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Patterns of Benzodiazepine Use and Risk of Injury in the Elderly

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment

of the requirements of the degree of Doctor of Philosophy.

ABSTRACT

Background Benzodiazepines are sedative-hypnotic medications frequently prescribed in elderly patients for several clinical indications. An association with increased risk for falls has been reported but there is continued debate regarding which specific benzodiazepines are associated with this risk.

Objectives To estimate the risk of injuries from falls associated with benzodiazepine use in an elderly cohort taking into account patient characteristics and changes in patterns of use over time.

Methods Using information from provincial administrative health databases, 462,543 community-dwelling, 66 year old Quebec residents were screened for benzodiazepine use in 1989. Subjects who did not use benzodiazepines in 1989 were observed for the next five years to estimate incidence rates and evaluate patient characteristics associated with new use for thirteen benzodiazepines. Patterns of use for incident users were characterized in terms of duration, dose and frequency of switching or adding benzodiazepines. New methods were developed to model the past cumulative dose and duration of benzodiazepine exposure. The impact of benzodiazepine exposure on risk of injury was estimated using Cox proportional hazards analyses with time-dependent covariates to take into account changes in dose and patterns of use.

Results The overall incidence rate for benzodiazepines was 88.7 per 1,000 person-years, with higher rates in women (95.0) than men (81.8). Predictors of incident use were different in individual products and there were systematic differences between users and non-users. Use of anti-depressants in 1989 was the strongest predictor for incident benzodiazepine use

(HR 1.45 to 3.07, p<0.0001). The median duration for uninterrupted periods of use was 31 days (mean=75.5 days, sd=137.2). The mean dose was almost half the recommended maximum adult daily dose and only 8.6% of subjects exceeded the maximum. Older age at date of first prescription significantly increased the likelihood of increasing duration and dose over time (OR=1.02, p<0.0001). All benzodiazepines except clonazepam were significantly associated with an increased risk of injuries from falls (p<0.05). The best predictive model for most benzodiazepines included a cumulative measure of duration and current dose.

Conclusion Benzodiazepines are associated with an increased risk of injuries from falls in elderly patients, however duration of exposure may be more critical than dose. Physiological dependence and withdrawal symptoms appear to play an important role in increasing the risk for many benzodiazepines.

word count: 350

RÉSUMÉ

Situation Les benzodiazépines sont des médicaments sédatifs-hypnotiques fréquemment prescrits aux patients âgés dans différentes indications. Ces médicaments ont été associés à un risque accru de chutes, mais il existe un débat continu sur les benzodiazépines spécifiquement associées à ce risque.

Objectifs Estimer le risque de blessures, consécutives à une chute, attribuable à la prise de benzodiazépines dans une cohorte de personnes âgées, en prenant en compte les caractéristiques des sujets et les variations de profils d'utilisation au cours du temps.

Méthodes A partir des informations contenues dans les banques de données administratives sanitaires de la province, l'utilisation de benzodiazépines a été recherchée au sein d'une cohorte de 462 543 résidents Québécois non institutionnalisés, âgés de 66 ans et plus, en 1989. Les sujets n'ayant pas utilisé de benzodiazépines en 1989 ont été observés pendant les cinq années suivantes afin d'estimer le taux d'incidence et les caractéristiques des patients ayant débuté une benzodiazépine parmi une liste pré-établie de 13. Le profil d'utilisation de ces nouveaux utilisateurs (utilisateurs incidents) a été défini en terme de durée d'utilisation, de dose et de fréquence de changements ou d'addition de benzodiazépines. Des méthodes originales ont été développées pour modéliser la dose cumulée et la durée d'exposition aux benzodiazépines. L'impact de l'exposition aux benzodiazépines sur le risque de blessures par chute a été estimé en utilisant le modèle à risques proportionnels de Cox incluant des variables dépendantes du temps afin de prendre en compte les changements de dose et de profil d'utilisation.

PREFACE

Notes on Manuscript-Based Thesis

This thesis was written as a collection of manuscripts to be submitted for publication. The following section is quoted from the Faculty of Graduate Studies and Research at McGill University *Guidelines for Submitting a Doctoral Thesis* (revised June 2000).

"As an alternative to the traditional thesis format, the dissertation can consist of a collection of papers that have a cohesive, unitary character making them a report of a single program of research. The structure for the manuscript-based thesis must conform to the following:

1. Candidates have the option of including, as part of the thesis, the text of one or more papers submitted, or to be submitted, for publication, or the clearly-duplicated text (not the reprints) of one or more published papers. These texts must conform to the 'Guidelines for Thesis Preparation' with respect to font size, line spacing and margin sizes and must be bound together as an integral part of the thesis.
2. The thesis must be more than a collection of manuscripts. All components must be integrated into a cohesive unit with logical progression from one chapter to the next. In order to ensure that the thesis has continuity, connecting texts that provide logical bridges between the different papers are mandatory.
3. The thesis must conform to all other requirements of the 'Guidelines for Thesis Preparation' in addition to the manuscripts. The thesis must include the following: (a) table of contents; (b) an abstract in English and French; (c) an introduction which clearly states the rationale and objectives of the research; (d) a comprehensive review

of the literature (in addition to that covered in the introduction to each paper); (e) a final conclusion and summary.

4. As manuscripts for publication are frequently very concise documents, where appropriate, additional material must be provided (e.g., in appendices) in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.

5. In general, when co-authored papers are included in a thesis the candidate must have made a substantial contribution to all papers included in the thesis. In addition, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. This statement should appear in a single section entitled 'Contributions of Authors' as a preface to the thesis. The supervisor must attest to the accuracy of this statement at the doctoral oral defense."

For this thesis, in cases of conflict between journal specific-formatting and thesis guidelines, I have followed the McGill conventions for thesis preparation. Papers included in this thesis will be modified to reflect journal criteria before submission for publication.

Contribution of Authors

As PhD candidate and first author on all the manuscripts, I was primarily responsible for conceptualizing, designing and carrying out the research described in this thesis. The overall scope of this research was determined together by myself, Dr. Michal Abrahamowicz and Dr. Robyn Tamblyn and extended some of the original objectives of an earlier study of which Dr. Tamblyn was the primary investigator and Dr. Abrahamowicz was co-primary investigator. Based on the literature review that I conducted and wrote, I developed the specific study objectives for the four manuscripts and prepared the necessary algorithms to generate the final database for these objectives. I also validated the data, performed the statistical analyses, and wrote all the scientific manuscripts as well as the other sections of the thesis.

Members of the thesis supervisory committee who were listed as co-authors provided written feedback on their respective areas of expertise. Drs. Michal Abrahamowicz and Robyn Tamblyn provided guidance and methodological expertise in the conduct of the research and in the interpretation of the results. Dr. Abrahamowicz also provided statistical expertise particularly for operationalizing some of the more complex exposure variables. Dr. Radon Capek provided pharmacological expertise. Clinical expertise was provided by Drs. Johanne Monette and Peter McLeod.

Although not part of the thesis supervisory committee, the contribution of Roxane du Berger as co-author is gratefully acknowledged. Ms. du Berger provided feedback on statistical programming and helped me with developing SAS programs for some of the analyses contained in Manuscripts 2 and 3.

As PhD candidate, I am responsible for the scientific quality of the research, the originality of the ideas and the accuracy of the data contained in these manuscripts.

Statement of Originality

The research in this thesis constitutes original scholarship and advances the knowledge in the domain of epidemiological database studies of post-marketing drug utilization in several ways. In the first manuscript, clinical differences between different types of benzodiazepine users were presented as well as incident rates for individual products. This research presented new information in several ways. First, most published information on benzodiazepine use in this population has been restricted to prevalence rates and does not indicate the rate of new use. The first manuscript provided this information and also demonstrated that the predictors of new use were quite different among the individual types of benzodiazepines. Furthermore, by examining patient characteristics before benzodiazepine therapy, a positive predictive association was found for several factors. Since several of these factors were independently associated with risk of injuries from falls, these original results confirmed the importance of controlling for these variables in any analyses of risk for falls in elderly in order to avoid confounding bias.

In the second manuscript, detailed information was provided on the different aspects of patterns of benzodiazepine use for a five year period. This required developing some new approaches that may be useful in future studies focusing on utilization of other medications. By examining how these patterns change over time, evidence of escalating dose and duration of benzodiazepine use over time was found and older age was implicated as a risk factor for this behavior. These results verified concerns regarding the risk of physiological dependence

with benzodiazepines, particularly for older patients.

The third manuscript presented new statistical methods to model complicated aspects of benzodiazepine exposure, such as estimating effects of cumulative dose, or separating the impact of dose from duration of use. Modeling using these methods provided new insights into the role that physiological dependence and withdrawal symptoms may play in increasing the risk of injuries from falls. These methods were also shown to reduce residual confounding bias in estimating risk of injuries from falls associated with benzodiazepine use and provided a new technique which can be used in future research for the evaluation of different risks associated with other types of medication. This is particularly relevant for the field of drug utilization studies where the drug exposures are often complex and change over time.

Finally, the fourth manuscript applied the results of earlier manuscripts to obtain more accurate estimates of the impact of specific benzodiazepines on the risks of injuries from falls. Specifically, methods proposed in the third manuscript were employed to account for different aspects of drug exposure patterns (Manuscript 2), while adjusting for potential confounders identified in the first manuscript. These methods allowed us to find an increased risk for injuries from falls for almost all benzodiazepines. However, unlike previous research, this risk was found to be associated more with duration of previous use than with current exposure or dose.

Overall, the original findings of this research provided new insights into the mechanisms by which benzodiazepines increase the risk of injuries from falls while the proposed methods offer new tools for other researchers investigating adverse effects of various medications.

ACKNOWLEDGMENTS

This thesis represents much more than the answer to a research question, it is the culmination of my training and experience received over the course of many years. As a result, I have many people to thank for helping me along the way and for enabling me to reach this point. I hope the reader will have the patience to peruse this section since this is one of the few opportunities to publicly acknowledge this help and a small way of saying thank you.

First, I would like to thank Michal Abrahamowicz for not only providing guidance and support throughout my entire graduate school experience, but also for being a fantastic supervisor and a true mentor. Thanks to Dr. Abrahamowicz' thoughtfulness, generosity and kindness, I have received many opportunities and have found a career path that I enjoy enormously and find very fulfilling. Despite an intense research schedule, Dr. Abrahamowicz has always had time for me and continually challenged me to increase my knowledge in both epidemiology and applied biostatistics.

I would also like to thank the members of my supervisory committee. Their enthusiasm and patience helped greatly throughout the process of completing this thesis. Specifically, Dr. Tamblyn provided me with the original data, initiated my interest in the field of pharmacoepidemiology and encouraged me in pursuit of my career. Dr. Radon Capek managed to provide me with an understanding of the complicated issues in pharmacokinetics and pharmacodynamics in a very short period of time and his kindness and meticulous attention to detail was greatly appreciated. Despite full clinical schedules, Drs. Johanne Monette and Peter McLeod had time to provide me with clinical insight as well as critical feedback during the writing process. All my committee members were very generous with their time and energy and have each contributed to my education in this field.

There are several people who were not members of my committee, but who contributed their help and made the completion of this thesis possible. Dr. Roland Grad, along with Dr. Johanne Monette, provided the necessary clinical expertise for deciding which diagnostic codes were included in the definition of the study variables. Jimmy Fragos generated the database from the original provincial administrative health records and showed

great patience in answering my questions and fixing my occasional "mistakes". Sylvain Dancausse went above and beyond the call of duty to ensure that the necessary computer resources were available for me to complete my analyses. Since the research for this thesis was very computer intensive, Sylvain sacrificed a great deal of time, often staying or answering calls after hours, to ensure that all was in working order for my computer. Roxane du Berger was also very generous, spending her time and energy answering my questions about statistical programming and in acting as an excellent sounding board for my ideas and thoughts. Roxane provided the necessary expertise for very complex and sophisticated programming as well as critical feedback, and she has been a great friend and a very understanding office mate. My friends and peers have been a constant source of positive encouragement but I would particularly like to thank Jim Yen for his insider's view on the community-based pharmacies.

Editorial assistance was provided by my long-suffering friends and family, namely Tracie Barnett, who helped put together several tables; my mother, Jackie Bartlett, who painstakingly edited my references and final thesis draft; and my husband, Jochen Esquilant, who edited the final draft and corrected my grammar (in the nicest way possible). I would also like to thank Drs. Karen Leffondré and Bruno Fautrel for their assistance in translating portions of my thesis from English to French. The Division of Clinical Epidemiology at the Montreal General Hospital has been very generous in the provision of physical resources and the secretarial staff, Jennifer Gardner, Barbara Cont, Nadine Bouchard and Tammy Allan, were always helpful and very patient.

I would be remiss in not thanking the many professors in the Department of Epidemiology and Biostatistics at McGill University for providing me with an excellent foundation in epidemiology and statistics, and for being so generous with their time. The department was exceptional in the open-door policy of so many of its faculty for academic and personal concerns of the graduate students. I would particularly like to acknowledge the support and guidance of Drs. Abby Lippman (who taught me that "irregardless" is not actually a word), Christina Wolfson, Margaret Becklake, Jim Hanley and Theresa Gyorkos. These faculty members all contributed to broadening my education and making my graduate

school experience very pleasant. I would like especially to thank Dr. Gyorkos, who acted in Dr. Abrahamowicz' stead during the PhD comprehensive exam process, and who has shown compassion, support, guidance and a sense of humor throughout many difficult times.

Finally, I would like to thank my family who not only put me on this path, but helped keep me there. I am grateful to my parents, Eric and Jackie Bartlett, who believed that I could do anything I set my heart on and made me believe that as well. Their support has never wavered and I must thank my mother for originally introducing me to the field of epidemiology and my father for giving me a love of puzzles in any form. Difficult though it is to admit that your parents were right, I have to say my mother was correct in saying that I would enjoy this field which is basically one giant puzzle. Last but certainly not least, I would like to thank my husband, Jochen Esquilant, for sustaining me throughout this process, for encouraging and inspiring me, and for showing an in-human amount of patience during times of stress.

To all of these people and to those whom I have not managed to include - thank you.

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Collection of the original data by Dr. Robyn Tamblyn was funded by a grant from the National Health Research and Development Program. Generation of data from the original administrative health databases and related programming support was funded, in part, by the Réseau FRSQ sur l'utilisation des médicaments and by an operating grant from the National Sciences and Engineering Research Council of Canada (NSERC) awarded to Dr. Michal Abrahamowicz.

Dedication

To my daughter, Lauren Esquilant, who made it all worthwhile.

and

To the elderly people of Quebec, who made it all possible.

