] (2010)**	**TOP[11] (2015)**
Treatment Recommendation Evidence Grading/Coding System* *MA=Meta-analysis RCT=Randomized Controlled Trial	GRADE adopted criteria for quality of evidence ratings: **High** **Moderate** **Low** **Insufficient** Strength of Recommendation: **Strong** **Weak**	-**Standard**: Generally accepted strategy with highest quality of evidence -**Guideline:** Moderate degree of clinical certainty. Moderate quality of evidence or consensus on lower quality evidence. -**Option:** Insufficient or inconclusive evidence. Mixed expert opinion. -**Consensus:** **S**hared judgement of guideline committee.	**no formal rating/grading assigned directly to recommendations in the guideline.** However, rigorous and transparent assessment of all examined clinical trials and studies from which recommendations were derived. -Only brief guideline on Z-Hypnotic use and NOT insomnia or sleep disorders in general	**Recommendation Grades**: **A**-MA or placebo RCT **B**- non-Placebo RCT **C**- non-experimental descriptive studies **D**- Consensus or expert opinion **S**-Standard care **Evidence Levels:** **Ia**: meta-analysis of randomized controlled trials **Ib**: ≥1 randomized controlled trial **IIa**: ≥1 controlled study without randomization **IIb:** ≥1 other type of quasi-experimental study **III:** evidence from non-experimental descriptive studies, **IV**: committee reports or expert opinion	**no formal rating/grading assigned directly to recommendations in the guideline.**

Practice Guideline	ACP (2016)	AASM (2008)	NICE (2004)	BAP (2010)	TOP (2015)
Pharmacologic Therapy Recommendations for BZDs/Z-Drugs (recommendation grade)	-Any sleep-aid medication should only be considered after an unsuccessful adequate trial of CBT **(Weak recommendation, Low quality evidence)** -benzodiazepines for insomnia treatment **(Insufficient evidence)** -Z-Drugs for insomnia treatment **(Low to Moderate quality evidence)**	- "Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible" **(Consensus)** -Short to intermediate acting Benzodiazepine receptor agonists or Ramelteon are first line agents for primary insomnia **(Consensus)**	1.1- "When, after due consideration of the use of nonpharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it is recommended that Z-hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications."	-CBT is a first line treatment choice for chronic insomnia **(A)** but Z-Drugs and short-acting benzodiazepines are efficacious for insomnia **(Ia)** -Treatment up to 1-year duration with Z-Drugs is not guaranteed to result in dependence **(Ib)**	-Initial treatment should be 1st line agent (Zopiclone or Temazepam) either in conjunction with CBT or preferably after an adequate unsuccessful trial of CBT. -Role of pharmacotherapy should always be adjunctive to behavioral and environmental interventions.

Practice Guideline	ACP (2016)	AASM (2008)	NICE (2004)	BAP (2010)	TOP (2015)
Specific Duration of Use and Dosing Recommendations for Benzodiazepines/Z-Drugs in Insomnia (recommendation grade)	-Reference to FDA approval of 4-5 week treatment duration **(Ungraded)** -Reference to FDA recommendation for reassessment after 7-10 days if no response **(Ungraded)** -Benefit-risk balance with long-term use in chronic insomnia **(Insufficient evidence)**	-Long-term use on a nightly, intermittent or as needed basis, with regular monitoring may be appropriate for refractory or comorbid insomnia in select patients **(Consensus)**	3.1-3.4-Reference to Summary of Product Characteristics (Official Monographs) state maximum durations of; 2 weeks (Zaleplon), 4 weeks (Zolpidem) and 4 weeks (Zopiclone)	-Short term Z-Hypnotic use for 3-7 days if insomnia is transient or expected to resolve according to acute life circumstances **(Ungraded)** -If insomnia is not expected to resolve according to acute stressor use Z-Hypnotic no longer than 4 weeks before reassessment **(Ungraded)**	-Short-term use is recommended not to exceed 7-14 days and this strategy may be used repeatedly during acute exacerbations of chronic insomnia where behavioral measures are temporarily failing -Intermittent use at 2-3 nights per week on a scheduled or on an as needed basis may be appropriate for acute or chronic insomnia.

Practice Guideline	ACP (2016)	AASM (2008)	NICE (2004)	BAP (2010)	TOP (2015)
Harm Reduction Recommendations Specific to Benzodiazepines/Z-Drugs (recommendation grade)	-Reference to FDA recommendation to use lower doses in women and elderly **(Ungraded)**	-Use lowest effective maintenance dose and attempt tapering whenever clinically appropriate **(Consensus)**	None specifically provided. Implication is to follow official product directions and avoid off-label use.	-Use only as clinically indicated **(A)** and when attempting to discontinue, try intermittent use with stopping at regular intervals every 3-6 months depending on clinical circumstances **(D)** -"CBT during taper improves outcomes" **(A)** - "Intermittent dosing may further reduce the risk of dependence and tolerance" **(Ib)**	-"Never exceed the recommended dose" -"[For new patients] always provide quantity limited prescriptions and no refills – this will motivate the patient to return for follow-up" -Schedule follow-up with chronic insomnia patients every 3-4 months for refills and maintain a stable dose -Tapering of Hypnotic should be gradual over 2-6 weeks but a duration of up to 1 year may be needed in exceptional situations

Appendix 2 – Aggregate Utilisation Data on BZD and Z-Drugs in Manitoba from 2001-2016

Table A2.1 – Annualized Age-Sex Utilization Statistics on BZD/Z-Drugs in Manitoba (2001-2016)

Age-Sex	Fiscal Year	Population	Users	Prescription Count	Treatment Days	Total DDDs	Total DMEs	DME Daily Dose	Prevalence (%)	DDD/1000 Persons/Day	DME-DDD/1000 Persons/Day
Female, 18-64	2000-2001	351783	33071	191470	5534051	4626141	76891527	13.9	9.4	36.0	59.9
Female, 65+	2000-2001	90846	20352	121515	4800774	3265933	41390630	8.6	22.4	98.5	124.8
Male, 18-64	2000-2001	352273	17509	111643	3065308	2934183	49448348	16.1	5.0	22.8	38.5
Male, 65+	2000-2001	66337	8600	50182	1981154	1538764	19129584	9.7	13.0	63.6	79.0
Female, 18-64	2001-2002	353781	38689	211273	6011105	5018941	83765319	13.9	10.9	38.9	64.9
Female, 65+	2001-2002	90885	23620	136141	5242206	3563269	45413423	8.7	26.0	107.4	136.9
Male, 18-64	2001-2002	353852	21808	129048	3415100	3241114	54890063	16.1	6.2	25.1	42.5
Male, 65+	2001-2002	66589	10920	58719	2274191	1744472	21531908	9.5	16.4	71.8	88.6
Female, 18-64	2002-2003	356511	40059	228773	6427161	5399388	91846444	14.3	11.2	41.5	70.6
Female, 65+	2002-2003	90991	24030	143963	5386069	3772797	48255458	9.0	26.4	113.6	145.3
Male, 18-64	2002-2003	357059	22671	140196	3679420	3547796	60758587	16.5	6.3	27.2	46.6
Male, 65+	2002-2003	66883	10996	61905	2362607	1817710	22908777	9.7	16.4	74.5	93.8
Female, 18-64	2003-2004	360325	41226	240427	6879230	5819702	99876747	14.5	11.4	44.3	75.9
Female, 65+	2003-2004	91196	24322	148507	5536673	3850296	49376209	8.9	26.7	115.7	148.3
Male, 18-64	2003-2004	360580	23146	148740	3954286	3858451	65857736	16.7	6.4	29.3	50.0
Male, 65+	2003-2004	67310	11145	63092	2401057	1883042	23813448	9.9	16.6	76.6	96.9

Age-Sex	Fiscal Year	Population	Users	Prescription Count	Treatment Days	Total DDDs	Total DMEs	DME Daily Dose	Prevalence (%)	DDD/1000 Persons/Day	DME-DDD/1000 Persons/Day
Female, 18-64	2004-2005	363693	42215	254977	7328560	6259280	106396394	14.5	11.6	47.2	80.1
Female, 65+	2004-2005	91306	24201	151465	5650775	3915984	52265478	9.2	26.5	117.5	156.8
Male, 18-64	2004-2005	363476	23811	158602	4249826	4227969	71085853	16.7	6.6	31.9	53.6
Male, 65+	2004-2005	67666	11031	64491	2466980	1928194	24973054	10.1	16.3	78.1	101.1
Female, 18-64	2005-2006	365829	43605	266466	7623064	6499492	110135201	14.4	11.9	48.7	82.5
Female, 65+	2005-2006	91718	24309	162374	5849017	4029767	52235519	8.9	26.5	120.4	156.0
Male, 18-64	2005-2006	365678	24577	169720	4450836	4360541	74506982	16.7	6.7	32.7	55.8
Male, 65+	2005-2006	68410	11221	68637	2584008	2023744	26049123	10.1	16.4	81.0	104.3
Female, 18-64	2006-2007	368396	44403	277968	7869799	6750565	114821857	14.6	12.1	50.2	85.4
Female, 65+	2006-2007	92212	24491	170087	6136411	4167992	54119521	8.8	26.6	123.8	160.8
Male, 18-64	2006-2007	367992	25037	179489	4568189	4474277	77353491	16.9	6.8	33.3	57.6
Male, 65+	2006-2007	69255	11370	71201	2666704	2094927	26818194	10.1	16.4	82.9	106.1
Female, 18-64	2007-2008	373757	46078	297656	8346175	7290789	122860292	14.7	12.3	53.4	90.1
Female, 65+	2007-2008	93374	24741	184027	6017436	4284494	55796981	9.3	26.5	125.7	163.7
Male, 18-64	2007-2008	372452	26143	191962	4870178	4798764	82232770	16.9	7.0	35.3	60.5
Male, 65+	2007-2008	70527	11445	74587	2644479	2149457	27552704	10.4	16.2	83.5	107.0
Female, 18-64	2008-2009	377922	47327	309479	8728908	7749164	129555213	14.8	12.5	56.2	93.9
Female, 65+	2008-2009	94439	25055	198345	6140473	4443513	57927038	9.4	26.5	128.9	168.0
Male, 18-64	2008-2009	376828	27230	197641	5130540	5110060	86615465	16.9	7.2	37.2	63.0