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1.0 INTRODUCTION

1.1 BACKGROUND

Benzodiazepines are sedative-hypnotics that are used for the management of a variety of disorders including anxiety, panic attacks, insomnia, seizure disorders, muscle spasticity, alcohol withdrawal, and as premedicants for surgical or diagnostics procedures (Canadian Pharmacists Association, 2000; Facts and Comparisons, 2000; Mosby Inc., 1999; Rall, 1990; Nelson et al., 1999). While different benzodiazepines vary in their potency and pharmacokinetic parameters, such as rate of absorption, metabolism and half-life, they tend to have similar chemical structures and overlapping clinical indications (Rall, 1990; Canadian Pharmacists Association, 2000; Nelson et al., 1999). Generally, benzodiazepines depress the central nervous system (CNS) producing anxiolytic effects, sedation and hypnosis, anti-convulsant effects, and a reduction in muscle tone and motor coordination (Facts and Comparisons, 2000; Canadian Pharmacists Association, 2000). For the fourteen different benzodiazepines available in Canada since 1990, different pharmacokinetic properties may play a role in drug selection and may also be the most important determinants of possible side effects (Facts and Comparisons, 2000).

Although one of the distinctive features of benzodiazepines that contribute to their popularity is the wide margin of safety between therapeutic and toxic doses,(Klein-Schwartz et al., 1991; Moller, 1999) there is evidence that the elderly are more likely to be sensitive to the effects of benzodiazepines and experience adverse CNS effects such as ataxia, dizziness, confusion and over-sedation (Canadian Pharmacists Association, 2000; Salzman et al., 1983; Kruse, 1990; Hammerlein et al., 1998; Sumner, 1998; Klotz, 1998; Ashton,

1994; Nelson et al., 1999). This is an important issue since benzodiazepines are commonly prescribed to the elderly in both community and institutional settings (Kruse, 1990; Grad, 1995; McNutt et al., 1994; Zisselman et al., 1994; Juergens, 1993; Avorn et al., 1995). Studies have estimated international point-prevalences of approximately 6% to17% for benzodiazepine use in people over the age of 65 who are dwelling in the community (Kirby et al., 1999; Taylor et al., 1998; Dealberto et al., 1997; Gleason et al., 1998; Jorm et al., 2000). In Canada, estimated point-prevalence rates for benzodiazepine use by community-dwelling elderly vary from 12% to 51% (Rojas-Fernandez et al., 1999; Tamblyn et al., 1994; D'Arcy et al., 1994). The large range in the estimated prevalence rates is, in part, attributed to differences in age groups and geographic regions. These figures tend to be slightly higher for hospitalized elderly with point-prevalences of approximately 42%(Woods et al., 1992; Zisselman et al., 1994) and 25% to 50% for elderly in institutions such as nursing homes (Kruse, 1990; Woods et al., 1992; Schjott et al., 1999). Incidence rates for benzodiazepine use in elderly people are more difficult to obtain but several studies estimate that approximately 12% of community-dwelling elderly become new users during the course of one year (Tamblyn et al., 1998b; Dealberto et al., 1997; D'Arcy et al., 1994).

While CNS depression leading to motor impairment may only occur at doses beyond those needed for anxiety relief,(Facts and Comparisons, 2000) benzodiazepine use in the elderly is often characterized by long term use, multiple prescriptions, and concurrent use of other types of medication (Kruse, 1990; Wilcock et al., 1999; Jorm et al., 2000; Taylor et al., 1998; Kirby et al., 1999; Rojas-Fernandez et al., 1999; Tamblyn et al., 1994; Woods et al., 1992; Simon et al., 1996; Egan et al., 2000b). Studies estimate that approximately 17% to

68% of elderly people taking benzodiazepines continue for longer than the recommended maximum of 30 days(Jorm et al., 2000; Rojas-Fernandez et al., 1999; Taylor et al., 1998) and that more than 10% continue for more than 90 days (Jorm et al., 2000; Rojas-Fernandez et al., 1999; Taylor et al., 1998; Egan et al., 2000b; Roberge et al., 1995). One study estimates that 18% of elderly people taking benzodiazepines are concurrently taking at least one other psychotropic drug (Kirby et al., 1999). Elderly women are more likely to be taking benzodiazepines longer and more frequently than men. (Jorm et al., 2000; Rojas-Fernandez et al., 1999; Tamblyn et al., 1994; Gleason et al., 1998; Taylor et al., 1998). These published data indicate that, among the elderly, prescriptions of excess duration with potentially cumulative doses of benzodiazepines are frequently dispensed (Juergens, 1993).

Due to the effects of benzodiazepines and the pattern of their use in elderly people, there is a great deal of concern about increasing the risk of injuries from falls and accidents (Juergens, 1993; Ryynanen et al., 1993; Cumming, 1998; Leipzig et al., 1999; Caramel et al., 1998; Neutel et al., 1996; Ebly et al., 1997; Tamblyn et al., 1998b). Injury from falls and accidents is an important and, unfortunately, relatively common problem in the elderly that has serious implications for morbidity and mortality (Leipzig et al., 1999; Neutel et al., 1996; Ryynanen et al., 1993; Juergens, 1993; Ebly et al., 1997; Mohane et al., 1996). This is especially true for females who are at higher risk for osteoporosis and who thus have a greater likelihood of experiencing fractures from a fall or accident (Scientific Advisory Board, 1996). While several other factors have been identified as risks for injuries from falling and accidents, benzodiazepine use is one of the few risk factors that is potentially

modifiable (Neutel et al., 1996; Ryynanen et al., 1993; Juergens, 1993; Canadian Pharmacists Association, 2000).

Despite the biological basis for a greater risk of injury from falls with benzodiazepine use,(MacDonald, 1985) the empirical research presents conflicting evidence (Kruse, 1990; Cumming, 1998; Leipzig et al., 1999; Juergens, 1993; MacDonald, 1985). A review of published studies indicates that there is an increased risk for injuries due to falls for certain benzodiazepines but there is no agreement as to what dosages, types, specific products or period of benzodiazepine use are associated with such a risk (Leipzig et al., 1999; Neutel et al., 1996; Ray et al., 1989; Ryynanen et al., 1993; Cumming et al., 1993). Limitations of previous studies include lack of control for other risk factors that are associated with risk of falling such as different medications and co-morbid conditions;(Grad, 1997; Mohane et al., 1996) arbitrary grouping of benzodiazepines by therapeutic category; combining benzodiazepines with differing metabolic half-lives and little or no detailed information on dosage (Cumming, 1998; Taggart, 1988; Sorock et al., 1988; Rashiq et al., 1986; Stevens et al., 1989; Ray et al., 1987; Leipzig et al., 1999).

1.2 OBJECTIVES

The objective of this thesis is to determine what aspects of benzodiazepine use put an elderly patient at risk of injury from falling. In order to do this, I will describe the magnitude of benzodiazepine use with the incidence and prevalence of individual products in a cohort of community-dwelling elderly in Quebec from 1990 to 1994. During this period, patient characteristics in terms of demographic factors and other risk factors for falls will be evaluated for different types of benzodiazepine use and to predict new use. Incident users

of benzodiazepines will be observed for a five year period in order to evaluate changes in patterns of use over time.

After completing this description, a cohort study will be conducted to determine the profiles of the patients' characteristics and benzodiazepine use that are associated with the highest risk of injury. Patterns of benzodiazepine use that may be associated with risk of injury will be determined, including cumulative dose, recent dose change, change of medication, and duration of past exposure. Interactions between variables related to benzodiazepine use and selected patients' characteristics will also be explored to determine to what extent the impact of benzodiazepine use depends on age, sex, co-morbidity and level of disability. This will allow for the identification of those elderly at highest risk and which specific benzodiazepines have the highest impact on injuries from falls. This information will be used to provide insight into the mechanism by which benzodiazepine use may increase this risk. The long term objective is the generation of scientific information that could be used to provide improved clinical management of benzodiazepine use in the elderly.

2.0 REVIEW OF LITERATURE

2.1 PHARMACOLOGY OF BENZODIAZEPINES

Benzodiazepines are central nervous system (CNS) depressants that produce their effects by facilitating the synaptic transmission mediated by the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) (Canadian Pharmacists Association, 2000). More precisely, this action is accomplished by binding to specific benzodiazepine receptor sites that are an integral part of the $GABA_A$ receptor-chloride channel protein. Single channel recordings reveal that benzodiazepines increase the frequency of channel openings induced by GABA (Facts and Comparisons, 2000). Evidence suggests that there are at least two distinct benzodiazepine receptors. One type is associated with sleep mechanisms while another is associated with memory, motor, sensory and cognitive functions (Facts and Comparisons, 2000). The clinically used benzodiazepines are not selective in this respect. With these different receptors in various areas of the CNS, benzodiazepines are psychotropic medications that are administered for the purpose of affecting the CNS to impact behavior or psychiatric symptoms.

In general, benzodiazepines are classified as sedative-hypnotics. A sedative drug tends to decrease activity, moderate excitement and calm the patient while a hypnotic drug produces drowsiness and facilitates the onset and maintenance of sleep (Rall, 1990). Despite the fact that benzodiazepines are widely used as anti-anxiety agents, their effects on wakefulness and anxiety are not truly distinct, therefore any classification of benzodiazepines as sedatives versus hypnotics would be somewhat artificial (Rall, 1990; Baldessarini, 1990). Benzodiazepines are also used in other therapeutic categories, namely as anti-convulsants

and muscle relaxants (Rall, 1990; Rall et al., 1990; Baldessarini, 1990; Canadian Pharmacists Association, 2000; Facts and Comparisons, 2000; Mosby Inc., 1999).

Clinical indications for benzodiazepines are numerous and include short term insomnia, anxiety and panic disorders, epilepsy, muscle spasticity, alcohol withdrawal, preoperative and perioperative sedation, as well as conscious sedation for diagnostic procedures (Mosby Inc., 1999; Rall, 1990; Marshall et al., 1990; Baldessarini, 1990; Rall et al., 1990; Uhlenhuth et al., 1999; Uhlenhuth et al., 1998; Nelson et al., 1999). Benzodiazepines are also prescribed for indications that the product is not labeled for or have not been investigated (Nelson et al., 1999). These unlabeled uses include management of irritable bowel syndrome; depression; premenstrual syndrome; chemotherapy induced nausea and vomiting; psychogenic catatonia; chronic insomnia; periodic leg movements during sleep; Parkinsonian dysarthria; acute manic episodes of bipolar affective disorder; multifocal tic disorders; and as adjunctive therapy in the treatment of schizophrenia and neuralgias (Facts and Comparisons, 2000; Moller, 1999). There are over fifty benzodiazepine derivatives available for clinical use worldwide(Rall, 1990; Nelson et al., 1999) but only fourteen were available by prescription in Canada in 1990 (Canadian Pharmacists Association, 2000).

2.1.1 CNS Depression

An interesting and unusual pharmacological feature of benzodiazepines is that the action of the drug changes with increased doses, but there is a wide margin of safety between therapeutic and toxic doses, even at extremely high doses (Facts and Comparisons, 2000; Kruse, 1990; Klein-Schwartz et al., 1991). Generally, sedative-hypnotics depress the CNS

in a relatively non-selective, dose-dependent method that progressively produces calming, drowsiness, sleep, unconsciousness, surgical anesthesia, coma and fatal depression of respiration and cardiovascular regulation (Rall, 1990). Although benzodiazepines are considered sedative-hypnotics and consequently, CNS depressants, by themselves they cannot induce general anesthesia and are essentially unable to cause a fatal respiratory depression or cardiovascular collapse (Rall, 1990; Argyropoulos et al., 1999). With increasing levels, the dose-related CNS depression caused by benzodiazepines first produces a relief of anxiety (calming or drowsiness) followed by anti-convulsant effects, a reduction in muscle tonus and finally, sedation and hypnosis (Canadian Pharmacists Association, 2000; Mosby Inc., 1999). Because of the CNS depression , some of the adverse events associated with benzodiazepines are CNS effects such as an inability to coordinate voluntary muscular movements (ataxia), dizziness and over sedation. These adverse events tend to manifest themselves more specifically as drowsiness; depression; impaired intellectual function; impaired memory; lethargy; impaired coordination; dizziness; nausea and/or vomiting; skin rash; and respiratory disturbances (Rawson et al., 1999; Lader, 1999).

The CNS depressant effects produced by benzodiazepines are additive when administered along with other psychotropic medications, anti-convulsants, anti-histaminics, ethanol and other drugs that also cause CNS depression (Mosby Inc., 1999). Even at recommend daily dosages and without other CNS depressant drugs, these adverse events are more likely to be experienced by the elderly (Canadian Pharmacists Association, 2000; Hammerlein et al., 1998; Kruse, 1990; Sumner, 1998; Klotz, 1998). In order to appreciate

Table 2.1 Pharmacokinetic properties of benzodiazepines available by prescription in Canada, 1990.*

Elimination Half-Life: Benzodiazepine	Properties						
	Approx. Equiv. Oral Dose (mg)	Time to Peak Plasma (hrs)	Protein Binding (%)	Active Metabolites (half-life, hrs)	Pathway of Metabolism	Half-life of Parent Compound (hrs)	Indication
Ultra-short: Midazolam	2	0.3-0.5	-	Yes (1-4)	Oxidation	1.0 - 2.8	anesthetic (i.v.)
Triazolam	0.25	1 - 5	89	No	Oxidation	1.5 - 5.5	insomnia
Short-intermediate: Alprazolam	0.5	1 - 2	80	Yes (6-20)	Oxidation	6 - 20	anxiety, panic
Bromazepam	3	1 - 4	70	Yes (8-19)	Conjugation	8 - 19	anxiety disorders
Lorazepam	1	1 - 5	85	No	Conjugation	10 - 20	anxiety, agitation
Oxazepam	15	2 - 4	97	No	Conjugation	5 - 20	anxiety disorders
Temazepam	30	2 - 3	96	No	Conjugation	8 - 24	insomnia
Nitrazepam	5	1 - 5	87	No	Nitro-Reduction	20 - 40	insomnia, seizure disorder
Long: Clonazepam	0.25	1 - 2	85	No	Nitro-Reduction	20 - 80	anxiety, panic, petit mal & myoclonic seizures
Clobazam	10	1 - 3	85	Yes (36-46)	Oxidation	10 - 30	seizure disorder
Chlordiazepoxide	10	1 - 4	96	Yes (14-100)	Oxidation	10 - 30	mild anxiety, tension states with muscle spasms
Clorazepate	7.5	0.5 - 2.5	95-98	Yes (30-100)	Oxidation	30 - 60	anxiety, tension in psychoneurotic patients, alcohol withdrawal
Diazepam	5	0.5 - 1.5	98	Yes (14-100)	Oxidation	20 - 80	mild anxiety
Flurazepam	30	0.5 - 1.5	97	Yes (40-100)	Oxidation	0	insomnia

* Compi'ed using information from: Compendium of Pharmaceuticals and Specialities, 35th edition (2000); Argyropoulos SV, Nutt DJ. (1999) The use of benzodiazepines in anxiety and other disorders. European Neuropsychopharmacology 9 Suppl 6:S407-S412; Nelson J, Chouinard G. (1999) Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal (Canadian Society for Clinical Pharmacology). Canadian Journal of Clinical Pharmacology 6(2):69-83.

on the strength of the binding (Benet et al., 1990). The binding varies from 70% for bromazepam to almost 99% for diazepam (Rall, 1990).