Age-Sex	Fiscal Year	Population	Users	Prescription Count	Treatment Days	Total DDDs	Total DMEs	DME Daily Dose	Prevalence (%)	DDD/1000 Persons/Day	DME-DDD/1000 Persons/Day
Male, 65+	2008-2009	71992	11744	80428	2722918	2219035	28606744	10.5	16.3	84.4	108.9
Female, 18-64	2009-2010	384061	49471	333342	9325819	8503695	139246293	14.9	12.9	60.7	99.3
Female, 65+	2009-2010	95647	25462	202905	6262721	4827117	62583913	10.0	26.6	138.3	179.3
Male, 18-64	2009-2010	383334	28585	215672	5548864	5609391	92336342	16.6	7.5	40.1	66.0
Male, 65+	2009-2010	73739	12022	84247	2831228	2375877	30987795	10.9	16.3	88.3	115.1
Female, 18-64	2010-2011	390916	50734	368247	9880290	9218232	148079369	15.0	13.0	64.6	103.8
Female, 65+	2010-2011	96711	25877	208762	6339675	5032954	65058584	10.3	26.8	142.6	184.3
Male, 18-64	2010-2011	389951	29525	237913	5890024	6090051	97766316	16.6	7.6	42.8	68.7
Male, 65+	2010-2011	75411	12460	87827	2905697	2459990	32206357	11.1	16.5	89.4	117.0
Female, 18-64	2011-2012	396628	52031	405650	10353553	9994062	155505928	15.0	13.1	69.0	107.4
Female, 65+	2011-2012	98696	26195	215690	6484651	4971987	64027634	9.9	26.5	138.0	177.7
Male, 18-64	2011-2012	396465	30429	270196	6263703	6779729	103907795	16.6	7.7	46.9	71.8
Male, 65+	2011-2012	77802	12781	92073	3010429	2552565	32963891	10.9	16.4	89.9	116.1
Female, 18-64	2012-2013	402783	51195	401214	10191217	9983735	154139503	15.1	12.7	67.9	104.8
Female, 65+	2012-2013	101513	26219	212740	6414679	4852975	62696929	9.8	25.8	131.0	169.2
Male, 18-64	2012-2013	403646	30360	277030	6265512	6882862	104358797	16.7	7.5	46.7	70.8
Male, 65+	2012-2013	80859	13030	94538	3058879	2620681	33628320	11.0	16.1	88.8	113.9
Female, 18-64	2013-2014	407735	51271	393276	9842898	9248682	147648757	15.0	12.6	62.1	99.2
Female, 65+	2013-2014	104241	26497	215718	6526592	4970252	64393358	9.9	25.4	130.6	169.2

Age-Sex	Fiscal Year	Population	Users	Prescription Count	Treatment Days	Total DDDs	Total DMEs	DME Daily Dose	Prevalence (%)	DDD/1000 Persons/Day	DME-DDD/1000 Persons/Day
Male, 18-64	2013-2014	409796	30203	270672	6000779	6291214	99863124	16.6	7.4	42.1	66.8
Male, 65+	2013-2014	83705	13375	96454	3134556	2703620	34930942	11.1	16.0	88.5	114.3
Female, 18-64	2014-2015	411618	51128	396393	9727818	8863112	144079878	14.8	12.4	59.0	95.9
Female, 65+	2014-2015	106514	26771	219587	6548288	5018549	65766034	10.0	25.1	129.1	169.2
Male, 18-64	2014-2015	414365	30464	276508	5997597	6091574	98662227	16.5	7.4	40.3	65.2
Male, 65+	2014-2015	86093	13640	100776	3193466	2756221	35536746	11.1	15.8	87.7	113.1
Female, 18-64	2015-2016	414809	51154	400797	9575476	8544840	141396558	14.8	12.3	56.4	93.4
Female, 65+	2015-2016	109000	26680	219367	6499215	4929090	64918409	10.0	24.5	123.9	163.2
Male, 18-64	2015-2016	418113	30743	288168	5999609	5944908	97711549	16.3	7.4	39.0	64.0
Male, 65+	2015-2016	88614	13590	100903	3181156	2739651	35521959	11.2	15.3	84.7	109.8

Table A2.2 – Annualized Drug Class Utilization Statistics on BZD/Z-Drugs in Manitoba (2001-2016)

Class	Fiscal Year	Population	Users	Treatment Days	Total DDD	Total DME-DDD	DME Daily Dose	DDD/1000 Persons/Day	DME/1000 Persons/Day
BDZ	2000-2001	861239	68987	12830813	9802463	21943892	17.1	31.2	69.8
Combined	2000-2001	861239	79205	15400092	12378382	23230578	15.1	39.4	73.9
Z-Drug	2000-2001	861239	17522	2569279	2575918	1286686	5.0	8.2	4.1
BDZ	2001-2002	865107	80297	13793557	10415779	23691898	17.2	33.0	75.0
Combined	2001-2002	865107	94431	16949957	13575124	25270019	14.9	43.0	80.0
Z-Drug	2001-2002	865107	22587	3156400	3159345	1578121	5.0	10.0	5.0
BDZ	2002-2003	871444	81792	14260198	10880852	25294351	17.7	34.2	79.5
Combined	2002-2003	871444	97169	17861901	14545010	27124628	15.2	45.7	85.3
Z-Drug	2002-2003	871444	24473	3601703	3664158	1830277	5.1	11.5	5.8
BDZ	2003-2004	879411	82117	14645862	11164966	26439716	18.1	34.8	82.4
Combined	2003-2004	879411	99188	18778142	15418365	28564318	15.2	48.0	89.0
Z-Drug	2003-2004	879411	26949	4132280	4253400	2124602	5.1	13.3	6.6
BDZ	2004-2005	886141	82341	15088299	11582782	27831307	18.4	35.8	86.0
Combined	2004-2005	886141	100648	19704058	16338388	30206759	15.3	50.5	93.4
Z-Drug	2004-2005	886141	28595	4615759	4755606	2375452	5.1	14.7	7.3

Class	Fiscal Year	Population	Users	Treatment Days	Total DDD	Total DME-DDD	DME Daily Dose	DDD/1000 Persons/Day	DME/1000 Persons/Day
BDZ	2005-2006	891635	82735	15349107	11570306	28159289	18.3	35.6	86.5
Combined	2005-2006	891635	102978	20513319	16918894	30830939	15.0	52.0	94.7
Z-Drug	2005-2006	891635	31302	5164212	5348588	2671650	5.2	16.4	8.2
BDZ	2006-2007	897855	82169	15364893	11476444	28462031	18.5	35.0	86.8
Combined	2006-2007	897855	104544	21246386	17492072	31466854	14.8	53.4	96.0
Z-Drug	2006-2007	897855	34288	5881493	6015628	3004824	5.1	18.4	9.2
BDZ	2007-2008	910110	83541	15566186	11830944	29596306	19.0	35.6	89.1
Combined	2007-2008	910110	107568	21885241	18529446	32942209	15.1	55.8	99.2
Z-Drug	2007-2008	910110	36291	6319055	6698502	3345902	5.3	20.2	10.1
BDZ	2008-2009	921181	84400	15838864	12172134	30591921	19.3	36.2	91.0
Combined	2008-2009	921181	110475	22729944	19527484	34265918	15.1	58.1	101.9
Z-Drug	2008-2009	921181	39074	6891080	7355350	3673997	5.3	21.9	10.9
BDZ	2009-2010	936781	86668	16468014	13248413	32933286	20.0	38.7	96.3
Combined	2009-2010	936781	114637	23973878	21321012	36965549	15.4	62.4	108.1
Z-Drug	2009-2010	936781	41569	7505864	8072600	4032263	5.4	23.6	11.8
BDZ	2010-2011	952989	87720	16931697	14037576	34762260	20.5	40.4	99.9
Combined	2010-2011	952989	117650	25020770	22805601	39141888	15.6	65.6	112.5

Class	Fiscal Year	Population	Users	Treatment Days	Total DDD	Total DME-DDD	DME Daily Dose	DDD/1000 Persons/Day	DME/1000 Persons/Day
Z-Drug	2010-2011	952989	43890	8089073	8768025	4379629	5.4	25.2	12.6
BDZ	2011-2012	969591	88297	17413137	14819867	35827526	20.6	41.9	101.2
Combined	2011-2012	969591	120242	26117466	24303779	40564740	15.5	68.7	114.6
Z-Drug	2011-2012	969591	46296	8704329	9483912	4737215	5.4	26.8	13.4
BDZ	2012-2013	988801	86962	17067366	14616200	35355341	20.7	40.5	98.0
Combined	2012-2013	988801	119649	25934160	24344214	40214496	15.5	67.5	111.4
Z-Drug	2012-2013	988801	46650	8866794	9728015	4859155	5.5	27.0	13.5
BDZ	2013-2014	1005477	86413	16214848	12975449	33183461	20.5	35.4	90.4
Combined	2013-2014	1005477	120167	25507927	23216197	38298738	15.0	63.3	104.4
Z-Drug	2013-2014	1005477	47918	9293079	10240748	5115277	5.5	27.9	13.9
BDZ	2014-2015	1018590	85565	15747168	12033845	31856716	20.2	32.4	85.7
Combined	2014-2015	1018590	120822	25470366	22731807	37200383	14.6	61.1	100.1
Z-Drug	2014-2015	1018590	49593	9723198	10697962	5343667	5.5	28.8	14.4
BDZ	2015-2016	1030536	85045	15354748	11403907	30927314	20.1	30.3	82.2
Combined	2015-2016	1030536	121012	25258858	22161098	36300576	14.4	58.9	96.5
Z-Drug	2015-2016	1030536	49952	9904110	10757191	5373262	5.4	28.6	14.3

Table A2.3 – Annualized Drug Utilization Statistics by Agent for BZD/Z-Drugs in Manitoba (2001-2016)

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Clonazepam	2000-2001	861239	68092	1914383	3077706	1.61	61554110	1.22	19.58
Diazepam	2000-2001	861239	47679	1440030	15968133	11.09	15968133	5.08	5.08
Chlordiazepoxide	2000-2001	861239	4465	121426	3957750	32.59	1583100	0.42	0.50
Oxazepam	2000-2001	861239	12851	491978	13910413	28.27	6955206	0.89	2.21
Potassium Clorazepate	2000-2001	861239	1323	52670	821651	15.60	547220	0.13	0.17
Lorazepam	2000-2001	861239	154138	5145954	8089591	1.57	80895905	10.29	25.73
Bromazepam	2000-2001	861239	9105	327277	2492612	7.62	4985223	0.79	1.59
Clobazam	2000-2001	861239	2876	84885	2033540	23.96	1016770	0.32	0.32
Alprazolam	2000-2001	861239	37757	1160502	1142863	0.98	22857255	3.64	7.27
Flurazepam	2000-2001	861239	6822	265990	7029435	26.43	2340802	0.75	0.74
Nitrazepam	2000-2001	861239	3887	139810	1286735	9.20	1286735	0.82	0.41
Triazolam	2000-2001	861239	9965	374125	101788	0.27	2035760	1.30	0.65
Temazepam	2000-2001	861239	41799	1311783	34825410	26.55	17412705	5.54	5.54
Zopiclone	2000-2001	861239	73468	2538838	19102023	7.52	12721947	8.10	4.05
Zaleplon	2000-2001	861239	1391	30441	289820	9.52	144910	0.09	0.05

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000 Person/ Day	DME-DDD /1000 Persons/ Day
Clonazepam	2001-2002	865107	79463	2217016	3448985	1.56	68979704	1.37	21.85
Diazepam	2001-2002	865107	50135	1446431	16198687	11.20	16198687	5.13	5.13
Chlordiazepoxide	2001-2002	865107	4328	117856	3812395	32.35	1524958	0.40	0.48
Oxazepam	2001-2002	865107	13112	499740	14035240	28.09	7017620	0.89	2.22
Potassium Clorazepate	2001-2002	865107	1247	48855	766658	15.69	510594	0.12	0.16
Lorazepam	2001-2002	865107	173623	5658844	8712980	1.54	87129800	11.04	27.59
Bromazepam	2001-2002	865107	9336	334909	2502008	7.47	5004015	0.79	1.58
Clobazam	2001-2002	865107	2958	88705	2109120	23.78	1054560	0.33	0.33
Alprazolam	2001-2002	865107	40091	1198037	1196605	1.00	23932100	3.79	7.58
Flurazepam	2001-2002	865107	6659	256272	7473375	29.16	2488634	0.79	0.79
Nitrazepam	2001-2002	865107	4115	138581	1293885	9.34	1293885	0.82	0.41
Triazolam	2001-2002	865107	9733	357176	97442	0.27	1948840	1.23	0.62
Temazepam	2001-2002	865107	46181	1431135	39671160	27.72	19835580	6.28	6.28
Zopiclone	2001-2002	865107	91920	3096347	23275276	7.52	15501334	9.83	4.91
Zaleplon	2001-2002	865107	2557	60053	559750	9.32	279875	0.18	0.09
Clonazepam	2002-2003	871444	88688	2469548	3919519	1.59	78390370	1.54	24.65