Circulating benzodiazepines are initially taken up in tissues with high blood perfusion, such as the brain, and subsequently redistribute into low perfusion tissues, such as muscle and then fat (Rall, 1990). Benzodiazepines are metabolized extensively through various complex pathways. Many are biotransformed by oxidative reactions, primarily N-demethylation and hydroxylation yielding often active metabolites. Oxidative reactions may be influenced by various factors, such as age, liver disease or co-administration of drugs that may induce or depress liver-metabolizing enzymes (see Table 2.1). Because some of the active metabolites are biotransformed more slowly than the parent compound, they contribute to the duration of action of many benzodiazepines (Rall, 1990). For example, benzodiazepines such as flurazepam, diazepam, clorazepate and chlordiazepoxide have active metabolites that are slowly metabolized, can accumulate with chronic dosing and produce prolonged effects. The active metabolites and some parent compounds undergo conjugation with glucuronic acid. This reaction results in loss of biological activity and is much less influenced by age, disease or drug interactions. Thus, benzodiazepines such as lorazepam, oxazepam, and temazepam that metabolize through conjugation and do not have active metabolites, are not susceptible to accumulation but may require multiple daily dosing to sustain therapeutic effects (Canadian Pharmacists Association, 2000; Salzman et al., 1983).

Within the wide range of therapeutic plasma concentrations, the elimination of benzodiazepines follows the first order kinetics. Thus the elimination half-life, defined as the

time required for half of the amount of the compound present in the body to be eliminated, is one of the main pharmacokinetic parameters (Benet et al., 1990). This parameter may be used to roughly categorize a benzodiazepine as ultra-short (half-life less than 5 hours), short-intermediate (half-life less than or equal to 24 hours) or long half-life (greater than 24 hours) as listed in Table 2.1. For the remainder of this review, the classification of benzodiazepines by half-life reported in Table 2.1 based on Nelson and Chouinard (1999), will be used (Nelson et al., 1999). It should be noted that this is not a universal method of classifying these drugs, therefore any exceptions will be noted in the text.

The length of the half-life determines when plasma concentrations of benzodiazepines reach a steady state assuming that the drug is administered repeatedly at the same dose and at the same time intervals (Benet et al., 1990). This usually occurs after approximately five elimination half-lives, varying between a few days and three weeks after the initial dose of the drug is administered depending on its pharmacological profile (Canadian Pharmacists Association, 2000; Nelson et al., 1999).

Although half-life is important, all the pharmacokinetic factors must be considered when prescribing a specific benzodiazepine for a given patient. For example, long half-life benzodiazepines, such as diazepam have been shown to be absorbed more quickly and with a faster onset of clinical effects than the intermediate-acting oxazepam despite the fact that oxazepam accumulates less and eliminates significantly faster (Salzman et al., 1983). Which drug is more appropriate will depend on the patient's situation. In other words, for a hypnotic agent, the ideal pharmacokinetic profile would provide a rapid onset of action when taken at bedtime with a sufficiently sustained action to facilitate sleep throughout the night

without residual drowsiness in the morning (Rall, 1990). The pharmacological properties of triazolam would theoretically fit this profile however, triazolam may eliminate too quickly therefore causing rebound early morning insomnia (Rall, 1990). Thus, the different profiles have different clinical consequences and prescribing has to be tailored to best fit the patients' needs.

2.1.3 Pharmacokinetics and Changes in the Elderly

Using the arbitrary but conventional age of 65 years used by governments and researchers to define a person as elderly, the age-related changes in the pharmacokinetics of benzodiazepines are fairly well characterized (Kruse, 1990). A similar dose of a benzodiazepine will be absorbed, distributed, metabolized and excreted less efficiently in an older patient (Salzman et al., 1983). Since the effects of benzodiazepines are partly determined by how long the drug remains active in the body, these age-related changes imply a increased risk of adverse events in the elderly (Salzman et al., 1983).

Specifically, one of the changes seen is a reduction in renal clearance of benzodiazepine as a result of decreased renal function in older adults (Sumner, 1998; Hammerlein et al., 1998). This reduction is more prominent in men than women and increases the amount of time the benzodiazepines remains in the body as well as the rate of accumulation and thus the effective dosage (Sweet et al., 1998; Sumner, 1998).

Another important change is one that occurs in body composition. Older adults tend to have less body water, lower levels of the protein that binds benzodiazepines (serum albumin), and, for females in particular, more body fat (Sumner, 1998; Hammerlein et al., 1998). These changes will result in higher concentrations of benzodiazepines in the plasma

Table 2.2 Changes in the pharmacokinetic properties of benzodiazepines in elderly people.*

Elimination Half-Life: Benzodiazepine	Properties†		
	Clearance Level	Decreased Clearance	Increased Half-Life
Ultra-short: Midazolam	High	in males	in males
Triazolam	High	in males & females	no
Short-intermediate: Alprazolam	High	in males	in males
Bromazepam	High	no	no
Lorazepam	High	no	no
Oxazepam	High	no	no
Temazepam	High	no	no
Nitrazepam	High	no	no
Long: Clonazepam	Low	no	no
Clobazam	Low	in males	in males & females
Chlordiazepoxide	Low	in males	in males
Clorazepate	Low	no	no
Diazepam	Low	in males	in males & females
Flurazepam	Low	no	no

* Adapted from: Kruse WH (1990). Problems and pitfalls in the use of benzodiazepines in the elderly. Drug Safety 5(5):328-44.
† Significant alteration in the elderly compared with younger subjects.

for discriminating among benzodiazepines (Nelson et al., 1999). They define potency as "the affinity of a benzodiazepine compound or its active metabolites for benzodiazepine receptors in vivo" and state that pharmacological potency is "believed to correlate with drug potency in the clinical sense."(Nelson et al., 1999). High potency benzodiazepines include triazolam, alprazolam, lorazepam, bromazepam and clonazepam. Oxazepam, temazepam and chlordiazepoxide are both low potency drugs and clorazepate, diazepam and flurazepam are medium potency (Nelson et al., 1999). Potency is not related to elimination half-life but relatively few researchers have made use of this type of categorization.

Furthermore, the pharmacodynamic changes in benzodiazepines due to aging are not as easily understood as the changes in pharmacokinetics and are only now beginning to be elucidated (Hammerlein et al., 1998; Sumner, 1998). A number of studies have shown a greater variability in the pharmacodynamic effects of benzodiazepines in the elderly that result in an increased sensitivity and an enhanced response to the CNS depressant effects of the medication (Kruse, 1990; Hammerlein et al., 1998; Sumner, 1998; Klotz, 1998). This sensitivity occurs even when pharmacokinetic reactions are similar so that even when absorption, distribution and elimination are the same for the elderly versus younger subjects, the effect of the drug is stronger in the elderly (Kruse, 1990; Hammerlein et al., 1998; Klotz, 1998; Rasmussen et al., 1999).

2.1.5 Tolerance, Dependence and Discontinuation Syndromes

Aside from the increased sensitivity to benzodiazepines and their adverse effects related to CNS depression, the pharmacokinetic and pharmacodynamic changes associated with aging have made elderly people particularly vulnerable to tolerance, physiological

and/or psychological dependence, and effects from discontinuation such as recurrence, rebound or withdrawal symptoms (Nelson et al., 1999; Moller, 1999). Tolerance is believed to occur with prolonged clinical exposure and is defined as a diminishment in the efficacy of the drug with a repeated use so that higher doses are required to produce the same effect (Mayo et al., 1993; Nelson et al., 1999). The development of tolerance to the anti-convulsant, sedative and psychomotor effects has been well documented in all age groups, however there seems to be less tolerance to the anxiolytic effect of benzodiazepines (Nelson et al., 1999; Trevor et al., 2000; Kruse, 1990).

While increasing dosage attributed to tolerance can facilitate the development of dependence, it is not a necessary factor and the two phenomena are distinct (Nelson et al., 1999; Trevor et al., 2000; Moller, 1999). Following conventions developed by the World Health Organization, benzodiazepine dependence is now defined as a syndrome that includes both the psychological aspects, previously described as "addictive behaviours", and the physiological aspects (Nelson et al., 1999; Kan et al., 1997). Traditionally, dependence referred to physical manifestations of withdrawal caused by the body's biological adaption to long term drug use (Puntillo et al., 1997). This physiological dependence can develop without the characteristics of addiction, which implies use for non-medical and/or pleasurable reasons, and can be defined as "the development of clinically meaningful discontinuation symptoms following abrupt withdrawal"(Salzman, 1998). Elderly people are particularly susceptible to benzodiazepine dependence since the factors that play a role in the development of physiological dependence include drug dose, duration, pharmacological properties of the particular benzodiazepine (such as speed of drug

elimination), co-morbidity and predisposition of different users (Martinez-Cano et al., 1999; Holroyd et al., 1997; Kan et al., 1997; Nelson et al., 1999; Ashton, 1994).

Information regarding the incidence and prevalence of benzodiazepine dependence is controversial since dependence may occur even at therapeutic doses making it difficult to distinguish between those who maintain therapy to avoid painful withdrawal symptoms and those who require it long term to treat chronic conditions such as anxiety (Moller, 1999; Woods et al., 1992; Marks, 1985; Kruse, 1990). Although experts agree that dependence can develop during treatment with any benzodiazepine, there is some evidence that those medications with a high potency and short elimination half-life pose a greater risk (Nelson et al., 1999; Moller, 1999; Uhlenhuth et al., 1999; Kruse, 1990; Ashton, 1994).

Dependence on benzodiazepines tends to be a problem because of the three types of symptoms associated with discontinuation: recurrence, rebound and withdrawal (Nelson et al., 1999). Recurrence or relapse symptoms are those symptoms that return after terminating benzodiazepine use and are similar in type and magnitude to pre-benzodiazepine levels. Rebound symptoms are also similar to the original symptoms, only more intense. Finally, withdrawal symptoms are new symptoms that occur with abrupt discontinuation and were not present before benzodiazepine use (Nelson et al., 1999). These symptoms can include depressed mood (dysphoria), depersonalization, loss of appetite, headache, nausea, fatigue, nausea, weakness, dizziness, muscle aches and twitches, and perceptual disturbances (Nelson et al., 1999; Schweizer et al., 1998; Lader, 1999). Any of these symptoms can cause serious difficulties in the elderly, especially if benzodiazepine termination is abrupt (Kruse, 1990; Schweizer et al., 1998; Nelson et al., 1999; Lader, 1999; Olivier et al., 1998).

A full understanding of the consequences of sensitivity to the effects of benzodiazepines and the implications for tolerance, dependence and discontinuation symptoms in elderly people is facilitated by a review of the extent and patterns of benzodiazepine use.

2.2 BENZODIAZEPINE USE IN THE ELDERLY

According to the U.S. Census Bureau, as of July 1, 1999, 12.6% of the United States' population was 65 years of age or older with 7.4% of that being female and 5.2% being male. In the United States in 1999, approximately 34.5 million people were 65 years of age or older. These estimates are mirrored in Canadian statistics. According to Statistics Canada, 12.4% of the 1999 population was 65 years of age or older with 7.1% females, and 5.3% males. In all of Canada, this equates to roughly 3.7 million elderly with 0.9 million of these residing in Quebec. Percentages throughout the provinces are similar and these figures have remained fairly stable since the early 1990's, with only slight increases.

2.2.1 Prevalence of Sedative-Hypnotic Use

This relatively small population is a large consumer of prescription drugs, in particular, benzodiazepines (Gleason et al., 1998; Dealberto et al., 1997; Jorm et al., 2000; Kirby et al., 1999; Tamblyn et al., 1994). However, the estimated rates of use vary considerably according to geographic locations, time frame, source of data and methodology. While there are some inconsistencies among reports, a review of available information will help provide an idea of the magnitude of benzodiazepine use. For instance, a study by Wysowski and Baum (1991) using data from two pharmaceutical marketing research databases in the United States, found that 20.8 million prescriptions were dispensed for

sedative-hypnotic drugs in 1989 (Wysowski et al., 1991). In the 1990 Canadian population, Rawson and D'Arcy (1998) estimate that the twelve month prevalence of sedatives-hypnotics was 10.7% for self-reported use (Rawson et al., 1998).

2.2.2 Prevalence of Sedative-Hypnotics Use in the Elderly

Wysowski and Baum (1991) also found that 17.9 million of the sedative-hypnotic prescriptions dispensed were for benzodiazepines (86%) and of these, 49% were dispensed to patients over the age of 60 years (Wysowski et al., 1991). While no specific details were provided for benzodiazepine use, information on sedative-hypnotic use in Canada showed similar estimates in older age groups. For example, information taken by Rawson and D'Arcy (1991) from a national survey conducted in 1985 determined that 20% of men and 30% of women aged 65 years and over reported using sedative-hypnotics in the last 12 months (Rawson et al., 1991). In 1989, 12% of elderly men and 17% of elderly women reported using this type of medication in the last 30 days (Rawson et al., 1991).

2.2.3 Prevalence of Benzodiazepine Use in the Elderly

A study in the Netherlands by van Hulten et al (1997), using pharmacy records for drugs dispensed, estimates that 11% of their total population received a benzodiazepine during 1990, with most of the users being over the age of 55 years (van Hulten et al., 1998). More detailed information on benzodiazepine use in the elderly was found in a cohort study of community dwelling elderly in the United States conducted by Dealberto et al (1996) in 1988 that estimated that 6% of their participants reported taking a benzodiazepine sometime in the two weeks prior to the interview (Dealberto et al., 1997). A similar study conducted by Gleason et al (1998) in a different location in the United States in 1990 that used

interviewers to establish a medical inventory for each subject, found a higher prevalence of almost 10% for benzodiazepine use during a two week period for participants 65 years or older (Gleason et al., 1998). This rate was close to the point prevalence found in a study by Taylor et al (1998) from Liverpool, England in 1991 where almost 11% of the elderly sample reported currently taking benzodiazepines when interviewed (Taylor et al., 1998). A population of community dwelling elderly in Ireland were interviewed by Kirby et al (1999) between 1993 and 1997 and 17% reported taking benzodiazepines at the time of the interview (Kirby et al., 1999). A similar estimate of point prevalence was also found in a study by Jorm et al (2000) from Australia that interviewed participants that were 75 years or older three times over a 5 year period starting in 1991 (Jorm et al., 2000). In this slightly older group, 16% of the participants reported taking benzodiazepines in all three interviews and 19% reported taking benzodiazepines in at least one of the interviews (Jorm et al., 2000).

Whereas the estimated prevalence rates of benzodiazepine use in the elderly for Canada vary according to province, they remain within a similar range. In the less densely populated province of Saskatchewan, D'Arcy and Blackburn (1994) found that based on records from the comprehensive health care databases, 12% of males and 20% of females over the age of 65 were dispensed a benzodiazepine prescription in 1989 (D'Arcy et al., 1994). This rate was lower than that previously estimated in Canada. Higher rates were found in Nova Scotia by Rojas-Fernandez et al (1999) where records from the provincial administrative database indicated that 28% of the senior population filled a prescription for benzodiazepines in 1993 and 24% in 1996 (Rojas-Fernandez et al., 1999). The highest rates of benzodiazepine prescription were found in Quebec by Tamblyn et al (1994) where drug

information from the provincial databases indicated that 51% of elderly females and 33% of elderly males filled prescriptions in 1989 (Tamblyn et al., 1994). It is difficult to establish if these differences reflect actual rates of benzodiazepine use and are simply due to differences methodologies used by the researchers to estimate the rates (Tamblyn et al., 1994; Rojas-Fernandez et al., 1999; D'Arcy et al., 1994).

All of these estimates are for elderly who were not institutionalized or hospitalized, i.e. were living in the community. Prevalence rates for institutions tend to be higher(Kruse, 1990) with a review by Kruse (1990) on survey data reporting an average point prevalence of 50% among nursing home residents in Denmark, 60% in Australia,(Woods et al., 1992) and 41% in the United States (Kruse, 1990; Woods et al., 1992). A more recent study by Schjott, Opedal and Rutledal (1999) conservatively estimated from drug administration records that 25% of the elderly in nursing homes received benzodiazepines on the day of the study (Schjott et al., 1999). Another study by Zisselman (1994) looked at benzodiazepine use in a university hospital for consecutive admissions during a six month period and using the pharmacy database, estimated that 41.2% of the patients over the age of 65 received benzodiazepines (Zisselman et al., 1994). This finding was similar to the findings from a study of a Toronto Hospital reported in a review by Woods et al (1992) that estimated using pharmacy records that during one month, 42% of elderly patients received a benzodiazepine prescription (Woods et al., 1992). These prevalence rates are considered separately, since factors influencing the use of benzodiazepines in institutions and/or hospitals tend to be very different from those factors influencing benzodiazepine use in the elderly living in the

community (Woods et al., 1992; Kruse, 1990; Grad et al., 1999). The remainder of this review will focus on community-dwelling elderly.

2.2.4 Incidence of Benzodiazepine Use in the Elderly

The incidence of benzodiazepine use in the elderly is not as well documented as the prevalence. In the 1988 study by Dealberto (1997) conducted in the United States, the researchers found that 12% of the elderly participants who had not reported using psychotropics at the first interview, reported starting use within 3 to 6 years (Dealberto et al., 1997). Rates restricted specifically to benzodiazepines were not provided. In the Taylor et al (1998) Liverpool study of the elderly, 2.5% of the cohort reported beginning to use benzodiazepines by the second interview that occurred 1 - 2 years after the initial contact (Taylor et al., 1998). The authors note that this relatively low incidence rate reflected the predominance of prevalent and long-term users of benzodiazepines in the original interview (Taylor et al., 1998).

In Canadian studies, based on administrative drug records D'Arcy and Blackburn (1994) found an incidence rate of 12.4 per 1,000 females in Saskatchewan aged 65 - 69 in 1990 and 10.7 per 1,000 males in the same age group (D'Arcy et al., 1994). In the Quebec study by Tamblyn et al (1998), also based on provincial drug records, exposure rate incidence was 10% in 1991 in the elderly (Tamblyn et al., 1998b). These relatively low incidence rates probably reflect the high levels of elderly already using benzodiazepines by the age of 65.

2.2.5 Patterns of Benzodiazepine Use in the Elderly

While the prevalence and incidence rates give an indication of the number of elderly either starting to or currently taking benzodiazepines, they do not give the whole picture. For a clearer idea of benzodiazepine use in the elderly, patterns of usage must be examined. In other words, which types of benzodiazepines are being used, how long they are used for, what dosage is used, how often one benzodiazepine is replaced by or added to another, and what other medications might be taken simultaneously.

First, benzodiazepine consumption tends to be characterized by long periods of use regardless of the age of the patient (van Hulten et al., 1998; Balestrieri et al., 1997; Wilcock et al., 1999). The maximum defined daily doses (DDD) as established by the World Health Organization(WHO Collaborating Centre for Drug Statistics Methodology, 2000) and the recommended period of usage for benzodiazepines by the drug manufacturers as published in the Compendium of Pharmaceuticals and Specialties(Canadian Pharmacists Association, 2000) are summarized in Table 2.3. Based on both self-reports and administrative databases, the misuse of benzodiazepines seemed to the highest in the 1970's and despite some tapering in the 1980's, a review of more recent literature indicates that recommended doses and time periods are still often exceeded (Kruse, 1990; Woods et al., 1992; Olfson et al., 1994; Simpson et al., 1990).

In a survey of over seven thousand consecutive Italian pharmacy patients presenting a hypnotic drug prescription in 1994, Balestrieri et al (1997) found that 96% of the dispensed prescriptions were for benzodiazepines and of these approximately 73% of the patients reported taking the drug for a year or more (Balestrieri et al., 1997). The long-term users

Table 2.3 Recommended daily doses according to the World Health Organization (WHO)* and Compendium of Pharmaceuticals and Specialities (CPS),† available dosages‡ and manufacturers' recommended use for benzodiazepines, 1990.

Benzodiazepine (Brand Name)	WHO Defined Daily Dose (mg)	Available Doses (mg)	CPS Defined Daily Doses for Elderly	Manufacturers' Recommended Duration of Use
Midazolam (Versed)	15	1 mg/ml 5 mg/ml	2 mg - 3 mg	Used as a premedicant injection under physician supervision.
Triazolam (Halcion)	0.25	0.125 0.25	0.125 mg	Treatment should not exceed 7 - 10 consecutive days.
Alprazolam (Xanax)	1	0.25, 0.5 1.0, 2.0	initial dose: 0.125 mg x 2 - 3 (total =.25-.375 mg)	Clinical studies are limited to 4 months but benefit seen up to 8 months.
Bromazepam (Lectopam)	10	1.5, 3.0 6.0	initial: ≤3 mg in divided doses	Initial course of treatment should not exceed 7 days.
Lorazepam (Ativan)	2.5	0.5, 1.0 2.0	initial: ≤0.5 mg in divided doses	Initial course of treatment should not exceed 7 days.
Oxazepam (Serax)	50	10.0, 15.0 30.0	10 mg x 3 (total = 30.0 mg)	Clinical studies limited to 4 months or less.
Nitrazepam (Mogadon)	5	5.0 10.0	initial dose: 2.5 mg max dose: 5.0 mg	Treatment should not exceed 7 - 10 consecutive days.
Temazepam (Restoril)	20	15.0 30.0	initial dose: 15 mg	Treatment should not exceed 7 - 10 consecutive days.
Clobazam (Frisium)	20	10.0	initial: 5-15 mg max dose: 80 mg	No information given -used as adjunctive for epilepsy.
Clonazepam (Rivotril)	8	0.25, 0.5 1.0, 2.0	8 - 10 mg divided in 3 doses	Minimum of 3 months - alone or adjunctive for seizures.
Chlordiazepoxide (Librium)	30	5.0, 10.0 25.0	5 mg x 2 - 4 (total = 10 - 20 mg)	No information given.
Clorazepate (Traxene)	20	discont. after 1990	3.75 mg	Should be limited to the duration of the episode requiring symptomatic relief.
Diazepam (Valium)	10	2.0, 5.0 10.0	initial:2 mg x 1 - 2 (total: 2 - 4 mg)	As short as possible but should not exceed 2-3 months.
Flurazepam (Dalmane)	30	15.0 30.0	15 mg	Treatment should not exceed 7 - 10 consecutive days.

* WHO Collaborating Centre for Drug Statistics Methodology. (2000) Anatomical therapeutic chemical classification index with defined daily doses.

† Compendium of Pharmaceuticals and Specialities, 35th edition (2000).

‡ List of Medications, Quebec Health Insurance Plan [Liste de medicaments, Regie de l'assurance maladie du Quebec].

were predominantly elderly (82%) and female. Over 71% of the patients taking a longer acting benzodiazepine (defined as a half-life greater than 24 hours; mainly flurazepam) exceeded 12 months of use and only 6% had used the drugs for less than a month (Balestrieri et al., 1997). In the Dutch 10 year cohort study by van Hulten et al (1998), according to pharmacy records, 31% of benzodiazepine users exceeded 180 days of continuous use during 1992 and another 30% had 30 to 180 days of use, resulting in over 60% of the sample exceeding 30 days of use (van Hulten et al., 1998). While the use of the long half-life benzodiazepines such as diazepam and flurazepam had decreased from the levels reported for 1983, in 1992 they still accounted for more than 20% of benzodiazepine prescriptions dispensed in this community in the Netherlands (van Hulten et al., 1998). Overall, these studies demonstrated that over half of the benzodiazepine users exceed the recommended 30 days for all adult age groups in the population (Woods et al., 1992; Balestrieri et al., 1997; van Hulten et al., 1998).

This trend of long term use tends to be even more pronounced in the elderly (Kruse, 1990). In the Australian cohort study of benzodiazepine use by elderly over the age of 75 in 1991, Jorm et al (2000) found that almost 38% of the participants reported using benzodiazepines for three years or more (Jorm et al., 2000). In the Liverpool longitudinal cohort study started in 1989, Taylor et al (1998) found that 70% of the elderly participants reported taking benzodiazepines for at least one to two years and 69% reported still taking them two years later (Taylor et al., 1998). The more recent study conducted in Nova Scotia by Rojas-Fernandez et al (1999), found that despite a decrease in the prevalence of benzodiazepine use exceeding 30 days from the beginning of the study in 1993 until the end

in 1996, according to provincial records, the rate was still 17%, with 10% exceeding 90 days (Rojas-Fernandez et al., 1999).

The potential risks associated with benzodiazepine use in the elderly tend to be increased not only by long term use but also by use of longer half-life benzodiazepines, multiple prescriptions, increased use for females, and concurrent use of other medications (Kruse, 1990; Wilcock et al., 1999; Taylor et al., 1998; Kirby et al., 1999; Rojas-Fernandez et al., 1999; Tamblyn et al., 1994; Woods et al., 1992; Simon et al., 1996). In the Liverpool study by Taylor et al (1998), at the last interview conducted sometime between 1993 to 1995, almost 13% of the reported medications were long half-life benzodiazepines of the type mainly used as hypnotics (Taylor et al., 1998). A study of questionable prescribing practices in Quebec in 1990 by Tamblyn et al (1994) found that according to database records, 36% of the elderly population were taking benzodiazepines longer than 30 days, 15% were taking long half-life benzodiazepines and almost 16% were taking either two benzodiazepines or a benzodiazepine and a sedative (Tamblyn et al., 1994). The prevalence of potentially inappropriate prescribing was higher in females and in the 75 to 79 year age group primarily because psychotropic drugs were more likely to be prescribed to this sub-population (Tamblyn et al., 1994). Another study of Quebec elderly by Egan et al (2000) reported a twelve-month prevalence of long-term continuous use of benzodiazepines of 19.8% (Egan et al., 2000b). The 1990 study in the United States by Gleason et al (1998) found that the second most frequently reported prescribed benzodiazepine for the elderly sample was the long half-life anxiolytic diazepam (18%) (Gleason et al., 1998). Although other medication use was not measured in that particular study, almost 10% of the participants reported using

more than one benzodiazepine (Gleason et al., 1998). In the elderly cohort study conducted by Rojas-Fernandez et al (1999) in Nova Scotia, according to database records, prescriptions of benzodiazepines with half-lives greater than 24 hours accounted for approximately 7% in 1993/94, and 6% in both 1994/95 and 1995/96 of all benzodiazepine prescriptions (Rojas-Fernandez et al., 1999). Almost twice as many elderly females used benzodiazepines (30%) compared to elderly males (17%) and females were also more likely to use the longer half-life benzodiazepines (Rojas-Fernandez et al., 1999). For most of the benzodiazepines, the mean daily dosages, calculated using prescription information, exceeded the recommended maximum daily doses for elderly patients (Rojas-Fernandez et al., 1999). The recommended maximum daily doses were established based on clinical guidelines and from drug monographs (Rojas-Fernandez et al., 1999).

The more recent study in Dublin by Kirby et al (1999) with data collected on the elderly from 1993 to 1997, found that as many as 51% of users reported a prescription for a benzodiazepine with a half-life greater than 24 hours (Kirby et al., 1999). This trend was more pronounced for benzodiazepines used as sedatives (77%) compared to those benzodiazepines used as hypnotics (35%). The Dublin study also found that 8% of benzodiazepine users reported using another benzodiazepine and 11% were using a psychotropic from a different class of drugs (Kirby et al., 1999).

The information from these studies along with other research on polypharmacy suggest that benzodiazepine prescriptions often diverge from recommended use in the elderly. This raises the issue of the sequella of such patterns of benzodiazepine usage. One of the major concerns is that non-optimal benzodiazepine use in the elderly could increase

the risk of injury from falls and/or accidents due to the CNS depression effects (Cumming, 1998; Leipzig et al., 1999; Tamblyn, 1996; Juergens, 1993).

2.3 BENZODIAZEPINES AND THE RISK OF INJURY

While the biological argument that certain of the CNS depression effects of benzodiazepines might increase the likelihood that an elderly user would fall or have an accident seems fairly straightforward,(MacDonald, 1985) empirical research findings have been less clear (Kruse, 1990; Cumming, 1998; Leipzig et al., 1999; Juergens, 1993; MacDonald, 1985). The results of studies using data from the 1970's and 1980's vary with several researchers concluding that benzodiazepines had no effect on the risk of fractures and falls (Taggart, 1988; Rashiq et al., 1986; Stevens et al., 1989; Sorock et al., 1988; Jensen et al., 1991; Weintraub et al., 1993). Some researchers even suggested that certain benzodiazepines might have a protective effect (Rashiq et al., 1986). Still other researchers concluded that there was a significant increase in risk(Ryynanen et al., 1993) but mainly for benzodiazepines with half-lives greater than 24 hours (Ray et al., 1987; MacDonald, 1985; Ray et al., 1989).