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Diazepam	2002-2003	871444	52373	1429282	16805254	11.76	16805254	5.28	5.28
Chlordiazepoxide	2002-2003	871444	3909	114763	3297825	28.74	1319130	0.35	0.41
Oxazepam	2002-2003	871444	13314	478360	14203535	29.69	7101768	0.89	2.23
Potassium Clorazepate	2002-2003	871444	1211	46533	726893	15.62	484110	0.11	0.15
Lorazepam	2002-2003	871444	183889	5872448	9074829	1.55	90748293	11.41	28.53
Bromazepam	2002-2003	871444	9029	327010	2463845	7.53	4927689	0.77	1.55
Clobazam	2002-2003	871444	3190	96760	2236320	23.11	1118160	0.35	0.35
Alprazolam	2002-2003	871444	40408	1192814	1226492	1.03	24529845	3.86	7.71
Flurazepam	2002-2003	871444	6281	222851	7194390	32.28	2395732	0.75	0.75
Nitrazepam	2002-2003	871444	3742	129192	1204285	9.32	1204285	0.76	0.38
Triazolam	2002-2003	871444	9658	345129	96431	0.28	1928623	1.21	0.61
Temazepam	2002-2003	871444	51208	1535508	43980495	28.64	21990248	6.91	6.91
Zopiclone	2002-2003	871444	105629	3538287	27029456	7.64	18001618	11.33	5.66
Zaleplon	2002-2003	871444	2592	63416	602305	9.50	301153	0.19	0.09
Clonazepam	2003-2004	879411	95373	2670390	4264679	1.60	85293575	1.66	26.57
Diazepam	2003-2004	879411	51490	1385982	17524198	12.64	17524198	5.46	5.46

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Chlordiazepoxide	2003-2004	879411	3457	100698	2908735	28.89	1163494	0.30	0.36
Oxazepam	2003-2004	879411	12957	462059	13755873	29.77	6877936	0.86	2.14
Potassium Clorazepate	2003-2004	879411	1066	43239	690356	15.97	459777	0.11	0.14
Lorazepam	2003-2004	879411	189315	6066260	9411543	1.55	94115433	11.73	29.32
Bromazepam	2003-2004	879411	8583	311238	2349774	7.55	4699548	0.73	1.46
Clobazam	2003-2004	879411	3050	94552	2252900	23.83	1126450	0.35	0.35
Alprazolam	2003-2004	879411	40003	1208390	1262131	1.04	25242610	3.93	7.86
Flurazepam	2003-2004	879411	6390	214350	6932235	32.34	2308434	0.72	0.72
Nitrazepam	2003-2004	879411	3681	123963	1199605	9.68	1199605	0.75	0.37
Triazolam	2003-2004	879411	9453	333976	94446	0.28	1888918	1.18	0.59
Temazepam	2003-2004	879411	53240	1630765	44994375	27.59	22497188	7.01	7.01
Zopiclone	2003-2004	879411	120794	4072498	31468189	7.73	20957814	13.07	6.53
Zaleplon	2003-2004	879411	2280	59782	576410	9.64	288205	0.18	0.09
Clonazepam	2004-2005	886141	103137	2850804	4655228	1.63	93104562	1.80	28.79
Diazepam	2004-2005	886141	50218	1365000	17389138	12.74	17389138	5.38	5.38
Chlordiazepoxide	2004-2005	886141	3162	88014	2790915	31.71	1116366	0.29	0.35

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Oxazepam	2004-2005	886141	12536	444481	13159606	29.61	6579803	0.81	2.03
Potassium Clorazepate	2004-2005	886141	1050	42629	662666	15.54	441336	0.10	0.14
Lorazepam	2004-2005	886141	195525	6226138	9687973	1.56	96879728	11.98	29.95
Bromazepam	2004-2005	886141	8617	307438	2328108	7.57	4656216	0.72	1.44
Clobazam	2004-2005	886141	3314	98262	2262860	23.03	1131430	0.35	0.35
Alprazolam	2004-2005	886141	40212	1243125	1346680	1.08	26933590	4.16	8.33
Flurazepam	2004-2005	886141	5972	202171	6474075	32.02	2155867	0.67	0.67
Nitrazepam	2004-2005	886141	3490	119825	1158750	9.67	1158750	0.72	0.36
Triazolam	2004-2005	886141	9290	314148	90303	0.29	1806053	1.12	0.56
Temazepam	2004-2005	886141	57705	1786264	49920465	27.95	24960233	7.72	7.72
Zopiclone	2004-2005	886141	133705	4560647	35266265	7.73	23487332	14.54	7.26
Zaleplon	2004-2005	886141	2080	55112	534370	9.70	267185	0.17	0.08
Clonazepam	2005-2006	891635	115688	3073504	4800048	1.56	96000954	1.84	29.50
Diazepam	2005-2006	891635	49095	1302022	16263641	12.49	16263641	5.00	5.00
Chlordiazepoxide	2005-2006	891635	3176	82160	2635520	32.08	1054208	0.27	0.32
Oxazepam	2005-2006	891635	12238	423827	12511893	29.52	6255946	0.77	1.92

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Potassium Clorazepate	2005-2006	891635	997	40194	609413	15.16	405869	0.09	0.12
Lorazepam	2005-2006	891635	203331	6368438	9886281	1.55	98862808	12.15	30.38
Bromazepam	2005-2006	891635	8250	294377	2243081	7.62	4486161	0.69	1.38
Clobazam	2005-2006	891635	3818	109823	2465490	22.45	1232745	0.38	0.38
Alprazolam	2005-2006	891635	39938	1222194	1315773	1.08	26315450	4.04	8.09
Flurazepam	2005-2006	891635	5384	188584	6139065	32.55	2044309	0.63	0.63
Nitrazepam	2005-2006	891635	3388	115672	1128460	9.76	1128460	0.69	0.35
Triazolam	2005-2006	891635	8855	304036	86474	0.28	1729480	1.06	0.53
Temazepam	2005-2006	891635	60080	1824276	51625725	28.30	25812863	7.93	7.93
Zopiclone	2005-2006	891635	151198	5103847	39662379	7.77	26415144	16.25	8.12
Zaleplon	2005-2006	891635	2202	60365	602705	9.98	301353	0.19	0.09
Clonazepam	2006-2007	897855	125783	3264319	5023976	1.54	100479510	1.92	30.66
Diazepam	2006-2007	897855	50479	1245853	16363351	13.13	16363351	4.99	4.99
Chlordiazepoxide	2006-2007	897855	2606	74427	2352905	31.61	941162	0.24	0.29
Oxazepam	2006-2007	897855	11848	393155	11706098	29.77	5853049	0.71	1.79
Potassium Clorazepate	2006-2007	897855	907	38433	599070	15.59	398981	0.09	0.12

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Lorazepam	2006-2007	897855	206016	6460387	9972414	1.54	99724139	12.17	30.43
Bromazepam	2006-2007	897855	8100	281055	2127728	7.57	4255455	0.65	1.30
Clobazam	2006-2007	897855	4200	115074	2592770	22.53	1296385	0.40	0.40
Alprazolam	2006-2007	897855	38231	1158125	1277397	1.10	25547935	3.90	7.80
Flurazepam	2006-2007	897855	5302	178700	6261570	35.04	2085103	0.64	0.64
Nitrazepam	2006-2007	897855	3376	114806	1128663	9.83	1128663	0.69	0.34
Triazolam	2006-2007	897855	8367	296762	85862	0.29	1717243	1.05	0.52
Temazepam	2006-2007	897855	60042	1743797	49658663	28.48	24829331	7.58	7.58
Zopiclone	2006-2007	897855	172408	5843175	44848680	7.68	29869221	18.25	9.11
Zaleplon	2006-2007	897855	1295	38318	358035	9.34	179018	0.11	0.05
Clonazepam	2007-2008	910110	135846	3411983	5317879	1.56	106357581	2.00	32.02
Diazepam	2007-2008	910110	51448	1229706	16506455	13.42	16506455	4.97	4.97
Chlordiazepoxide	2007-2008	910110	2217	66552	2063520	31.01	825408	0.21	0.25
Oxazepam	2007-2008	910110	11231	361106	10957320	30.34	5478660	0.66	1.65
Potassium Clorazepate	2007-2008	910110	787	32824	499676	15.22	332784	0.08	0.10
Lorazepam	2007-2008	910110	218215	6482306	10209281	1.57	102092810	12.29	30.73

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Bromazepam	2007-2008	910110	7900	272530	2074140	7.61	4148280	0.62	1.25
Clobazam	2007-2008	910110	4467	115917	2671085	23.04	1335543	0.40	0.40
Alprazolam	2007-2008	910110	40438	1176202	1385127	1.18	27702538	4.17	8.34
Flurazepam	2007-2008	910110	4835	162861	4827912	29.64	1607695	0.48	0.48
Nitrazepam	2007-2008	910110	3233	107782	1091235	10.12	1091235	0.66	0.33
Triazolam	2007-2008	910110	8210	282157	82629	0.29	1652570	0.99	0.50
Temazepam	2007-2008	910110	65108	1864260	53663010	28.79	26831505	8.08	8.08
Zopiclone	2007-2008	910110	194496	6317851	50230360	7.95	33453419	20.16	10.07
Zaleplon	2007-2008	910110	46	1204	11205	9.31	5603	0.00	0.00
Clonazepam	2008-2009	921181	141954	3578946	5593359	1.56	111867180	2.08	33.27
Diazepam	2008-2009	921181	50985	1210486	16577933	13.70	16577933	4.93	4.93
Chlordiazepoxide	2008-2009	921181	2006	61379	1876935	30.58	750774	0.19	0.22
Oxazepam	2008-2009	921181	9990	332387	10254343	30.85	5127171	0.61	1.52
Potassium Clorazepate	2008-2009	921181	740	31568	480338	15.22	319905	0.07	0.10
Lorazepam	2008-2009	921181	225574	6530636	10331643	1.58	103316434	12.29	30.73
Bromazepam	2008-2009	921181	7015	248079	1914149	7.72	3828297	0.57	1.14