A similar pattern is found in research on automobile accidents and benzodiazepines, with several researchers finding no relationship(Jick et al., 1981; Barbone et al., 1998; Leveille et al., 1994)while others reported an increased risk(Skegg et al., 1979; Ray et al., 1992) especially for benzodiazepines with half-lives greater than 24 hours (Hemmelgarn et al., 1997; Ray, 1997). The factors affecting driving are very diverse and only affect those elderly who are still active drivers. The intensity of driving, which is very difficult to measure accurately, is potentially a major confounder since the subjects at higher risk of

cognitive impairment are less likely to drive often. These factors make driving accidents a problematic outcome, especially for database studies. On the other hand, falling is a significant risk for all elderly people with potentially serious sequellae. For this reason, most of the research focus has been on the risk of injury from falls and the remainder of this review will focus on this specific risk.

Many of the studies that evaluated the risk of falls associated with benzodiazepine use grouped the medications as sedatives and hypnotics, and failed to control for differing half-lives or to adequately control for confounders (Kruse, 1990; Rall, 1990). Any factor that is related to either increasing or decreasing the risk of falls in the elderly is a potential confounder in an analysis of the association between benzodiazepines and injuries from falls (Rothman et al., 1998b). Given the serious implications for falls in the elderly, many studies have identified a variety of potential risk factors for injuries from falls in this population (O'Loughlin et al., 1993; Prudham et al., 1981; Campbell et al., 1989; Mayo et al., 1993; Tinetti et al., 1988; Campbell et al., 1990; Close et al., 1999; Tinetti et al., 1989). Table 2.4 summarizes the results from studies that focused specifically on risk factors in community-dwelling elderly. Several other studies have focused on specific risk factors and have identified loss of bone density due to osteoporosis and/or aging in women,(Melton et al., 1986; Cummings et al., 1993; Melton et al., 1987; Melton et al., 1988; Scientific Advisory Board, 1996; Campbell et al., 1990) and the number of chronic disabilities, including visual impairment,(Felson et al., 1989; Tinetti et al., 1986; Mohane et al., 1996) as increasing the risk for injurious falls. Other factors that may increase the risk of injuries from falls included certain chronic diseases such as stroke, heart disease, cognitive impairment and arthritis

Table 2.4 Summary of published prospective studies on risk factors for injuries from falls among community-dwelling elderly.

Study	Study Description	Factors Associated with Significant Increased Risk of Injurious Falls
O'Loughlin, Robitaille, Boivin & Suissa (1993)	1.5 year follow-up of 409 elderly (65 years +)	-older age -days of limited activity -respiratory disorder -high activity levels
Prudham & Evans (1981)	survey of 2,793 elderly (65 years +)	-older age -sex -diuretics, anti-psychotics -history of stroke or heart disease
Campbell, Borrie & Spears (1989)	1 year follow-up of 761 elderly (70 years +)	-stroke -lower extremity arthritis -total number of medications -psychotropic medications
Tinetti, Speechley & Ginter (1988)	1 year follow-up of 336 elderly (75 years +)	-sedatives -cognitive impairment -lower extremity disabilities
Koski, Luukinen, Laippala, & Kivela. (1996)	1 year follow-up of 979 elderly (70 years +)	-cardiac medications -lower extremity disabilities

(Buchner et al., 1987; Prudham et al., 1981; Campbell et al., 1989; Tinetti et al., 1988; Stevens et al., 1989; Ryynanen et al., 1993). Many studies have also focused on the role medications play in altering the risk of falling (Mohane et al., 1996; Cumming, 1998; Leipzig et al., 1999; MacDonald, 1985). Certain drugs such as thiazide diuretics have been found to have a protective effect for the risk of injury(Cumming, 1998; O'Loughlin et al., 1993; Taggart, 1988; Rashiq et al., 1986) while other drugs such as psychotropic medications other than benzodiazepines, contribute to an increased risk of falls or injury from falls (Tinetti et al., 1988; Mayo et al., 1993; Campbell et al., 1989; Prudham et al., 1981; Ebly et al., 1997; Jensen et al., 1991; Ryynanen et al., 1993; Sobel et al., 1983; Mohane et al., 1996).

2.3.1 Review of Published Studies of the Association Between Benzodiazepine Use and Risk of Injury from Falls

In a recent review of psychotropic medication and the risk of falls in the elderly, Cumming (1998) listed 16 studies from 1981 to 1995 that dealt with community-dwelling elderly (Cumming, 1998). Of these studies, only three examined benzodiazepines specifically and results were inconclusive, with statistically non-significant odds ratios of 0.6, 1.5 and 1.7 (no confidence interval given) (Cumming, 1998). Cumming (1998) also noted the same conflicting evidence for short versus long acting benzodiazepines and concluded that the dosing may be more important than type of benzodiazepine (Cumming, 1998). None of the studies in the review included information on dosing for benzodiazepines. Several other studies conducted in the early to mid 1980's found no significant effects for benzodiazepines on the risk of falls or fractures. However, most of these studies did not control for any confounders other than age or gender (Taggart, 1988; Sorock et al., 1988; Rashiq et al., 1986), one study used hospital controls for hip fractures (Stevens et al., 1989)

and the other study did not classify benzodiazepines separately from other psychotropic medications (Ray et al., 1987).

Similar methodological problems were found in a meta-analysis by Leipzig et al (1999) of 40 studies conducted during the period from 1983 to 1993 (not including the above-mentioned studies) that examined the link between psychotropic drugs and falls in patients over 60 years old. Leipzig et al (1999) reported a pooled odds ratio of 1.44 (95% CI, 1.09 - 1.90) for short acting (half-life ≤24 hours) benzodiazepines but no significant effect for long acting (half-life >24 hours) products (O.R.=1.32; 95% CI, 0.98 - 1.77) (Leipzig et al., 1999). However, only 14 out of the 40 studies included information specific to benzodiazepines and the authors noted that only nine of these studies were able to provide separate data on short and/or long acting benzodiazepines (Leipzig et al., 1999). Furthermore, although stratified analyses were used to control for age, with a cut-off at 75 years, residence and use of other medication, few of the studies reported information on any other confounders for falling and no mention was made of dosing (Leipzig et al., 1999).

More recent studies have reported some significant findings but still seem to have apparently conflicting conclusions. For instance, Neutel et al (1996) found that in a case control study of hospital admissions due to injuries from falls in the Saskatchewan Health Databases from 1979 to 1986 for all ages, the highest risk of serious injury due to falls for people over 60 years was for men filling a prescription for benzodiazepine hypnotics (triazolam or flurazepam) four weeks prior to the injury with an adjusted odds ratio of 4.0 (95% CI, 2.4 - 6.6). The next highest risk was also for men filling a prescription for benzodiazepine sedatives (oxazepam, lorazepam or diazepam) four weeks prior to the injury

with a reported adjusted odds ratio of 2.5 (95% CI, 1.4 - 4.3). Women filling a prescription for benzodiazepine hypnotics and sedatives, four weeks prior to an injury had a lower risk for injuries due to falls with odds ratios of 2.3 (95% CI, 1.7 - 3.2) and 1.6 (95% CI, 1.2 - 2.3) respectively (Neutel et al., 1996). When examining the five individual benzodiazepines, the authors found that all the drugs had statistically significant increased risks among subjects 60 years and older, however the long acting flurazepam had the highest odds ratio of 3.4 (95% CI, 2.5 - 4.7) followed by the short acting triazolam with 2.7 (95% CI, 2.0 - 3.6) (Neutel et al., 1996). While the authors did adjust for age, sex and concomitant use of other sedatives, a lack of information in the database did not allow for control of mental and physical status, or dosage (Neutel et al., 1996).

In another case control study using the Saskatchewan Health Database conducted over a similar time frame, from 1977 - 1985, Ray, Griffin and Downey (1989), estimated the risk of hip fracture in subjects over 65 years of age (Ray et al., 1989). The authors compared current benzodiazepine use in short acting (half-life $\leq$24 hours) versus long acting (half-life >24 hours) benzodiazepines. After adjusting for sex, age, calendar year, residence status, and history of hospitalization, the relative risk of hip fracture associated with filling a long-acting benzodiazepine prescription within the preceding 30 days was 1.7 (95% CI, 1.5 - 2.0) however, the risk for short-acting benzodiazepines was non-significant (relative risk=1.1; 95% CI, 0.9 - 1.3) (Ray et al., 1989). Unlike the previous study, the authors did not find a statistically significant effect for individual drugs but this study focused on hip fractures and excluded other injuries due to falls (Ray et al., 1989).

In an interesting case control study conducted from 1987 to 1988, Ryynänen et al (1993) investigated medications and chronic diseases as risk factors for falls that required medical treatment (Ryynanen et al., 1993). Both cases (n=380) and controls (n=342) were required to give a sample of blood to determine serum benzodiazepine concentration. In a multiple logistic regression analysis, after adjusting for an extensive list of chronic diseases, mental capacity, other medication use, and age, serum benzodiazepine was found to have a significant odds ratio of 3.3 (95% CI, 1.6 - 6.9) for men and 3.9 (95% CI, 1.6 - 6.9) for women for the risk of falls. The researchers found that information from interviews on medications taken 24 hours before the fall showed an under-reporting of 10 - 15% for benzodiazepine use compared with serum concentrations (Ryynanen et al., 1993). The authors believed that this under-reporting may be due to some of the longer acting benzodiazepines still having derivatives in the blood several days after taking the medication (Ryynanen et al., 1993). While the evidence for benzodiazepines increasing the risk of a fall seems very convincing, the study design did not allow for further investigations of specific products and patterns of use.

In another study, using data collected in 1991 by the Canadian Study of Health and Aging, Ebly et al (1997) collected self-reported information on history of falls and medication use to examine the risk of falls in 10,263 elderly subjects (Ebly et al., 1997). Benzodiazepines were classified according to short versus long acting with duration of use dichotomized into less than or greater than 30 days. However, the authors did not indicate what specific criterion was used for classifying short versus long or what specific benzodiazepines were included (Ebly et al., 1997). After adjusting for age, sex, mental

health status, depression, other medication, Parkinson's disease and narcotic use, benzodiazepines remained a significant predictor for adverse outcomes including falls (Ebly et al., 1997). In subjects that were cognitively normal, the frequency of falls was 60% greater in benzodiazepine users than in non-drug users (Ebly et al., 1997). The authors did not find a difference for short versus long acting benzodiazepines or for use less than 30 days compared to use greater than 30 days (Ebly et al., 1997). Ebly et al (1997) caution against extrapolation of their results to the general elderly population since the original study pre-selected subjects mainly on the basis of cognitive impairment and residency (Ebly et al., 1997).

In an Australian case control study, Cumming and Klineberg (1993) estimated the risk of hip fractures for self-reported benzodiazepine use in 209 elderly cases and 207 controls during 1991. Four different benzodiazepines were examined (diazepam, nitrazepam, oxazepam and temazepam). A significant increase in risk with use was found only for the short acting temazepam with an adjusted odds ratio of 3.52 (95% CI, 1.07-11.54) (Cumming et al., 1993). After adjusting for age, sex, type of residence, alcohol consumption, body mass index, cognitive status, dairy product consumption, health status, physical activity, proxy status, smoking history and use of other medications, the odds ratio for any benzodiazepine use was not significant (1.55; 95% CI, 0.95-2.54) (Cumming et al., 1993). However, the study also failed to find a statistically significant effect for many other medications that have previously been implicated as risk factors for hip fractures; likely because the study lacked statistical power to detect these effects (Cumming et al., 1993).

The differences in statistically significant findings among these more recent studies are depicted graphically in Figures 2.1 and 2.2.

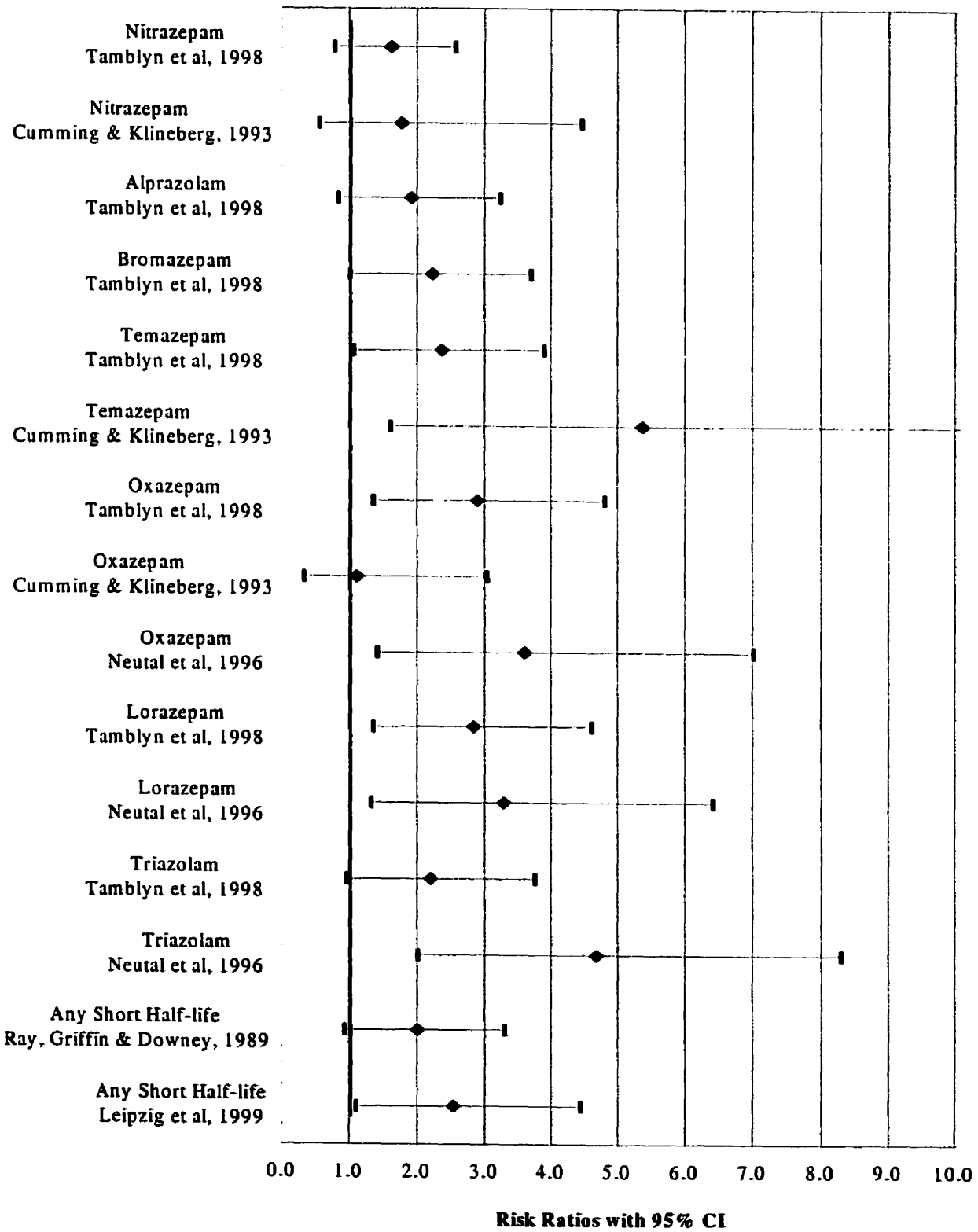
2.3.2 Comparison of Methods Used in Published Studies of Association Between Benzodiazepine Use and Risk of Injury from Falls

The lack of consistency in results for published studies on the use of benzodiazepines and the risk of injury from falls may be due to differences in methodology and sources of data. A detailed examination of the methods used in the previously reviewed studies show substantial deficiencies in sources of data; study design and population; ascertainment and representation of different aspects of benzodiazepine use; measurement and type of injury used for outcomes; adjustment for confounders; and methods for statistical analyses. Each of these methodological features will be reviewed in brief.