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Clobazam	2008-2009	921181	4765	124676	2872715	23.04	1436358	0.43	0.43
Alprazolam	2008-2009	921181	41463	1199522	1481695	1.24	29633891	4.41	8.81
Flurazepam	2008-2009	921181	4137	140726	4085115	29.03	1360343	0.40	0.40
Nitrazepam	2008-2009	921181	3062	105154	1080325	10.27	1080325	0.64	0.32
Triazolam	2008-2009	921181	7808	271202	79903	0.29	1598055	0.95	0.48
Temazepam	2008-2009	921181	71201	2004103	58045080	28.96	29022540	8.63	8.63
Zopiclone	2008-2009	921181	215475	6891080	55165123	8.01	36739972	21.88	10.93
Clonazepam	2009-2010	936781	151863	3769022	5904769	1.57	118095388	2.16	34.54
Diazepam	2009-2010	936781	53242	1204319	16583414	13.77	16583414	4.85	4.85
Chlordiazepoxide	2009-2010	936781	1778	56077	1679545	29.95	671818	0.16	0.20
Oxazepam	2009-2010	936781	9304	312835	9478090	30.30	4739045	0.55	1.39
Potassium Clorazepate	2009-2010	936781	697	28763	437831	15.22	291596	0.06	0.09
Lorazepam	2009-2010	936781	228359	6587173	11081928	1.68	110819283	12.96	32.41
Bromazepam	2009-2010	936781	6557	236770	1837007	7.76	3674013	0.54	1.07
Clobazam	2009-2010	936781	5113	130632	2948230	22.57	1474115	0.43	0.43
Alprazolam	2009-2010	936781	47322	1324488	1744198	1.32	34883968	5.10	10.20

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Flurazepam	2009-2010	936781	3659	125440	3678060	29.32	1224794	0.36	0.36
Nitrazepam	2009-2010	936781	3108	106374	1113895	10.47	1113895	0.65	0.33
Triazolam	2009-2010	936781	7730	257915	77461	0.30	1549210	0.91	0.45
Temazepam	2009-2010	936781	83818	2328206	68424645	29.39	34212323	10.01	10.01
Zopiclone	2009-2010	936781	233816	7505864	60544496	8.07	40322635	23.61	11.79
Clonazepam	2010-2011	952989	166190	3903271	6169520	1.58	123390409	2.22	35.47
Diazepam	2010-2011	952989	57297	1177324	16282962	13.83	16282962	4.68	4.68
Chlordiazepoxide	2010-2011	952989	1597	50741	1527725	30.11	611090	0.15	0.18
Oxazepam	2010-2011	952989	8662	297824	9007488	30.24	4503744	0.52	1.29
Potassium Clorazepate	2010-2011	952989	643	26604	403710	15.17	268871	0.06	0.08
Lorazepam	2010-2011	952989	233116	6596557	11366897	1.72	113668970	13.07	32.68
Bromazepam	2010-2011	952989	6407	230970	1781384	7.71	3562767	0.51	1.02
Clobazam	2010-2011	952989	5371	133946	3088095	23.05	1544048	0.44	0.44
Alprazolam	2010-2011	952989	56524	1486844	2044674	1.38	40893473	5.88	11.76
Flurazepam	2010-2011	952989	3232	107634	3166560	29.42	1054464	0.30	0.30
Nitrazepam	2010-2011	952989	3025	107075	1064945	9.95	1064945	0.61	0.31

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Triazolam	2010-2011	952989	3492	107820	33314	0.31	666278	0.38	0.19
Temazepam	2010-2011	952989	100878	2705087	80221155	29.66	40110578	11.53	11.53
Zopiclone	2010-2011	952989	256515	8089073	65760188	8.13	43796285	25.21	12.59
Clonazepam	2011-2012	969591	174817	3973285	6242725	1.57	124854497	2.20	35.28
Diazepam	2011-2012	969591	68294	1167560	16532864	14.16	16532864	4.67	4.67
Chlordiazepoxide	2011-2012	969591	1534	46387	1344710	28.99	537884	0.13	0.15
Oxazepam	2011-2012	969591	8379	272637	8112853	29.76	4056426	0.46	1.15
Potassium Clorazepate	2011-2012	969591	515	21906	348263	15.90	231943	0.05	0.07
Lorazepam	2011-2012	969591	238390	6632888	10716179	1.62	107161787	12.11	30.28
Bromazepam	2011-2012	969591	6234	217644	1649484	7.58	3298968	0.47	0.93
Clobazam	2011-2012	969591	5688	134224	3054720	22.76	1527360	0.43	0.43
Alprazolam	2011-2012	969591	71111	1701696	2580238	1.52	51604751	7.29	14.58
Flurazepam	2011-2012	969591	1683	59557	1671360	28.06	556563	0.16	0.16
Nitrazepam	2011-2012	969591	2804	96118	938850	9.77	938850	0.53	0.27
Triazolam	2011-2012	969591	2354	60431	18267	0.30	365343	0.21	0.10
Temazepam	2011-2012	969591	125881	3028804	93216045	30.78	46608023	13.17	13.17

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Zopiclone	2011-2012	969591	276107	8703275	71120985	8.17	47366576	26.80	13.38
Zolpidem	2011-2012	969591	53	1054	11140	10.57	5570	0.00	0.00
Clonazepam	2012-2013	988801	175893	3927036	6156485	1.57	123129692	2.13	34.12
Diazepam	2012-2013	988801	68796	1113486	16184820	14.54	16184820	4.48	4.48
Chlordiazepoxide	2012-2013	988801	1193	37288	943295	25.30	377318	0.09	0.10
Oxazepam	2012-2013	988801	7387	235818	7075542	30.00	3537771	0.39	0.98
Potassium Clorazepate	2012-2013	988801	458	19414	299554	15.43	199503	0.04	0.06
Lorazepam	2012-2013	988801	233590	6452484	10123665	1.57	101236647	11.22	28.05
Bromazepam	2012-2013	988801	6136	205334	1566257	7.63	3132513	0.43	0.87
Clobazam	2012-2013	988801	6153	134123	3009915	22.44	1504958	0.42	0.42
Alprazolam	2012-2013	988801	76405	1796181	2876403	1.60	57528060	7.97	15.94
Flurazepam	2012-2013	988801	1551	56504	1583925	28.03	527447	0.15	0.15
Nitrazepam	2012-2013	988801	2478	85820	844545	9.84	844545	0.47	0.23
Triazolam	2012-2013	988801	3204	82252	25258	0.31	505151	0.28	0.14
Temazepam	2012-2013	988801	119865	2921626	89689965	30.70	44844983	12.43	12.43
Zopiclone	2012-2013	988801	281420	8843974	72784657	8.23	48474581	26.89	13.43

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Zolpidem	2012-2013	988801	1116	22820	233940	10.25	116970	0.06	0.03
Clonazepam	2013-2014	1005477	178816	3965661	6177665	1.56	123553297	2.10	33.67
Diazepam	2013-2014	1005477	68961	1080586	15446779	14.29	15446779	4.21	4.21
Chlordiazepoxide	2013-2014	1005477	1090	34434	813870	23.64	325548	0.07	0.09
Oxazepam	2013-2014	1005477	6712	214422	6475990	30.20	3237995	0.35	0.88
Potassium Clorazepate	2013-2014	1005477	499	18417	299509	16.26	199473	0.04	0.05
Lorazepam	2013-2014	1005477	235679	6394105	9901651	1.55	99016508	10.79	26.98
Bromazepam	2013-2014	1005477	5857	187218	1458090	7.79	2916179	0.40	0.79
Clobazam	2013-2014	1005477	6510	132842	2882350	21.70	1441175	0.39	0.39
Alprazolam	2013-2014	1005477	72693	1642048	2455557	1.50	49111130	6.69	13.38
Flurazepam	2013-2014	1005477	1398	51869	1438860	27.74	479140	0.13	0.13
Nitrazepam	2013-2014	1005477	2337	83028	802154	9.66	802154	0.44	0.22
Triazolam	2013-2014	1005477	2726	68851	20940	0.30	418796	0.23	0.11
Temazepam	2013-2014	1005477	97976	2341367	69772875	29.80	34886438	9.51	9.51
Zopiclone	2013-2014	1005477	293115	9245388	76461013	8.27	50923035	27.78	13.88
Zolpidem	2013-2014	1005477	1856	47691	459465	9.63	229733	0.13	0.06

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Clonazepam	2014-2015	1018590	193852	4080904	6259604	1.53	125192084	2.10	33.67
Diazepam	2014-2015	1018590	69782	1041876	14609506	14.02	14609506	3.93	3.93
Chlordiazepoxide	2014-2015	1018590	902	29871	701775	23.49	280710	0.06	0.08
Oxazepam	2014-2015	1018590	6279	197628	6021488	30.47	3010744	0.32	0.81
Potassium Clorazepate	2014-2015	1018590	454	17911	298553	16.67	198836	0.04	0.05
Lorazepam	2014-2015	1018590	236852	6260476	9660372	1.54	96603722	10.39	25.98
Bromazepam	2014-2015	1018590	5432	171452	1320059	7.70	2640119	0.36	0.71
Clobazam	2014-2015	1018590	6702	130693	2746345	21.01	1373173	0.37	0.37
Alprazolam	2014-2015	1018590	66327	1510605	2073993	1.37	41479863	5.58	11.16
Flurazepam	2014-2015	1018590	1098	42612	1182390	27.75	393736	0.11	0.11
Nitrazepam	2014-2015	1018590	2560	88705	832083	9.38	832083	0.45	0.22
Triazolam	2014-2015	1018590	1465	34617	11570	0.33	231408	0.12	0.06
Temazepam	2014-2015	1018590	91115	2139818	63442365	29.65	31721183	8.53	8.53
Zopiclone	2014-2015	1018590	307857	9650549	79708397	8.26	53085792	28.59	14.28
Zolpidem	2014-2015	1018590	2695	72649	701755	9.66	350878	0.19	0.09
Clonazepam	2015-2016	1030536	208816	4169247	6322550	1.52	126450999	2.10	33.62

Drug	Fiscal Year	Population	Prescription Count	Treatment Days	Dispensed Milligrams	Daily Dose	Total DME	DDD/ 1000/ Persons/Day	DME-DDD /1000 Persons/ Day
Diazepam	2015-2016	1030536	69760	990227	13653735	13.79	13653735	3.63	3.63
Chlordiazepoxide	2015-2016	1030536	1067	28954	639580	22.09	255832	0.06	0.07
Oxazepam	2015-2016	1030536	5692	175322	5330375	30.40	2665188	0.28	0.71
Potassium Clorazepate	2015-2016	1030536	399	14898	248036	16.65	165192	0.03	0.04
Lorazepam	2015-2016	1030536	236926	6020130	9215195	1.53	92151952	9.80	24.50
Bromazepam	2015-2016	1030536	5036	160760	1209587	7.52	2419175	0.32	0.64
Clobazam	2015-2016	1030536	7122	129568	2643845	20.41	1321923	0.35	0.35
Alprazolam	2015-2016	1030536	64640	1488467	1963440	1.32	39268803	5.22	10.44
Flurazepam	2015-2016	1030536	1108	39985	1103970	27.61	367622	0.10	0.10
Nitrazepam	2015-2016	1030536	2336	78419	802816	10.24	802816	0.43	0.21
Triazolam	2015-2016	1030536	2051	50516	16432	0.33	328638	0.17	0.09
Temazepam	2015-2016	1030536	86434	2008255	58842540	29.30	29421270	7.82	7.82
Zopiclone	2015-2016	1030536	314794	9810134	80004583	8.16	53283052	28.36	14.17
Zolpidem	2015-2016	1030536	3156	93976	899130	9.57	449565	0.24	0.12