2.3.2.1 Study Design and Data Source

Cumming and Klineberg (1993) in their Australian study and Ryynanen et al (1993) in their Finnish study both used a case-control design,(Cumming et al., 1993; Ryynanen et al., 1993) while Ray, Griffin and Downey (1989) used a nested case-control design drawn from the Saskatchewan Health Databases (Ray et al., 1989). Ebly, Hogan and Fung (1997) used collected data to conduct a retrospective analysis (Ebly et al., 1997). The data was obtained from a cohort enrolled in the Canadian Study of Health and Aging that was originally designed to determine the prevalence of dementia in Canadians 65 years and older (Canadian Study of Health and Aging Working Group, 1994). Finally, Tamblyn et al (1998) and Neutel et al (1996) used extensive databases to conduct cohort studies on the elderly populations in Quebec and Saskatchewan, respectively (Neutel et al., 1996; Tamblyn et al., 1998b). Population based studies are more robust in that they are less susceptible to selection

Figure 2.2 **Risk ratios with 95% confidence intervals (CI) for recent published studies that reported results for specific benzodiazepines with long elimination half-lives (≥24 hours).**



controls with a lower rate for controls. The non-responders may have differed systematically from the responders on an important factor, for example health status, and with the different rates among cases and controls, these studies would be susceptible to non-differential missclassification bias.

In the first nested case-control study from the Saskatchewan Health Databases, both cases and controls were drawn from the community as well as nursing homes (Ray et al., 1989). The cases in this study were diagnosed between 1977 to 1985 with a fracture of the proximal femur (hip) according to International Classification of Diseases 9th Revision (ICD-9(Practice Management Information Corporation, 1993)) codes 820.0 - 820.9 (n=4501). Cases were excluded based on a history of hip fracture from 1970 to 1976, neoplastic disease, or if the cause of injury was major trauma. Five controls were selected for each case (n=24,041) and matched on sex and year of birth (± 1 year). The controls had to be alive at the time of the hip fracture for the matching case. Both cases and controls were excluded if they were Aboriginals or if they were hospitalized 30 days prior to the admission for hip fracture since no medication information would be available in either scenario. Although this was based on a population cohort, the exclusion criteria for the cases differed from those applied to the controls, again raising the question of selection bias

In comparison, the study using data from February, 1991 to May, 1992 in the Canadian Study of Health and Aging, was based on a sample of 10,263 elderly subjects (Ebly et al., 1997). These subjects had been assessed for cognitive abilities and included those who scored <78 on the Modified Mini-Mental State or who could not take the exam (n=1165), all institutionalized subjects (n=1225) and a random sample of the community

laceration or fall-related admissions to hospital. Since the authors of this study effectively used the entire elderly population, the possibility of selection bias was greatly reduced.

For all of these studies, the operational definitions differed for the outcome of interest which may have reduced the precision of the studies that limited their outcome to one type of injury related to falls. Also, the age and source of the elderly population varied considerably. This might not have affected the generalizability of the results, however the inclusion of nursing home residents would have limited the comparability of the study results. Since nursing home residents are frequently more frail, often with restricted levels of activity and mobility, the risk factors among these elderly and community-dwelling elderly may be quite different (Stoudemire et al., 1996; Sobel et al., 1983; Ruthazer et al., 1993; Granek et al., 1987).

2.3.2.3 Classification for Benzodiazepine Exposure

Assessment of exposure to benzodiazepines varied among studies. In the two case-control studies and the study that used data from the Canadian Study of Health and Aging, all medication use was mainly self-reported (Cumming et al., 1993; Ryynanen et al., 1993; Ebly et al., 1997). In the remaining studies, medication information was retrieved from pharmacy billing records contained in provincial databases (Ray et al., 1989; Neutel et al., 1996; Tamblyn et al., 1998b).

For the case-control study based in Australia, the self-reported current use of a benzodiazepine (before hospital admission for cases) was represented as a yes/no independent binary variable for the prediction of hip fractures (Cumming et al., 1993). In the Finnish case-control subjects, self-reported benzodiazepine use in the last 24 hours was also

benzodiazepine use were represented as independent binary variables for the risk of hip fracture and modeled in separate analyses (Ray et al., 1989).

The study, based on information collected for the Canadian Study of Health and Aging, also used five categories to classify the type of benzodiazepine use according to self-reports of current medication use (Ebly et al., 1997). The main variable was a binary indicator of benzodiazepine use as a predictor for a history of self-reported falls. Further analyses compared the following groups represented by indicator variables: (i) long acting benzodiazepines used less than 30 days; (ii) short acting benzodiazepines used less than 30 days; (iii) long acting benzodiazepines used more than 30 days; (iv) short acting benzodiazepines used more than 30 days; and (v) the use of more than one benzodiazepine (Ray et al., 1989). The authors did not provide information as to which specific benzodiazepines were included in each group, or how they characterized the length of the half-life.

In the earlier study that used the Saskatchewan Health Database, Neutel et al (1996) used pharmacy billing records to assess benzodiazepine use 60 days before a fall-related hospitalization (Neutel et al., 1996). The authors also used a binary variable to assess the impact of filling a prescription for a benzodiazepine on the risk of injuries from falls. Benzodiazepines were grouped as sedatives or hypnotics but were also examined individually (triazolam, flurazepam, diazepam, lorazepam, oxazepam). The benzodiazepine users were also further categorized into three groups according to how much time had passed between filling the most recent prescription and the occurrence of an injury (less than 15 days, 15-28 days, 29-60 days).

Since most of these studies used a binary variable for current benzodiazepine use, this did not allow for time-dependent changes in benzodiazepine exposure. Therefore, a subject who filled only one benzodiazepine prescription for a five day period would have been considered equivalent to a subject that continually filled benzodiazepine prescriptions for a much longer period of time. Given that benzodiazepine exposure is characterized by periods of use and non-use, this over-simplification would be expected to lead to missclassification and possibly bias the estimate of association. Furthermore, only Tamblyn et al (1998) went beyond on/off classification of benzodiazepine exposure and attempted to look at daily dose (Tamblyn et al., 1998b).

In their analysis of Quebec database information, Tamblyn et al (1998) used pharmacy billing records to assess benzodiazepine use in the elderly (Tamblyn et al., 1998b). Benzodiazepines were grouped as short-acting (half-life $\leq$ 10 hours; triazolam, temazepam, oxazepam), intermediate-acting (half-life $\geq$ 11 hours and $\leq$48 hours; alprazolam, nitrazepam, bromazepam, lorazepam) and long-acting (half-life > 48 hours; chlordiazepoxide, flurazepam, diazepam). The drugs were also assessed by individual products. The use of a benzodiazepine was treated as a time-dependent variable in a survival analysis for the risk of injury from falls. Two types of analyses were conducted. In the first, periods of benzodiazepine use were compared to periods of non-use in persons using the same drug and in the second, periods of use and non-use in new users were compared to a random sample of non-users. Dose was also included as a covariate and standardized using the World Health Organization defined daily dose for benzodiazepines (Tamblyn et al., 1998b; WHO Collaborating Centre for Drug Statistics Methodology, 2000). In order to facilitate the

interpretation of the results, the analyses were restricted to users of a single benzodiazepine who did not switch medications. Subjects who did not have a fall were censored at the time when they either changed benzodiazepine products or added an additional benzodiazepine.

The main reason for not including the period after such a switch was the expectation, confirmed by preliminary analyses,(Tamblyn et al., 1998b) that the change of medication may have been a marker for adverse effects, likely related to some unaccounted for frailty of the individual. In other words, the association between a new (changed) medication and injuries among "switchers" might be confounded by indication bias. Patients experiencing problems with their initial medication may be prescribed a "safer" medication creating a spurious association between negative outcomes and such medications (Tamblyn et al., 1998b). The reason for censoring when a subject added another benzodiazepine was to focus on independent effects of specific benzodiazepines while avoiding additional methodological problems that could arise in modeling the effects of simultaneous exposure to different benzodiazepines and the subsequent complex additive effects (Tamblyn et al., 1998b; Tamblyn et al., 1998a).

2.3.2.4 Adjustment for Potential Confounders

While all the reviewed studies adjusted for age and sex, the categorization of age and the method of adjustment for both age and sex varied between studies, from strata sampling to matching in control selection. Furthermore, there was a great deal of heterogeneity among the remaining variables that were included in the analyses in order to control for potential confounders for the risk of falls. Previous reviews of the role of medications in the risk of

falls concluded that any evaluation of falls must have adequate, uniform assessment of confounders (Mohane et al., 1996; Tinetti et al., 1988).

2.3.2.5 Statistical Methodology

All of the studies, with one exception, used multiple logistic regression to model the risk of benzodiazepine use on injuries or falls (Cumming et al., 1993; Ryynanen et al., 1993; Ray et al., 1989; Ebly et al., 1997; Neutel et al., 1996). Like all methods of analysis, use of logistic regression analysis is limited by the assumptions underlying the model. Since one of the assumptions in logistic regression is that the log of the odds will have a linear relationship with the main variable of interest, this method will not detect risks that might peak within a short time or at a specific dose (Hosmer et al., 1989). Furthermore, if there is an effect that changes over time, this information will be lost altogether (Tamblyn et al., 1998a). The assumption of linearity was not tested in these studies and it is plausible that the risks change over time. This is supported by evidence from the study in which Neutel et al (1996) dichotomized the duration of risk, and found the greatest risk for serious injury due to falls was within 15 days of filling a benzodiazepine prescription (Neutel et al., 1996). Several other authors did attempt to model the time dependent effect of the benzodiazepines by categorizing users according to time since prescription (Ray et al., 1989; Ebly et al., 1997), however the results were dependent on the cut-offs established by the authors.

Tamblyn et al (1998) attempted to account for changes over time by using survival analyses to model the time-dependence of benzodiazepine use on the risk of falls (Tamblyn et al., 1998b). This approach allowed benzodiazepine exposure to change over time providing the most refined classification of differentiating use from non-use by day.

Table 2.5 Summary of methods review for published studies of association between benzodiazepine use and risk of injury from falls.

Study	Design/Sample Size	Study Population	Outcome	Exclusion Criteria	Benzodiazepine Exposure	Statistical Methodology	Confounders
Cumming & Klineberg (1993)	case-control sample size: cases=209 controls=207	elderly in a circumscribed geographical area of Sydney incl. nursing homes: 1990 - 1991	hip fracture	-neoplastic disease	binary, self-report of current use: - diazepam - nitrazepam - oxazepam - temazepam	- bivariate analyses to pick confounders - multiple logistic regression	- 5 year age groups - sex - type of residence -alcohol consump. - body mass index - cognitive status - diary products - health status - physical activity - proxy status - smoking history - other medications
Ryynänen et al (1993)	case-control sample size: cases = 380 controls = 342	elderly in a circumscribed geographical area of Finland incl. nursing homes: 1987 - 1988	injury from first fall of year	none	- binary, self-report of any use 24 hrs before fall - binary, presence of serum benzodiazepine in blood	- bivariate analyses to select confounders - multiple logistic regression with step-wise selection - stratified analysis by sex	- age (65-74 vs 75+) - cognitive status - depression - diabetes - heart disease - oesteoarthrosis - musculoscletal dx - urinary tract infect. - resp. disease - lower ext. arthrosis - hypertrophy prost. - other medications
Ray, Griffin & Downey (1989)	nested case-control matched on sex and birth year ± 1 year cases=4,501 controls=24,041	elderly alive at time of event incl. nursing homes, in Saskatchewan Health Database: 1977-1985	fracture of proximal femur (hip)	- previous hip fracture - cancer - cause of injury code for major trauma -native status - hospitalized 30 days before event	- binary, 5 groups for long acting use: current (script in last 30 days), indeterminate (31-90 days), former (91-365 days), other drugs (short-acting, antidepressants, antipsychotics) - binary, 2 groups for current users: first time users, dose (high vs low)	- unconditional multiple logistic regression	- age (65-74, 75-84, 85+) - sex - index year (4 x 2 year categories) - type of residence - hospitaliz. history

Table 2.5 Continued

Study	Design/Sample Size	Study Population	Outcome	Exclusion Criteria	Benzodiazepine Exposure	Statistical Methodology	Confounders
Ebly, Hogan & Fung (1997)	retrospective cohort; random selection of stud population: N= 2,053	elderly from the Canadian Study of Health and Aging incl. nursing homes (N=10,263): 1991 - 1992	answer to "Did or does the subject have falls?"	- moderate to severe dementia	- binary, self-report of current use - 5 groups: long acting < 30days, >30 days, short acting <30 days, >30 days, multiple use	-stepwise multiple logistic regression stratified by cognitive status	- age (? categories) - sex - mental score - depression - Parkinson's - stroke - lower ext. problems - visual impairment - antidepressant use
Neutel et al (1996)	comparative cohort, 2 controls matched on sex, 10 year age groups: N=321,422 (for over 60 yrs: N=132,873)	adults over 20 years old in Saskatchewan Health Database: 1979-1986	injury due to first fall 60 days after filling script (controls given same date)	none	binary, billing records of use: - triazolam - flurazepam - diazepam - lorazepam - oxazepam time since filling script: <15 days, 15-28 days, 29-60 days	-multiple logistic regression restricted to 60 years plus, stratified by sex	- other medication (30 days prior) - drug/alcohol abuse - social assistance
Tamblyn et al (1998)	cohort 66 years or older: N=273,248	elderly in Quebec Health Databases: 1989-1990	injury due to first fall	- nursing home resident - use of benzo. in 1989	- time-dependent, billing record of use (13 types) - continuous, standardized dose	- multi-variate survival analysis comparing period of use with non-use	- drug half-life - age (5 year groups) - sex - visual impairment - stroke - lower ext. arthritis - dementia/Parkinson - other psychotropics - injury in 1989

2.4 OBJECTIVES

The overall objective of this thesis is to estimate the risk of injury due to falls associated with complex patterns of use including cumulative duration of use and cumulative dose using a prospective cohort design. In order to do this, the further objectives are:

1.a To estimate the incidence and prevalence of benzodiazepine use in Quebec elderly during a five year period, overall and for individual products.