Appendix 3 – Supplemental Results and Methods to Chapter 4

Table A3.1 – Logistic Regression Methodology

Criteria	Approach
Variable Selection	-Informal selection via published literature -Simple logistic regression; β values ($p < 0.25$)
Variable Coding	-Dichotomous Categorical; 0 or 1 -Ordinal; discrete number scale starting at 1 -Polychotomous Categorical; 0 or 1 with auto-generated dummy variables -No continuous variables retained
Events-per-Variable	-Minimum 10 events per independent variable rule
Conformity of Linear Gradient	-Ordered categorical variables assessed for conformity of linear gradient; nonconformity handled by variable transformation or separation into additional (design) variables (i.e fiscal year was shown to be linear with respect to outcome so condensed variable into 5-year increments)
Interaction effects	-Assessed at $p < 0.01$. Suspected interactions included; age*sex, residential mobility*SEFI*income assistance, psychotropic use*opioid use, RUB*CCI
Collinearity	-Analysis of variance inflation factor, correlation coefficients, eigenvalues -Significant collinearity; combine variables or removal of inferior explanatory variable
Statistical Significance	-Wald 95% CI for β and OR's
Goodness-of-Fit Measures	-C-statistic, Log-Likelihood Ratio, Hosmer-Lemeshow Statistic
Fitting Procedure	-Stepwise addition/subtraction of variables -Assessment of clinical significance

Table A3.2 - Proportion of Long-Term Z-Drug Use by Differing Parameters and Duration

Scenario	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Sub-Cohort
A1	First-Use Episode ≥ 180 days	30 days or 50% of previous Day Supply	8,206	7.41%
A2	First-Use Episode ≥ 90 days	30 days or 50% of previous Day Supply	12,155	11.0%
A3	First-Use Episode ≥ 60 days	30 days or 50% of previous Day Supply	17,126	15.5%
A4	First-Use Episode ≥ 180 days	60 Days or 50% of previous Day Supply	10,437	9.43%
A5	First-Use Episode ≥ 180 days	90 Days	12,719	11.49%
A6	First-Use Episode ≥ 270 days	90 Days	11,117	10.04%
A7	First-Use Episode ≥ 365 days	90 Days	10,045	9.07%
B1	User Mean Episode Duration ≥ 180 days	30 days or 50% of previous Day Supply	21,859	19.75%
B2	User Mean Episode Duration ≥ 90 days	30 days or 50% of previous Day Supply	32,020	28.92%
B3	User Mean Episode Duration ≥ 60 days	30 days or 50% of previous Day Supply	39,690	35.85%
B4	User Mean Episode Duration ≥ 180 days	60 Days or 50% of previous Day Supply	24,098	21.77%
B5	User Mean Episode Duration ≥ 180 days	90 Days	26,477	23.92%
B6	User Mean Episode Duration ≥ 270 days	90 Days	21,040	19.01%
B7	User Mean Episode Duration ≥ 365 days	90 Days	17,358	15.68%

Table A3.3 – Patient Characteristics of BZD/Z-Drug Users by First Use Episode Duration

		Short-term	Long-term	Total
Number of Users (%)		**197,606 (100%)**	**9,327 (100%)**	**206,933 (100%)**
Sex Distribution	*Male (%)*	74,487 (37.7%)	4,295 (46.1%)	78,782 (38.1%)
	Female (%)	123,057 (62.3%)	5,029 (53.9%)	128,086 (61.9%)
Age Category	*18-44 (%)*	101,709 (51.5%)	2,776 (29.8%)	104,485 (50.5%)
	45-64 (%)	66,752 (33.8%)	3,320 (35.6%)	70,072 (33.9%)
	65+ (%)	29,143 (14.8%)	3,231 (34.6%)	32,374 (15.6%)
SEFI-2 Score	*<-1*	24,955 (12.63%)	1,089 (11.7%)	26,044 (12.6%)
	-1 to 0	81,718 (41.4%)	3,835 (41.1%)	85,553 (41.3%)
	0 to 1	64,967 (32.9%)	3,274 (35.1%)	68,241 (33.0%)
	>1	25,966 (13.1%)	1,129 (12.1%)	27,095 (13.1%)
Residence Distribution	*Rural*	71,656 (36.3%)	3,525 (37.8%)	75,181 (36.3%)
	Urban	125,950 (63.7%)	9,327 (62.2%)	135,277 (65.4%)
High Residential Mobility		36,392 (18.4%)	2,385 (25.6%)	38,777 (18.7%)
Receipt of Income Assistance		18,530 (9.4%)	1,222 (13.1%)	19,752 (9.5%)
Marriage Record		102,461 (51.9%)	4,618 (49.5%)	107,079 (51.7%)

		Short-term	Long-term	Total
Number of Users (%)		**197,606 (100%)**	**9,327 (100%)**	**206,933 (100%)**
Johns Hopkins Healthcare Resource Utilization Band	*0 (no utilization)*	3001 (1.5%)	349 (3.7%)	3,350 (1.6%)
	1	5,798 (2.9%)	182 (2.0%)	5,980 (2.9%)
	2	33,974 (17.2%)	1,192 (12.8%)	35,166 (17.0%)
	3	127,824 (64.7%)	5,151 (55.2%)	132,975 (64.3%)
	4	20,065 (10.2%)	1,486 (15.9%)	21,551 (10.4%)
	5 (high-utilization)	6,882 (3.5%)	964 (10.3%)	7,846 (3.8%)
Charlson Comorbidity index Score	*0*	148,257 (75.0%)	5,783 (62.0%)	154,040 (74.4%)
	1	36,261 (18.4%)	2,031 (21.8%)	38,292 (18.5%)
	2+	13,088 (6.6%)	1,513 (16.2%)	14,601 (7.1%)
Non-BZD Psychotropic Prescription Dispensations	*0*	111,216 (56.3%)	3,862 (41.4%)	115,078 (55.6%)
	1	17,661 (8.9%)	518 (5.6%)	18,179 (8.8%)
	2+	68,729 (34.8%)	4,947 (53.0%)	73,676 (35.6%)
Opioid Prescription Dispensations	*0*	132,027 (66.8%)	5,855 (62.8%)	137,882 (66.6%)
	1	30,530 (15.5%)	1,011 (10.8%)	31,541 (15.2%)
	2+	35,049 (17.7%)	2,461 (26.4%)	37,510 (18.1%)
Sex of Prescriber	*Male*	143,619 (72.7%)	6,928 (74.3%)	150,547 (72.7%)
Age of Prescriber Issuing First Prescription	*50+ Years*	95,629 (48.4%)	4,775 (51.2%)	100,404 (48.5%)
Type of Prescriber Issuing First Prescription	*General Practitioner*	146,823 (74.3)	7,013 (75.2%)	153,836 (74.3%)
	Psychiatrist	6,338 (3.2%)	624 (6.7%)	6,962 (3.4%)
	Other	7,183 (3.6%)	375 (4.0%)	7,558 (3.7%)
Period of First Prescription	*2001-2006*	90,008 (45.5%)	2,608 (28.0%)	92,616 (44.7%)
	2006-2011	65,750 (33.3%)	3,170 (34.0%)	68,920 (33.3%)
	2011-2016	41,848 (21.2%)	3,549 (38.0%)	45,397 (21.9%)

Table A3.4 – Patient Characteristics of Z-Drug Users by First Use Episode Duration

		Short-term	Long-term	Total
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Sex Distribution	*Male*	40,516 (39.5%)	3,473 (42.3%)	43,989 (39.8%)
	Female	61,943 (60.5%)	4,731 (57.7%)	66,674 (60.2%)
Age Category	*18-44*	42,663 (41.6%)	1,795 (21.9%)	44,458 (40.2%)
	45-64	39,817 (38.9%)	3,184 (38.8%)	43,001 (38.9%)
	65+	20,011 (19.5%)	3,227 (39.3%)	23,238 (21.0%)
SEFI-2 Score	*<-1*	13,678 (13.3%)	981 (12.0%)	14,659 (13.2%)
	-1 to 0	45,136 (44.1%)	3,674 (44.8%)	48,810 (44.1%)
	0 to 1	33,719 (32.9%)	2,885 (35.2%)	36,604 (33.1%)
	>1	9,958 (9.7%)	666 (8.1%)	10,624 (9.6%)
Residence Distribution	*Urban*	63,207 (61.7%)	3,313 (40.4%)	66,520 (60.1%)
	Rural	39,284 (38.3%)	4,893 (59.6%)	44,177 (39.9%)
High Residential Mobility		22,408 (21.9%)	2,523 (30.8%)	24,931 (22.5%)
Receipt of Income Assistance		8,351 (8.2%)	758 (9.2%)	9,109 (8.2%)
Marriage Record		57,308 (55.9%)	4,595 (56.0%)	61,903 (55.9%)
Johns Hopkins Healthcare Resource Utilization Band	*0 (no utilization)*	1,771 (1.7%)	234 (2.9%)	2,005 (1.8%)
	1	3,205 (3.1%)	175 (2.1%)	3,380 (3.1%)
	2	17,523 (17.1%)	1,012 (12.3%)	18,535 (16.7%)
	3	65,067 (63.5%)	4,699 (57.3%)	69,766 (63.0%)
	4	10,810 (10.6%)	1,259 (15.3%)	12,069 (10.9%)
	5 (high-utilization)	4,083 (4.0%)	825 (10.1%)	4,908 (4.4%)

		Short-term	Long-term	Total
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Charlson Comorbidity index Score	*0*	72,490 (70.8%)	4,528 (55.2%)	77,018 (69.6%)
	1	19,495 (19.0%)	1,905 (23.2%)	21,400 (19.3%)
	2+	10,506 (10.3%)	1,773 (21.6%)	12,279 (11.1%)
Non-BZD Psychotropic Prescription Dispensations	*0*	27,797 (27.1%)	1,784 (21.7%)	29,581 (26.7%)
	1	36,939 (36.1%)	2,156 (26.3%)	39,095 (35.3%)
	2+	37,755 (36.8%)	4,266 (52.0%)	42,021 (38.0%)
Opioid Prescription Dispensations	*0*	47,427 (46.3%)	3,298 (40.2%)	50,725 (45.8%)
	1	34,505 (33.7%)	2,772 (33.8%)	37,277 (33.7%)
	2+	20,559 (20.1%)	2,136 (26.0%)	22,695 (20.5%)
Sex of Prescriber Issuing First Prescription	*Male*	71,485 (69.8%)	5,627 (68.6%)	77,112 (69.7%)
	Female	28,485 (27.8%)	2,273 (27.7%)	30,758 (27.8%)
Age of Prescriber Issuing First Prescription	*50+ Years*	47,871 (46.7%)	4,014 (48.9%)	51,885 (46.9%)
	<50 Years	49,257 (48.1%)	3,758 (45.8%)	53,015 (47.9%)
Type of Prescriber Issuing First Prescription	*General Practitioner*	78,610 (76.7%)	6,366 (77.6%)	84,976 (76.8%)
	Psychiatry	3,912 (3.8%)	475 (5.8%)	4,387 (4.0%)
	Other	3,881 (3.8%)	381 (4.6%)	4,262 (3.9%)
Period of First Prescription	*2001-2006*	34,360 (33.5%)	1,526 (18.6%)	35,886 (32.4%)
	2006-2011	37,752 (36.8%)	2,808 (34.2%)	40,560 (36.7%)
	2011-2016	30,379 (29.6%)	3,872 (47.2%)	34,251 (31.0%)

Table A3.5 – Frequency of Charlson Comorbidity Group Diagnoses by First Use Episode Duration for BZD/Z-Drug Cohort

Charlson Diagnosis	Short-Term 'First-Episode' Users *(n=197,606)*	Long-Term 'First-Episode' Users *(n=9,327)*	Z-Test of Two Proportions
Myocardial Infarction	2,474 (1.3%)	281 (3.0%)	$p < 0.01$
Congestive Heart Failure	3,943 (2.0%)	628 (6.7%)	$p < 0.01$
Peripheral Vascular Disease	2,367 (1.2%)	256 (2.7%)	$p < 0.01$
Cerebrovascular Disease	3,690 (1.9%)	544 (5.8%)	$p < 0.01$
Dementia	2,928 (1.5%)	796 (8.5%)	$p < 0.01$
COPD	23,064 (11.7%)	1,163 (12.5%)	$p = 0.02$
Connective Tissue/Rheumatic Disease	2,793 (1.4%)	222 (2.4%)	$p < 0.01$
Peptic Ulcer Disease	2,140 (1.1%)	114 (1.2%)	$p = 0.20$
Mild Liver Disease	2,406 (1.2%)	135 (1.4%)	$p = 0.05$
Moderate/Severe Liver Disease	341 (0.1%)	28 (0.0%)	$p < 0.01$
Uncomplicated Diabetes	14,131 (7.2%)	1,099 (11.8%)	$p < 0.01$
Complicated Diabetes	1,611 (0.8%)	252 (2.7%)	$p < 0.01$
Paraplegia and Hemiplegia	794 (0.4%)	136 (1.5%)	$p < 0.01$
Renal Disease	1,858 (0.9%)	238 (2.6%)	$p < 0.01$
Cancer	829 (0.4%)	64 (0.1%)	$p < 0.01$
Metastatic Carcinoma	64 (0.0%)	13 (0.0%)	$p < 0.01$
HIV/AIDS	50 (0.0%)	10 (0.0%)	$p < 0.01$

Table A3.6 – Frequency of Charlson Comorbidity Group Diagnoses by First Use Episode Duration for Z-Drug Cohort

Charlson Diagnosis	**Short-Term 'First-Episode' Users** *(n=102,459)*	**Long-Term 'First-Episode' Users** *(n=8,204)*	**Z-Test of Two Proportions**
Myocardial Infarction	1,836 (1.8%)	306 (3.7%)	$p < 0.01$
Congestive Heart Failure	3,174 (3.1%)	700 (8.5%)	$p < 0.01$
Peripheral Vascular Disease	1,772 (1.7%)	284 (3.5%)	$p < 0.01$
Cerebrovascular Disease	2,321 (2.3%)	550 (6.7%)	$p < 0.01$
Dementia	1,925 (1.9%)	865 (10.5%)	$p < 0.01$
COPD	12,357 (12.1%)	1,171 (14.3%)	$p < 0.01$
Connective Tissue/Rheumatic Disease	1,906 (1.9%)	243 (3.0%)	$p < 0.01$
Peptic Ulcer Disease	1,111 (1.1%)	123 (1.5%)	$p < 0.01$
Mild Liver Disease	1,672 (1.6%)	139 (1.7%)	$p = 0.33$
Moderate/Severe Liver Disease	275 (0.2%)	38 (0.4%)	$p < 0.01$
Uncomplicated Diabetes	9,317 (9.1%)	1,150 (14.0%)	$p < 0.01$
Complicated Diabetes	1,639 (1.6%)	328 (4.0%)	$p < 0.01$
Paraplegia and Hemiplegia	508 (0.5%)	136 (1.7%)	$p < 0.01$
Renal Disease	1,543 (1.5%)	293 (3.6%)	$p < 0.01$
Cancer	2,109 (2.1%)	247 (3.0%)	$p < 0.01$
Metastatic Carcinoma	429 (0.4%)	45 (0.5%)	$p = 0.04$
HIV/AIDS	118 (0.1%)	16 (0.2%)	$p = 0.02$

Table A3.7– Statistical Associations between Predictor Variables and Long-term Use of Z-Drugs

		Use Duration					
Independent Variable		***≥180 days***		***≥90 days***		***≥60 days***	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Male		1.12 (1.07-1.18)	1.04 (0.99-1.09)	1.13 (1.08-1.17)	1.05 (1.01-1.10)	1.08 (1.05-1.12)	1.04 (1.00-1.08)
Age	*18-44*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.90 (1.79-2.02)	2.02 (1.89-2.17)	1.74 (1.66-1.82)	1.78 (1.68-1.88)	1.71 (1.64-1.78)	1.68 (1.60-1.76)
	65+	3.83 (3.61-4.07)	3.71 (3.44-4.00)	3.24 (3.08-3.40)	3.08 (2.90-3.28)	2.99 (2.87-3.12)	2.78 (2.64-2.93)
Rural Residence		0.92 (0.88-0.96)	1.13 (1.07-1.19)	0.99 (0.96-1.03)	1.02 (0.98-1.07)	1.08 (1.04-1.11)	0.95 (0.91-0.99)
High Residential Mobility		1.59 (1.51-1.67)	1.26 (1.19-1.33)	1.53 (1.46-1.59)	1.21 (1.15-1.27)	1.30 (1.26-1.35)	1.12 (1.07-1.17)
Income Assistance		1.15 (1.06-1.24)	1.47 (1.34-1.61)	1.02 (0.95-1.09)	1.29 (1.19-1.40)	0.82 (0.77-0.87)	1.08 (1.00-1.17)
SEFI-2 Score	*<-1*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.14 (1.06-1.22)	1.07 (0.99-1.16)	1.03 (0.97-1.09)	0.98 (0.92-1.04)	0.95 (0.91-1.00)	0.94 (0.89-0.99)
	0 to 1	1.19 (1.11-1.29)	1.08 (0.99-1.17)	1.04 (0.98-1.11)	0.99 (0.93-1.06)	0.92 (0.87-0.97)	0.93 (0.88-0.99)
	>1	0.93 (0.84-1.03)	0.84 (0.75-0.94)	0.80 (0.73-0.87)	0.77 (0.70-0.85)	0.68 (0.63-0.73)	0.72 (0.66-0.78)
Married		1.00 (0.96-1.05)	0.86 (0.82-0.91)	1.07 (1.03-1.10)	0.93 (0.89-0.98)	1.13 (1.10-1.17)	0.98 (0.94-1.01)
Opioid Use		1.28 (1.22-1.34)	1.15 (1.09-1.21)	1.26 (1.21-1.31)	1.15 (1.11-1.20)	1.18 (1.14-1.21)	1.11 (1.07-1.15)

Independent Variable		Use Duration					
		≥180 days		≥90 days		≥60 days	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Psychotropic Rx Use (Non-BZD)		1.34 (1.27-1.41)	1.24 (1.17-1.32)	1.35 (1.29-1.41)	1.27 (1.20-1.33)	1.22 (1.17-1.27)	1.19 (1.14-1.24)
Charlson Comorbidity Index Score	*0*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.56 (1.48-1.65)	1.25 (1.18-1.33)	1.45 (1.39-1.52)	1.21 (1.15-1.27)	1.33 (1.28-1.38)	1.13 (1.08-1.19)
	2+	2.70 (2.55-2.87)	1.46 (1.36-1.58)	2.34 (2.22-2.46)	1.38 (1.29-1.47)	2.02 (1.93-2.12)	1.30 (1.22-1.37)
Resource Utilization Band	*0-3 (≤Moderate)*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4 (High)	1.67 (1.56-1.78)	1.16 (1.08-1.25)	1.47 (1.39-1.56)	1.09 (1.01-1.16)	1.30 (1.24-1.37)	1.00 (0.95-1.07)
	5 (Very High)	2.89 (2.67-3.13)	1.55 (1.41-1.70)	2.43 (2.26-2.61)	1.42 (1.30-1.55)	1.97 (1.85-2.11)	1.22 (1.12-1.32)
Male Prescriber of First Prescription		0.99 (0.94-1.04)	0.97 (0.92-1.03)	0.98 (0.94-1.02)	0.98 (0.93-1.02)	0.94 (0.90-0.97)	0.93 (0.90-0.97)
Prescriber Age ≥50 Years		1.10 (1.05-1.15)	0.98 (0.93-1.03)	1.10 (1.06-1.15)	0.98 (0.94-1.02)	1.15 (1.11-1.19)	1.05 (1.01-1.09)
Prescriber of First Prescription	*GP*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Psychiatrist	1.50 (1.36-1.66)	1.96 (1.76-2.17)	1.36 (1.25-1.49)	1.72 (1.57-1.89)	1.11 (1.02-1.20)	1.38 (1.27-1.51)
	Other	1.21 (1.09-1.35)	0.92 (0.82-1.03)	1.18 (1.07-1.29)	0.91 (0.83-1.00)	1.19 (1.10-1.29)	0.98 (0.91-1.07)
Period of First Prescription	*2001-2006*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	2006-2011	1.68 (1.57-1.79)	1.57 (1.46-1.68)	1.67 (1.59-1.76)	1.56 (1.47-1.66)	1.53 (1.46-1.60)	1.46 (1.39-1.54)
	2011-2015	2.87 (2.70-3.05)	2.45 (2.28-2.65)	2.83 (2.69-2.97)	2.44 (2.30-2.59)	2.20 (2.10-2.29)	1.96 (1.86-2.07)

Appendix 4 – Examples of SAS Programming Code

This appendix provides some examples of programming code for Chapters 3 and 4. The entire project was organized and programmed over 4 files; one for the drug utilisation study, one for deriving the cohort from the raw admin data, one for characterising and assignment of co-variate values to all eligible individuals in the cohort and one for the statistical analysis of the cohort. Below are some specific examples and their denoted purpose but they should be interpreted cautiously as they are necessarily taken out of the programming context. Complete programming code can be requested by contacting the author.