1.b To determine the characteristics associated with incident use relative to non-use in terms of demographic features (age, sex, level of urbanization), and health status (co-morbidity, disabilities and contraindications, use of health care services).

1.c To estimate, for new users, the prevalence of labeled indications for use in the year before filling the first prescription.

2. To describe, among new users of benzodiazepines, initial and evolving patterns of use over time in terms of duration of uninterrupted use, dosage, switching or adding of prescriptions, and specific benzodiazepines.

3. To investigate methodological issues associated with modeling complex benzodiazepine exposure, such as cumulative dose and duration.

3.0 OVERVIEW OF STUDY DESIGN AND DATA SOURCE

3.1 STUDY DESIGN

In order to achieve the thesis objectives, a historical cohort of Quebec residents who were 66 years old as of 1989, was assembled through provincial population health databases. Detailed information was collected from provincial demographic, billing, prescription and hospitalization databases for one calendar year, 1989, to assess health status and benzodiazepine exposure for 462,543 subjects. Using a cohort analytic design, the 252,811 subjects who did not fill a benzodiazepine prescription for that year were followed for an additional five year period to allow for time-dependent assessments of new benzodiazepine exposure and occurrence of injuries from falls.

This study utilizes similar data to that collected by Tamblyn et al(Tamblyn et al., 1998b) for a study funded by the National Health Research and Development Program (File 952249). Tamblyn et al examined current use and dose for individual benzodiazepines to determine which products were associated with the risk of fractures, lacerations, soft tissue injury and accident-related hospital admissions in a cohort of Quebec elderly who had not filled a benzodiazepine prescription during the baseline period. The cohort of 273,248 subjects was selected from the provincial databases and studied over five years to determine the relative safety of different benzodiazepines. The current study utilized similar eligibility criteria for collection of the data from the same original administrative databases, however, benzodiazepine exposure was measured in greater detail and focused on changes in patterns of exposure over time in terms of duration, dose and switching or adding of different products. This study received a certification of ethical acceptability for research involving

data were available for all medical services billed to RAMQ by any physician for the patients defined in database (1);

(3) the prescription claims database from RAMQ contains all the prescriptions filled in any community-based pharmacy in Quebec. It contains the PID, professional class, prescribing physician identification, encrypted pharmacy identification, codes for prescription drug, dosage, strength, and generic name, American Hospital Formulary class, quantity, duration of prescription, codes for substitution, renewal and type of prescription, date of prescription, and cost. These data were available for prescriptions billed to RAMQ by any community-based pharmacy for the patients in database (1);

(4) the hospitalization database (MED-ECHO) from the Ministère de la Santé et des Services Sociaux (Quebec Ministry of Health and Social Services) consists of the PID, type of institute, date of admission and discharge, total number of days of stay, death, death 48 hours before or after admission, type of physician, principal diagnosis, secondary diagnoses (up to 8), date of accident, code of accident (if applicable), discharge destination and treatment codes. This information was available for all hospital admissions for the patients in database (1).

The detailed description of the variables contained in each database is listed in Appendix II.

There were several advantages to using these population-based provincial databases for this study. The almost universal level of health care coverage for people over the age of 65 provided high external validity and increased levels of statistical power (Miller et al., 1996). The complex modeling that was necessary to evaluate changes in exposure over time

required a large cohort of subjects with comprehensive patient information as well as a range of detailed information on different types of benzodiazepine use. This level of information is uncommon,(Miller et al., 1996) however the provincial administrative health databases of the elderly population in Quebec offered an excellent data source for such analyses. Recent research by Tamblyn et al (1995) comparing prescription claims against clinical data indicates that the prescription claims database in Quebec may be one of the most accurate methods of determining drugs dispensed to individuals (Tamblyn et al., 1995). Furthermore, research on injury ascertainment concludes that the combination of treatment procedure codes and diagnostics codes in the medical services database is a sensitive indicator of fall-related injuries (Tamblyn et al., 2000). The elderly cohort enabled us to look at changes in incident benzodiazepine use over time and to assess even small increases in risk associated with injuries from falls (Rothman et al., 1998a).

3.3 STUDY POPULATION AND PERIOD

From these databases, a sub-population within the cohort was selected comprising all elderly subjects who were 66 years of age or older as of January 1, 1989 and lived in Quebec for at least the first two years of the study. This first restriction was applied in order to have comparable data for all the study participants and the second restriction was applied so that there would be at least one year of follow-up time for all subjects. Because of incomplete data on benzodiazepine exposure, injury ascertainment, or both, individuals were ineligible if:

- the health insurance number was temporary or non-unique (4,186; 0.6 %);

3.4.1 Benzodiazepine Exposure

Benzodiazepine exposure was classified into three groups. Each subject was categorized as either (i) a prevalent user if a benzodiazepine prescription was filled during the baseline period, 1989, or if the first prescription issued during the study period was a refill; (ii) an incident user if there was no benzodiazepine prescription issued during the baseline and at least one prescription was issued sometime during the study period; or (iii) a non-user if there was no benzodiazepine dispensed for the entire baseline and study period (see page A3-3 of Appendix III). The period of one year without a benzodiazepine prescription was chosen to define new users based on conventions of previous research on incidence measures of medication use (van Eijk et al., 2000; Egan et al., 2000b). The period of one year is a more conservative method since other researchers often consider a period of 180 days without use to be adequate for defining new users (van Eijk et al., 2000; Egan et al., 2000b).

Among incident users, benzodiazepine exposure was measured dynamically over the study period and was represented by several different variables depending on the specific study objective being addressed. Information on benzodiazepine prescriptions included start and end dates; type of benzodiazepine; and dosage for the thirteen products available by prescription in community-based pharmacies in Quebec (Appendix III, pages A3-11 to A3-17). In order to avoid periods of artificial overlap or artificial non-usage that would result if a patient refilled their prescription a few days early or late, a rule was applied to the data so that gaps or overlaps of three days between refills would be ignored (page A3-14). An

example of the records for a single subject are contained in Appendix IV. All other benzodiazepine exposure variables were constructed from these records.

For the first objective that evaluated incidence use and its predictors, variables recording the type of benzodiazepine product and the date that the first prescription was filled were constructed.

For the next objective of evaluating patterns of use that change over time, several more sophisticated variables were generated to represent benzodiazepine exposure. First, to facilitate between-drug comparisons, a standardized daily dose was calculated for each prescription according to the following formula:

$$\left(\frac{\text{total number of pills}}{\text{duration of prescription in days}}\right) \times \left(\frac{\text{dosage per pill in mg}}{\text{WHO recommended adult daily dosage in mg}}\right)$$

where the first term represents the average number of pills per day and the second term converts a given dosage into the percent of the World Health Organization (WHO) recommended adult daily dose(WHO Collaborating Centre for Drug Statistics Methodology, 2000)(pageA3-11) for the respective drug (page A3-13). If the prescribed dose was close to the recommended daily dose for this specific product then the standardized dose would be close to 1.0.

Second, several time-dependent covariates representing different aspects of benzodiazepine exposure were constructed using January 1, 1990 as the start of the observation period. Cumulative exposure to benzodiazepines was calculated as the sum of all daily doses since the beginning of the follow-up period, January 1, 1990, until censoring occurred from loss-to-follow-up or due to the end of the study on December 31, 1994.

Cumulative duration of benzodiazepine exposure was also calculated as the sum of all time intervals during which there was benzodiazepine exposure between the beginning of the follow-up period until censoring occurred. These summary measures were created for overall benzodiazepine exposure, i.e. cumulative dose and duration across different products, as well as for exposure to individual benzodiazepines. Given that most elderly may occasionally forget to take a pill, may reduce their dosage, or may have difficulty seeing their physician to obtain a refill prescription, periods of less than two weeks between consecutive prescriptions were unlikely to be "true" periods of non-use. To avoid under-estimating the cumulative duration of uninterrupted use, periods of less than 15 days between two consecutive benzodiazepines prescriptions were considered as continued use at the dosage of the earlier prescription. This rule did not apply if the period of interruption was due to hospitalization.

Third, summary measures were made for changes in dosage, the number of times that there was a switch to a different benzodiazepine or an addition of another benzodiazepine. Again, to avoid bias by over-estimating how often a subject was filling more than one benzodiazepine prescription at a time, when the period of time where there was a record for more than one benzodiazepine script was less than five days, the overlap was ignored and the overlap period was assumed to reflect only information from the earlier prescription. The period of five days was chosen based on the distribution of the duration for periods of overlap between more than one benzodiazepine within the study. This rule was applied whether the later prescription was for the same benzodiazepine as the earlier one or for a different type. For the analyses of changes in dosage over time, periods were considered

uninterrupted as long as the subject did not change the dose of the medication (either by changing the dose of the currently prescribed medication or by adding or switching to another benzodiazepine).

Since benzodiazepine exposure would be affected by the length of observation, January 1, 1990 was also used as time zero (T_0) for the calculation of the total person-time of observation. A second variable was also constructed with T_0 set at the date of the first prescription. No prescription information was available during hospitalization so periods of hospitalization longer than seven days were temporarily censored (pages A3-16 and A3-17) and not included in the calculation of total person-time of observation or in the construction of the time-dependent covariates.

In the methodological investigations and for the final objective of evaluating risk of injuries associated with patterns of benzodiazepine use, a set of time-dependent exposure variables was constructed for modeling in time-to-event analyses. First, a binary time-dependent covariate was constructed to represent the standardized daily dose. To avoid implausible values, the range of the standardized dose was truncated at the 99th percentile for the distributions of average dose among incident users. For periods of benzodiazepine use where dose information was missing, the value was set to the dose for all subjects exposed to that particular benzodiazepine.

Second, a set of time-dependent covariates, representing past duration of use and past cumulative dose incorporating weighing by recency, was calculated. Specifically, the weighted duration was calculated by first multiplying the binary indicator of benzodiazepine use for a given day by the value of the weight function $w(\Delta t)$ corresponding to the distance

from that day to the current day (Δt). The resulting products were summed across all days from time zero (T_0) to current day. Two different variables were calculated for weighted duration corresponding to w(30 days)=0.5 and w(4 days)=0.5, respectively, with the latter function weighting recent exposure much more heavily than the distant past. Similar calculations defined the two time-dependent variables corresponding to alternative versions of weighted cumulative dose.

3.4.2 Patient Demographics and Potential Confounders

Patient characteristics that were measured in 1989 and treated as fixed covariates included age in 1989; sex; region of residence; the total number of prescriptions filled in 1989 for medications that may influence the risk of injury (other than benzodiazepines); injuries; and measures of disability, illness and health care use. Region of residence was set by the Quebec Ministry of Health and divided Quebec into eighteen regions (Appendix 2, page A2-2). These regions were then collapsed into five categories based on geographical proximity to a university teaching hospital (Savard et al., 1999). The condensed categories are as follows: (i) regions containing a teaching hospital (Québec, Estrie, Montréal-Centre); (ii) peripheral regions (Chaudière/Appalaches, Laval, Montérégie); (iii) intermediate regions (Mauricie/Bois-Francs, Outaouais, Lanaudière, Laurentides); (iv) remote regions (Bas/Saint-Laurent, Saguenay/Lac-Saint-Jean, Abitibi/Témiscamingue, Côte-Nord, Gaspésie/Îles-de-la-Madeleine); and (v) isolated regions (Nord-du-Québec, Nunavik, Terres-Cries-de-la-Baie-James) (Savard et al., 1999). Given the restricted access to health care that exists in the isolated regions due to geographical constraints and the availability of prescription medications through nursing stations, the few subjects residing these areas (n=697) were excluded from the study.

For subjects who were classified as incident users, a variable was created to indicate whether a diagnosis for one of the main labeled indications for benzodiazepines appeared in the patients' billing or hospitalization records anytime in the 365 days before the date of the first prescription (pageA3-3). The International Classification of Diseases 9th Revision (ICD-9) codes(Practice Management Information Corporation, 1993) corresponding to each diagnosis were compiled in consultation with a panel of expert clinicians. Approved indications included a diagnosis for anxiety disorders (ICD-9 codes: 300.0, 300.2, 309.0 308.0, 309.2), insomnia (ICD-9 codes: 307.4, 780.5), seizure disorders (ICD-9 codes: 345, 780.3), muscle spasticity (ICD-9 codes: 728.8, 781.0) and alcohol abuse (303, 305.0, 291, 265.2,425.5, 535.3, 571.0 - 571.3). This variable was assessed only in benzodiazepine users and was not constructed for prevalent users since it would not have been possible to establish which occurred first, the diagnosis or the benzodiazepine use.

The measurement of other prescriptions was restricted to drugs that were identified in at least one study as influencing the risk of falls and fractures (see Chapter 2.0). Table 3.1 presents a detailed list of these drugs. The general categories of medications that decrease the risk of fractures included thiazides and estrogens. Medications that were associated with an increased risk of injuries included psychotropics other than benzodiazepines, grouped as anti-depressants, anti-psychotics, and sedative-hypnotics (other than benzodiazepines); and medications altering motor stability grouped as cardiac drugs, anti-hypertensive agents, vasodilating agents, opiate agonists, opiate partial agonists, and diuretics other than thiazides. These drugs were characterized at baseline by number of prescriptions (page A3-4).

Table 3.1 Prescription medications that influence the risk of injury from falls.

Class (AHFS* Code)	Medications
Thiazides	
Diuretics (402800)	hydrochlorothiazide
Potassium Sparing Diuretics (402810)	amiloride, spironolactone, triamterene
Estrogens	
Oral Contraceptives (681200)	ethinyl estradiol
Estrogens (681600)	chlorotrianisene, estradiol, esterified estrogens, estradiol valerate, conjugated estrogens, estrone
Psychotropics	
Anti-Depressants (281604)	amitriptyline, amoxapine, clomipramine, desipramine, doxepine, fluoxetine, fluvoxamine, imipramine, maprotiline, moclobemide, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine
Anti-Psychotics (281608)	chlorpromazine, flupenthixol, fluphenazine, fluspirilene, haloperidol, loxapine, mesoridazine, pericyazine, perphenazine, pimozide, pipotiazine, prochlorperazine, promazine, thioproperazine, thioridazine, thiothixene, trifluoperazine
Misc. Anxiolytics Sedatives, Hypnotics (282492)	buspirone, chloral, hydroxyzine, methotrimeprazine, promethazine
Misc. Psychotropics (282800)	lithium, l-tryptophan
Drugs Altering Motor Stability	
Cardiac Drugs (240400)	acebutolol, amiodarone, atenolol, digitoxine, digoxine, diltiazem, disopyramide, flecainide, metoprolol, mexiletine, nadolol, nicardipine, nifedipine, pindolol, procainamide, propafenone, propanolol, quinidine, sotalol, timolol, tocainide, verapamil
Anti-Hypertensive Agents (240800)	amlodipine, benazepril, captopril, cilazapril, clonidine, diazoxide, doxazosine, enalapril, felodipine, fosinopril, guanethidine, hydralazine, indapamide, labetalol, lisinopril, methyldopa, minoxidil, oxprenolol, pindolol, prazosin, quinaprel, reserpine, terazosine
Vasodilating Agents (241200)	isosorbide dinitrate, nitroglycerin
Opiate Agonists (280808)	anileridine, codeine, hydromorphone, levorphanol, meperidine, morphine, opium, oxycodone, oxymorphine
Opiate Partial Agonists (280812)	pentazoine
Diuretics (excluding Hydrochlorothiazide) (402800)	bendroflumethiazide, ethacrynate sodium, enthacrynic acid, furosemide, indapamide, methyclothiazide, metolazone

* American Hospital Formulary Service.