Chapter 3 Code

Macro to generate intermediate DME/DDD dataset from raw Rx data.

```
%macro bdzrx;
data work.bdzrx;
      set project.jadenb_thesis_dpin project.jadenb_thesis_clobazam;
      keep SCRPHIN PRVDDT atc drug DAYSUPP MQTYCLM strength baseno mdyear;
      if atc in
('N05BA12','N05BA08','N05BA02','N05BA09','N03AE01','N05BA04','N05BA01','N0
5CD01','N05BA06','N05CD02','N05BA05','N05CD07','N05CD05','N05CF01','N05CF0
2','N05CF03');
      drug=atc;
      format PRVDDT;
      if PRVDDT LE 14700 then delete;
run;

proc sort data=bdzrx;
by drug PRVDDT;
run;

data bdzrx;
      set bdzrx;
      if PRVDDT GE 14701 AND PRVDDT LE 15065 then pharmyear=1; else
      if PRVDDT GE 15066 AND PRVDDT LE 15430 then pharmyear=2; else
      if PRVDDT GE 15431 AND PRVDDT LE 15795 then pharmyear=3; else
      if PRVDDT GE 15796 AND PRVDDT LE 16161 then pharmyear=4; else
      if PRVDDT GE 16162 AND PRVDDT LE 16526 then pharmyear=5; else
       if PRVDDT GE 16527 AND PRVDDT LE 16891 then pharmyear=6; else
      if PRVDDT GE 16892 AND PRVDDT LE 17256 then pharmyear=7; else
      if PRVDDT GE 17257 AND PRVDDT LE 17622 then pharmyear=8; else
      if PRVDDT GE 17623 AND PRVDDT LE 17987 then pharmyear=9; else
      if PRVDDT GE 17988 AND PRVDDT LE 18352 then pharmyear=10; else
      if PRVDDT GE 18353 AND PRVDDT LE 18717 then pharmyear=11; else
      if PRVDDT GE 18718 AND PRVDDT LE 19083 then pharmyear=12; else
      if PRVDDT GE 19084 AND PRVDDT LE 19448 then pharmyear=13; else
      if PRVDDT GE 19449 AND PRVDDT LE 19813 then pharmyear=14; else
      if PRVDDT GE 19814 AND PRVDDT LE 20178 then pharmyear=15; else
```

```
      if PRVDDT GE 20179 AND PRVDDT LE 20544 then pharmyear=16; else
      if PRVDDT GE 20545 AND PRVDDT LE 20909 then pharmyear=17;
      format pharmyear pharmacare_year_simple.;
      format drug $ATC_drugname.;
      label drug = "BDZ/Z-Drug Name";
      label pharmyear = "Pharmacare Benefit Period (March 31 - April 1)";
run;

data work.bdzrx  /*daily_dispense*/;
      set bdzrx;
      if MQTYCLM = 0 then delete;  /*dropping 960 "nulluse" observations
as the day supply is either 0 or qty is 0*/;
      if DAYSUPP = 0 then delete;
      if MQTYCLM >=1000 and DAYSUPP <=30 then delete; /*dropping 608
extreme "absurd use" observations*/
      *if DAYSUPP LE 7 then delete;
run;

proc sort data=bdzrx;
      by drug pharmyear;
run;

data bdzrx;
      set bdzrx;
      total_rx_mg=MQTYCLM*strength;
      label total_rx_mg = "Total mg dispensed for Rx";
run;

data bdzrx;
      set bdzrx;
      daily_dose=total_rx_mg/DAYSUPP;
      label daily_dose= "Prescribed Daily Dose";
run;

data bdzrx;
      set bdzrx;
      DME=.;
      DDD=.;
      if drug='N05BA01' then DME=daily_dose*1; /*diazepam*/
      if drug='N05BA01' then DDD=daily_dose/10;
      if drug='N05BA12' then DME=daily_dose*10; /*alprazolam*/
      if drug='N05BA12' then DDD=daily_dose/1;
      if drug='N05BA08' then DME=daily_dose*1; /*bromazepam*/
      if drug='N05BA08' then DDD=daily_dose/10;
      if drug='N05BA02' then DME=daily_dose*0.5; /*chlordiazepoxide*/
      if drug='N05BA02' then DDD=daily_dose/30;
      if drug='N05BA09' then DDD=daily_dose/20; /*clobazam*/
      if drug='N05BA09' then DME=daily_dose*0.5;
      if drug='N03AE01' then DME=daily_dose*20; /*clonazepam*/
      if drug='N03AE01' then DDD=daily_dose/8;
      if drug='N05CD01' then DME=daily_dose*0.33; /*flurazepam*/
      if drug='N05CD01' then DDD=daily_dose/30;
      if drug='N05BA05' then DME=daily_dose*0.66; /*clorazepate*/
      if drug='N05BA05' then DDD=daily_dose/20;
```

```
      if drug='N05BA06' then DME=daily_dose*5; /*lorazepam*/
      if drug='N05BA06' then DDD=daily_dose/2.5;
      if drug='N05CD02' then DME=daily_dose*1; /*nitrazepam*/
      if drug='N05CD02' then DDD=daily_dose/5;
      if drug='N05BA04' then DME=daily_dose*0.5; /*oxazepam*/
      if drug='N05BA04' then DDD=daily_dose/50;
      if drug='N05CD07' then DME=daily_dose*0.33; /*temazepam*/
      if drug='N05CD07' then DDD=daily_dose/20;
      if drug='N05CD05' then DME=daily_dose*40; /*triazolam*/
      if drug='N05CD05' then DDD=daily_dose/0.25;
      if drug='N05CF01' then DME=daily_dose*1.33; /*zopiclone*/
      if drug='N05CF01' then DDD=daily_dose/7.5;
      if drug='N05CF02' then DME=daily_dose*0.5; /*zolpidem*/
      if drug='N05CF02' then DDD=daily_dose/10;
      if drug='N05CF03' then DME=daily_dose*0.5; /*zaleplon*/
      if drug='N05CF03' then DDD=daily_dose/10;
      label DME='Diazepam Milligram Equivalent Daily Dose';
      label DDD='Defined Daily Dose';
run;
%mend;

%bdzrx;
```

Example Code to Generate Figure (figure 3.9)

```
ODS LISTING file='C:\Users\Jaden\Desktop\RxProportions.jpeg'
image_dpi=600;
title;
proc sgplot data=bdz_by_drug nowall noautolegend;
styleattrs datacontrastcolors=(grey black);
      hbar drug / response=first_year_percent outline fill
outlineattrs=(color=black thickness=1) fillattrs=(color=darkgrey)
barwidth=1
datalabel=change1 datalabelattrs=(style=italic weight=bold)
datalabelpos=data;
      hbar drug / response=last_year_percent datalabel=change2
datalabelattrs=(style=italic weight=bold) datalabelpos=data
fillattrs=(color=lightgrey)
barwidth=0.6;
yaxis discreteorder=data label='Benzodiazepine / Z-Drug'
labelattrs=(style=italic weight=bold);
xaxis min=0 max=0.4 label='Proportion of Total Annual Prescriptions'
labelattrs=(style=italic weight=bold) valuesformat=data;
keylegend / across=2 down=2 border location=outside position=bottom
title='Fiscal Year'
titleattrs=(family=timesnewroman weight=bold size=12)
valueattrs=(family=timesnewroman size=12) linelength=2cm
fillheight=0.5cm;
run;
```

Chapter 4 Code

Processing Rx Use Episode Duration

```
data cohort_rx;
      set cohort_rx;
      by SCRPHIN;
            prev_drug=lag(drug);
            drug=prev_drug;
            prev_rx_start_dt=lag(PRVDDT);
            prev_rx_end_dt=lag(rx_end_dt);
            prev_lapse_dt=lag(lapse_dt);
      if first.SCRPHIN then do;
            prev_drug=""; prev_rx_start_dt=.; prev_lapse_dt=.;
prev_rx_end_dt=.; lapse_dt=.;
            end;
      else do;
            if hosp=1 then
            end;
      format prev_drug $20.;
run;

data cohort_rx;
      set cohort_rx;
      if lapse_dt GE prev_rx_start_dt AND prev_lapse_dt GE PRVDDT then
overlap=1; else
      overlap=0;
run;

data cohort_rx2;
retain cohort SCRPHIN drug prev_drug atc strength MQTYCLM DAYSUPP
PRVDDT rx_end_dt prev_rx_start_dt
overlap epi_start_dt epi_end_dt prev_overlap;
      set cohort_rx;
      by SCRPHIN /*drug*/;
      prev_overlap=lag(overlap);
      drop lapse_dt prev_lapse_dt;
run;

data cohort_rx2;
      set cohort_rx2;
      by SCRPHIN /*drug*/;
      if first.scrphin then do overlap=0; prev_overlap=.;
prev_rx_start_dt=.; prev_rx_end_dt=.; epi_start_dt=PRVDDT; end; else
      if overlap=1 AND prev_overlap=0 AND drug=prev_drug then do
epi_start_dt=prev_rx_start_dt; epi_end_dt=.; end; else
      if overlap=0 AND prev_overlap=1 AND drug=prev_drug then do
epi_start_dt=.; epi_end_dt=prev_rx_end_dt; end; else
```

```
     if overlap=0 AND prev_overlap=0 then do; epi_start_dt=PRVDDT;
epi_end_dt=rx_end_dt; end; else
     if overlap=1 AND prev_overlap=1 then do; epi_start_dt=.;
epi_end_dt=.; end;
     if last.SCRPHIN AND overlap=1 then epi_end_dt=rx_end_dt; else
     if last.SCRPHIN AND overlap=0 then do; epi_start_dt=PRVDDT;
epi_end_dt=rx_end_dt; end;
run;

data cohort_rx2;
     set cohort_rx2;
     format PRVDDT rx_end_dt prev_rx_start_dt prev_rx_end_dt
epi_start_dt epi_end_dt date.;
run;

data cohort_rx3;
     set cohort_rx2;
     if epi_start_dt=. AND epi_end_dt=. then delete;
run;

proc freq data=cohort_rx3;
     format _CHAR_ $missfmt.; /*apply format for the duration of this
proc*/
     tables _CHAR_ / missing missprint nocum nopercent;
     format _NUMERIC_ missfmt.;
     tables _NUMERIC_ / missing missprint nocum nopercent;
run;

data cohort_rx4;
     set cohort_rx3;
     prev_scrphin=lag(scrphin);
     prev_start_dt=lag(epi_start_dt);
     if scrphin=prev_scrphin AND epi_end_dt NE . AND epi_start_dt=.
then epi_start_dt=prev_start_dt;
run;

data cohort_rx4;
     set cohort_rx4;
     if overlap=1 AND prev_overlap=0 then delete; /*deleting all
extraneous observations that have been integrated into one ob in
previous data step*/
run;

proc sql;
select count(distinct(SCRPHIN) from cohort_rx4;
quit;

data cohort_rx4;
     set cohort_rx4;
     if prev_overlap=. then epi_end_dt=rx_end_dt;
run;
```

```
data cohort_rx4;
      set cohort_rx4;
      keep SCRPHIN drug firstrxdate epi_start_dt epi_end_dt;
run;

data use_episodes;
      set cohort_rx4;
      retain SCRPHIN drug firstrxdate epi_start_dt epi_end_dt
epi_length;
      epi_length=epi_end_dt-epi_start_dt;
      keep SCRPHIN firstrxdate epi_start_dt epi_end_dt epi_length;
run;
```

Main Effects Log-Reg Model

```
proc logistic data=cohort descending outest=betas covout;
      class sex (ref=last) age_cat mdsex (ref='2') md_age_group
c_score_cat sefi_cat (ref='Higher SES Status') rub rx_period specialty
/ param=ref ref=first;
      model long_term_use = sex             /*sex*/
                        age_cat          /*age category*/
                         rub             /*resource utilisation band*/
                        frequent_mover  /*high residential mobility*/
                        c_score_cat      /*charlson comorbidity index*/
                        married          /*record of marriage*/
                        income_assist /*record of income assistance*/
                        urbrha           /*region of residence */
                        opioid_use       /*prescription opioid use*/
                        psych_use  /*prescription psychotropic use*/
                        sefi_cat         /*SEFI category*/
                         mdsex           /*Sex of prescriber*/
                        md_age_group     /*Prescriber >50 years old*/
                        rx_period  /*Period of first prescription */
                        specialty  /*prescriber type */
       clodds=both;
run;
```

Appendix 5 – Institutional Review Board Project Documentation

UNIVERSITY of MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)
[illegible] Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone: 204 789 3223
Fax: 204 789 3414

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Jaden Brandt	U of M/Pharmacy	HS20498 (H2017:052)

APPROVAL DATE:	EXPIRY DATE:
March 3, 2017	March 3, 2018

STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):
Dr. C. Leong

PROTOCOL NUMBER: N/A

PROJECT OR PROTOCOL TITLE:
Benzodiazepine and Z-Hypnotic Users in Manitoba from 2001-2015: a Retrospective Population-Based Cohort Study and Analysis of Prescription Drug Utilization Trends

SPONSORING AGENCIES AND/OR COORDINATING GROUPS:
College of Pharmacy, U of M Internal Funds

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
January 24 and February 23, 2017	January 25 and February 23, 2017

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol:		
Protocol		January 31, 2017
Protocol Revisions		February 21, 2017
Consent and Assent Form(s):		
Other:		
Database Extraction Tools		submitted February 23, 2017

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices Tri Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5

of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with the approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

Removed for Privacy

Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary Telephone: (204) 789-3209 Fax: (204) 789-3414

Manitoba
Health, Healthy Living and Seniors
Health Information Privacy Committee
4043-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-786-7204 F 204-944-1911
www.manitoba.ca

April 11, 2017

Jaden Brandt
College of Pharmacy, University of Manitoba
750 McDermot Ave, Winnipeg, MB

HIPC No. 2016/2017 – 62
File number to be quoted on correspondence

Dear Jaden,

Re: Benzodiazepines and Z-Hypnotics in Manitoba (2001-2016): a Retrospective Cohort Study and Analysis of Drug Utilisation Trends

The Health Information Privacy Committee has considered and ***approved*** your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Healthy Living and Seniors for review. Specifically, manuscripts must be submitted *at least 30 calendar days* prior to the intended publication and presentation materials must be submitted *at least 10 calendar days* prior to the presentation.

Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by **MCHP**. If you have any questions or concerns, please do not hesitate to contact xxxxxx Committee Coordinator at (204)786-7204.

Yours truly,

Removed for Privacy

Chair, Health Information Privacy Committee

Manitoba
spirited energy

Appendix 6 – International Correspondence: Knowledge Dissemination and Acquisition Communications

This appendix collects the emails sent and received, related to my thesis topic. The purpose of this section is to document, for my own satisfaction, my professional communication practices as it relates to discussion and dissemination efforts of my research findings. Names of individuals have been removed to protect privacy. However, obsessive investigation on the part of any reader would still likely yield a name. Nonetheless, there were no sensitive matters or confidentiality notices in any emails received.

Correspondence 1:

Dear Dr. XXXX

My name is Mr. Jaden Brandt, Canadian Pharmacist and fellow benzodiazepine researcher (Msc. student). I read with great interest your BZD taskforce's editorial in the journal *Psychotherapy and Psychosomatics.* I agree that a negative rhetoric has accrued over decades of clinical research on BZD. Therefore, the scientific record is indeed deserving of *careful* correction by you and your collaborators. I no doubt suspect that this rhetoric is at least partially attributable to two prominent British clinician researchers who have published extensively on BZD since the 1970's and 80's.

Nevertheless, I write this email to you as an inquiry into the sentence; "a full review on benzodiazepines will be the topic of a number of papers and presentations in the near future." While I eagerly await the work from this taskforce, I am hoping in the interim you would be willing to disclose the sub-topics for planned review. I ask this because I am *considering* conducting a short communication review detailing the proportion of clinical reviews, observational studies etc. (non basic science articles) on BZD, published in the past 10 years, that have unduly emphasized BZD harm at the expense of effectiveness. While I hope to do this in a systematic way, it would likely not be a complete systematic review (more of a rapid review). This would be in an effort to independently verify the broader claims put forth in your teams editorial by a researcher unaffiliated with your group and thus assist in "correcting the record" by making readers aware of the prevailing bias in the literature. Knowing what is planned will ensure my effort is not wasted if your group is planning to pursue the same or similar project on a larger scale.

Warm regards,

Mr. Jaden Brandt, Bsc.Pharm
College of Pharmacy, Rady Faculty of Health Sciences,
University of Manitoba,

Winnipeg, MB, CAN
Orcid ID: https://orcid.org/0000-0003-4571-1079

Dear Mr. Brandt,
thank you for your email. We do not have an exact agenda. Nothing of what you plan to do in making or planning right now. Thus, I encourage to go ahead and put your review together and get it published. I will be happy to assist with advice (but it will be totally your work!).
I think your idea is good and you are right what you write about.
Good luck!
Take care

Correspondence 2:

Dear, Dr. Jaden Brandt

Hello, I am a clinical fellow of department of psychiatry of Seoul National University Hospital in South Korea.

We will publish a review article titled "Clinical characteristics and application of clonazepam" in the Journal of Korean Neuropsychiatric Association. Our authors want to refer to the table 1 in your article "Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs in R&D 2017" in this review article as a reference.

I think your article "Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs in R&D 2017" table 1 is excellent in content and composition. I am looking forward to your agreement and permission.

Send your paper attached.
I will wait for your reply.
Thank you.

XXXXXXX. M.D.

Clinical fellow,
Department of Psychiatry, Seoul National University Hospital
101, Daehak-ro, jongnogu, Seoul, 03080, Rep. of KOREA

Hello Dr. XXXXXX,

I am happy to provide you with permission to refer to or reproduce the table from my article (with appropriate citation of course). Good luck with the review article. Look forward to reading.

Best regards,

Mr. Jaden Brandt (Bsc.Pharm)
College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba Winnipeg, MB, CAN

Correspondence 3 (no response) – To INCB Secretariat

Dear Sir/Madam,

My name is Mr. Jaden Brandt, graduate student in pharmacy at the college of pharmacy, University of Manitoba, Canada. My reasons for emailing you are two-fold:

1) I would like permission to reproduce a few of your figures from your most recent annual technical report on psychotropics. In particular, figures 20 and 23 would be useful to depict regional global consumption rates in an early chapter of my thesis, as my research focus is on the pharmacoepidemiology and drug utilisation of benzodiazepines.

2) On your website, the technical reports only go back as far as 2011. Would you be willing to either share earlier reports, provide benzodiazepine consumption data for Canada as far back as possible or direct me to a Canadian federal government contact who may be able to provide me such data?

Warm regards,

Mr. Jaden Brandt, Bsc.Pharm
College of Pharmacy, University of Manitoba
Winnipeg, MB, CAN

ORCID ID: https://orcid.org/0000-0003-4571-1079

Correspondence 4 (no response) – To WHO Collaborating Centre

Dear Sir/Madam,

My name is Jaden Brandt, I am a pharmacist as well as a pharmacoepidemiology and drug utilization researcher in Canada. I write this email as a proposal for you to consider.

As a brief preface, there is no question that the DDD/ATC methodology, developed and maintained by you (i.e the Collaborating Centre for Drug Statistics Methodology), is important for consistent measurement and reporting of drug use among all international researchers. Indeed, it has been of great value to me and others to ensure general consistency in standardized calculation and interpretation of drug utilization results.

However, recent work has been conducted to adjust the DDD unit based on pharmacologic equivalence between drugs in a class. This is especially important for opioid and benzodiazepine utilization as these drug classes remain highly applicable for public health monitoring in various jurisdictions.

I implore you to consider two publications which present an argument for adoption of this method to be used in addition to the standard DDD method. Please understand that one publication attached (mine) is very recent and, though this contribution has been rigorously peer reviewed, I recognize my bias towards its use and dissemination.

1. Svendsen et al. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliat Med*, 2011. 25(7): 725-732
2. Brandt et al. Translating benzodiazepine utilisation data into meaningful population exposure: integration of two metrics for improved reporting. *Clin Drug Inv. (2018)* https://doi.org/10.1007/s40261-018-0648-y
    - Free shareable link: https://rdcu.be/KFr9

My request is that, upon your expert review of these articles, to consider the suitability of this method for posting and explanation on your website, specifically in regards to these two important drug classes. This should probably be done after this topic is consulted on by your International Working Group for Drug Statistics Methodology. If this method is either endorsed or acknowledged by the collaborating centre it will enable further transparency among those in the DU international research community.

With warmest regards,
Mr. Jaden Brandt (Bsc.Pharm)

Correspondence 5

To umbrand2@myumanitoba

Email Heading: Benzodiazepines and Z-Drugs

[no written text in email from Dr.XXXXX. Only contained attachment of two published articles he authored previously with no explanation of why he was sending them to me]

Dr. XXXXX,

Thank you for the two articles you provided as attachments in the email. Recognizing your longstanding scholarship on this clinical subject, I am quite familiar with your published work already actually. By contrast, as a junior researcher (second year Masters student), I have only produced two relevant publications in this field (attached) which you may or may not be familiar with. In fact, when my review paper was undergoing peer-review last year, an important criticism that was made by a reviewer was to recognize the perspective you put forth in your paper entitled "sleep promoting medications: weighing thehazards of use vs. non-use" for the section on motor-vehicle accidents.

I look forward to following your ongoing work with the International Taskforce on Benzodiazepines.

Warm regards,

Mr. Jaden Brandt, Bsc.Pharm
College of Pharmacy, Rady Faculty of Health Sciences,
University of Manitoba
Winnipeg, MB, CAN

Correspondence 6

Dear Dr. XXXXXX,

I read with interest your editorial in Acta Psychiatrica as a brief commentary on a BZD-Dementia study published in (x month). Your points were well made. These studies are becoming very common it seems in the literature over the past few years. Interestingly, you raised the Bradford-Hill criteria in your paper. Attached you will find a review article of mine from last year that used the Hill causality criteria after careful appraisal of the literature on all major harms purported with BZD and Z-Drugs. Figured you may find it interesting.

Regards,
J. Brandt (Bsc.Pharm)

Dear Jaden Brandt

Thank you for your excellent paper, which I did not know. I can see there is also some references which escaped me. I will take a closer look.
Furthermore I am a bit skeptical about the interpretation of some of the studies on motoric impairment .. and of their external validity. For instance it appears that also melatonin is associated with increased risk of falls and that elderly drivers (more sensitive to benzo sideeffect?) as opposed to younger benzodrivers are not at increased risk (Barbone Lancet 1998; 352: 1331–36. This in spite of more prescriptions in that age group.
Please find attached a small review which they did not allow us to cite (in Danish) – you can easily google translate – it comes out ugly but comprehensible.

Bets

XXXXXX
Professor of Psychiatry
Psychiatric Center XXXXXX and Institute of Clinical Medicine, University of XXXXXXX.

Appendix References

1. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.
2. Swinson RP, Antony MM, Bleau P, et al. Clinical practice guidelines. Management of anxiety disorders. *Can J Psychiatry*. 2006;51(Suppl 2):9S-91S. doi:10.1002/da.1018.
3. NICE. Generalised anxiety disorder and panic disorder in adults: Management. 2011;(January). https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-35109387756997.
4. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi:10.3109/13651501.2012.667114.
5. Davidson JR, Zhang W, Connor KM, et al. A psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). *J Psychopharmacol*. 2010;24(1):3-26. doi:10.1177/0269881108096505.
6. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-439. doi:10.1177/0269881114525674.
7. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175.
8. Sateia MJ, Buysse D, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin sleep Med JCSM Off Publ Am Acad Sleep Med*. December 2016.
9. National Institute for Clinical Excellence. *Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia*.; 2004. https://www.nice.org.uk/guidance/ta77/resources/guidance-on-the-use-of-zaleplon-zolpidem-and-zopiclone-for-the-shortterm-management-of-insomnia-2294763557317.
10. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol*. 2010;24(11):1577-1601. doi:10.1177/0269881110379307.
11. Towards Optimized Practice. Guideline for Adult Primary Insomnia: Diagnosis to Management. *Alberta Clin Pract Guidel*. 2010:1-9.