Disabilities that increased the risk of fall-related injuries were measured during the baseline period. These included visual impairment, stroke, neurological disorders, arthritis or lower extremity instability, seizure disorders, osteoporosis, depression, alcohol abuse/dependence and drug abuse/dependence. The ICD-9 codes corresponding to these variables are listed in Appendix V.

The Charlson Co-Morbidity Index (CCI) was calculated for the calendar year for each patient to measure disease severity and co-morbid conditions in 1989 (Charlson et al., 1987). This measure was chosen since it was specifically adapted by Deyo et al (1992) for administrative databases that use ICD-9 diagnostic codes and was found to be a strong predictor of mortality in different populations (Deyo et al., 1992). The codes included in the CCI are listed in Appendix VI. This measure supplemented the variables described previously that recorded the presence of other disabilities or illnesses since previous research indicates that this score does not adequately control for confounding due to co-morbidity (Schneeweiss et al., 2000; Wang et al., 2000)

Several variables were measured for the baseline period to assess health care use. These variables included the number of physicians prescribing medication, physicians visited in the calendar year, number of distinct days with billed visits (maximum of 365), and total number of billed visits for the entire year (can exceed 365), the number of discharges from all institutions, and discharges from acute-care hospitals (page A3-5).

3.4.3 Outcome Assessment and Censoring

The number of injuries during the baseline year, 1989, were counted and used as a covariate in the predictive models. Injuries during the study period were assessed

dynamically as the main outcome (pages A3-18 to A3-19). An injury was considered any fracture or soft-tissue injury recorded in the medical services or hospitalization databases. The variables used to define the occurrence of an injury were based on a study of the sensitivity of diagnostic and procedure codes for injury ascertainment in the elderly in Quebec (Tamblyn et al., 2000). The type of injuries that were mainly fall-related included fractures of the hip, upper extremity, lower extremity and soft-tissue injuries. The definition of the codes and diagnoses used to identify injuries is listed in Appendix VII. A rule was applied in order to avoid identifying the follow-up visits as separate occurrences of the same injury (see page A3-18 for details). A record was generated for each subject with a date on which the first distinct injury occurred after January 1, 1990.

For most of the study, the date of the first injury in the study period was determined to be the end of the observation for that subject. Subjects who did not have any injury during the study period were permanently censored at the end the five year follow-up (December 31, 1994) or at the date of loss to follow-up caused by moving out of province, placement in a nursing home or long term care facility, or death (see page A3-15).

Since hospitalization databases were used to obtain this information, some of the injuries may have occurred after hospitalization (i.e. falls from hospital beds). In order to exclude these events and to take into account the imprecision of administrative dates, only injuries recorded in the first five days of hospitalization where considered as an outcome for our study and observation for these subjects was stopped at the time of the event. If there was an event, the subject was not recorded as being hospitalized for these five days. A subject with an event that occurred more than five days after hospital admission but before

hospital discharge was permanently censored at that time as lost to follow-up. Furthermore, since no prescription information was available during hospitalization temporary censoring was applied during each distinct hospital stay longer than seven days. These periods of hospitalization were subtracted from the total observation time for all subjects.

Detailed information on methods specific to the study objective is provided in the subsequent articles.

MANUSCRIPT 1: Prevalence, Incidence and Predictors of Benzodiazepine Use in Quebec Elderly

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Abstract

Background Benzodiazepines are sedative-hypnotics that are frequently prescribed to elderly patients. However, there is a lack of detailed information on incidence rates and on specific patients' characteristics associated with incident use of specific benzodiazepine products.

Objectives To estimate the annual prevalence and incidence of the use of different benzodiazepines in an elderly population and to identify potential predictors of new use.

Methods Using information from provincial administrative databases, 462,543 community-dwelling Quebec residents 66 years of age or older were assessed in 1989 for benzodiazepine use and patient characteristics. Subjects were classified as prevalent users if they filled a script in 1989, incident users if the first prescription was during the follow-up (1990-1994), or non-users. Subject demographics, use of other selected medications, health care utilization and presence of certain disabilities were compared among the three groups. Prevalence for 1989 was estimated by sex and age group. After excluding prevalent users, sex and age specific incidence rates were estimated for each benzodiazepine and subjects were observed for 5 subsequent years. Cox regression models were used to identify potential predictors of incidence use from patients' baseline characteristics.

Results The overall incidence rate for benzodiazepines was 88.7 per 1,000 person-years, with higher rates in women (95.0) than men (81.8). Incidence rates varied considerably across different products with lorazepam being by far the most popular choice. There were systematic differences between users and non-users and predictors of incident use were different among individual products. Use of anti-depressants in 1989 was the strongest and most consistent predictor of incident use across different benzodiazepines (hazard ratios: 1.45 to 3.07, $p<0.0001$).

Conclusions The identification of predictors for incident benzodiazepine use emphasizes the importance of individual benzodiazepine evaluation and adequate control of confounders.

4.0 PREVALENCE, INCIDENCE AND PREDICTORS OF BENZODIAZEPINE USE IN QUEBEC ELDERLY (MANUSCRIPT 1)

4.1 INTRODUCTION

Benzodiazepines are sedative-hypnotic medications frequently prescribed for the elderly.[1-6] Due to changes in pharmacokinetics and pharmacodynamics associated with aging, elderly people are particularly sensitive to the effects of these medications and are more likely to experience adverse events such as dizziness, ataxia, over-sedation and withdrawal symptoms.[1;7-11] These symptoms have been linked to an increase risk of injuries from falls.[12-16]For this reason, clinicians are often advised to provide elderly people with lower doses, to avoid long term use and to limit the use of benzodiazepines that may be susceptible to accumulation due to long elimination half-lives.[1;11;17-20]

In spite of these recommendations, there is convincing epidemiological evidence that benzodiazepine use is less than optimal in elderly people. In an Australian cohort study of benzodiazepine use by elderly over the age of 75 in 1991, Jorm et al (2000) found that almost 38% of the participants reported using benzodiazepines for three years or more.[3] In a similar study started in 1989 in England, Taylor et al (1998) found that 70% of the elderly participants reported taking benzodiazepines for at least one to two years and 69% reported still taking them two years later.[4] A more recent study conducted in Nova Scotia by Rojas-Fernandez et al (1999), found that despite a decrease in the prevalence of benzodiazepine use exceeding 30 days from the beginning of the study in 1993 until the end in 1996, according to provincial records, the rate was still 17%, with 10% exceeding 90 days.[21] A study of questionable prescribing practices in Quebec in 1990 by Tamblyn et al (1994) found that according to

database records, 36% of the elderly population were taking benzodiazepines for longer than 30 days, 15% were taking long half-life benzodiazepines and almost 16% were taking either two benzodiazepines or a benzodiazepine and another sedative.[22] This finding in the Quebec elderly was confirmed by Egan et al (2000) who reported a twelve-month prevalence of long-term continuous use of benzodiazepines of 19.8%.[6]

Most studies that have investigated the magnitude of benzodiazepine use in elderly people have grouped all benzodiazepines together, or classified the medications by elimination half-life.[2;3;5;6;23] However, recent evidence suggests that the sensitivity to adverse effects experienced by elderly patients may only occur with selected products due to pharmacodynamic characteristics that are not shared by the entire class of benzodiazepines.[11;17] With this possibility, and given that the associations between the use of different benzodiazepines and risks of injuries from falls may differ,[12-16] it is important to determine if there are systematic baseline differences between individuals who are prescribed different benzodiazepines as the apparent differences in the impact on injuries from falls may be due to residual confounding.[24]

In order to assess the use of specific benzodiazepines in elderly people, the rate of current and new use needs to be estimated for individual drugs. Some studies report prevalence rates for specific benzodiazepines[4;21]but we were unable to find any information on incident use of specific benzodiazepines. Investigation of predictors of new use should provide some insight into the characteristics of the patients starting a course of benzodiazepine therapy. Due to the high prevalence rates previously reported by Tamblyn et al (1994) and the extensive administrative records available with the provincial health

In order to protect confidentiality, information on age was limited to the year of birth. There was no way of differentiating between a subject who turned 65 in January, 1989 and a subject who turned 65 in December, 1989. Both subjects would be included in the database and would have qualified for the government drug plan in 1989, however we would have had a full year of information for one subject but only one month or less of information for the other subject. To have comparable information, subjects who were 65 years old or younger in 1989 were excluded from the cohort (205,547; 28.3%). Subjects who resided in extremely isolated regions (Northern Quebec, Nunavik and James Bay) were also excluded from the analysis since prescription medications may be dispensed through nursing stations as well as community pharmacies and this would underestimate the rate of benzodiazepine use for these areas (n=697; 0.09%).[28]

For the final, fixed cohort of 462,543 subjects, data was retrieved on age, sex, area of residence, disabilities, co-morbidity, benzodiazepine use, hospitalization, health care use, use of other selected prescription drugs and treatment and procedure codes for fractures and soft tissue injuries.[27] Further details on the construction of the study cohort are provided in Chapter 3.0. This study was conducted in accordance with the ethical standards of the McGill Faculty of Medicine Institutional Review Board for research involving human subjects.

4.2.2 Benzodiazepine Use

In order to discriminate between prevalent use of benzodiazepines and incident use, the active follow-up was restricted from 1990 to 1994 while 1989 was considered a baseline period. All subjects were followed until the end of the study at December 31, 1994 or until loss to follow up due to death, moving out of the province or institutionalized.

Each subject was categorized as a prevalent user if a benzodiazepine prescription was filled during the baseline year, anytime from January 1 to December 31, 1989 or if the first prescription issued after December 31, 1989 was a refill. A subject was considered an incident user if there was no benzodiazepine prescription issued during the baseline year and at least one prescription was issued during follow-up from January 1, 1990 to December 31, 1994. Subjects for whom there was no benzodiazepine dispensed for the entire baseline and study period were considered non-users.

4.2.3 Measurement of Predictors

Predictors were chosen to assess the characteristics associated with benzodiazepine use in elderly. Since factors or characteristics that might increase the risk of injuries due to falls from central nervous system effects, besides those caused by benzodiazepine use, were of interest, the covariates used to model potential predictors of incident benzodiazepine use were selected if they had been identified in at least one published study as a risk factor for injuries from falls in the elderly (Chapter 2.0, Section 2.3). These predictors included patient demographics, other medications, disabilities or impairments, co-morbidity, and health care use.[13;24;29-37]

Baseline characteristics measured in 1989 included age, sex and region of residence. The eighteen regions of residence were established by RAMQ and were then categorized into four groups according to the proximity of a university teaching hospital, immediate vicinity of a teaching hospital, peripheral, intermediate, and remote.[28]

The disabilities recorded included visual impairment, stroke, neurological disorders including dementia and Parkinson's disease, arthritis, seizure disorders including epilepsy, osteoporosis, depression, alcohol abuse/dependence and drug abuse/dependence. ICD-9 codes

were used to detect the impairments in the hospitalization database as well as the medical services billing database (diagnostic codes are listed in Appendix V). Since patients diagnosed with both upper and lower extremity arthritis are given a separate diagnosis for the lower extremity arthritis, the presence of both upper and lower extremity arthritis was recorded. The Charlson Co-Morbidity Index (CCI)[38] adapted by Deyo et al (1992) for administrative databases[39] was calculated for each patient in 1989 to obtain an aggregate measure of disease severity and co-morbid conditions (diagnostic codes listed in Appendix VI).

Prescriptions for drugs other than benzodiazepines were determined based on the RAMQ prescription database. The drugs that were recorded included thiazides, estrogens, antidepressants, anti-psychotics, non-benzodiazepine sedative-hypnotics, miscellaneous psychotropics (lithium, l-tryptophan), cardiac drugs, anti-hypertensive agents, vasodilating agents, opiate agonists, opiate partial agonists, and non-thiazide diuretics.

Baseline health care use was estimated for each subject in 1989. A count was made of the number of physicians prescribing medication, the number of physicians visited during the year, the total number of billed visits, the number of billed visits made on distinct days, the number of discharges from all hospitals, and the number of discharges from acute care hospitals.

Whether or not a subject had an injury in 1989 was recorded using the medical services and hospitalization databases. The variables used to define the occurrence of an injury were based on a study of the sensitivity of diagnostic and treatment procedure codes for injury ascertainment in the elderly in Quebec.[27] The type of injuries considered were any

fracture or soft tissue injury including fractures of the hip, upper extremity fractures, lower extremity fractures. Hip fractures accounted for 17% of the fractures and 10% of all injuries.

The likely reason for prescribing the benzodiazepine was assessed by inspecting the diagnostic codes in the medical services claims and hospitalization records for evidence of the labeled therapeutic indications (anxiety disorders, insomnia, seizure disorders, muscle spasticity and alcohol abuse)[20] in the 365 days before the date of the first prescription. The ICD-9 codes corresponding to each diagnosis were compiled in consultation with a panel of expert clinicians (Appendix V). Presence or absence of any one of the listed indications was treated as a binary variable in the analysis.

4.2.4 Statistical Analyses

4.2.4.1 Descriptive

Frequency distributions of categorical baseline characteristics were determined and the means and standard deviations (sd) were reported for continuous variables. Comparisons were made by benzodiazepine exposure status and by individual benzodiazepine product. Chi-square tests and one-way analysis of variance using Tukey-Kramer tests for multiple comparisons[40;41] were used to compare the distribution of categorical and continuous variables, respectively.

4.2.4.2 Prevalence

Period prevalence rates for filling at least one benzodiazepine prescription during the year from January 1 to December 31, 1989 were estimated separately for men and women. The prevalence rates were estimated for five different age groups using all subjects in the cohort for total benzodiazepine use and for individual product use.

4.2.4.3 Incidence

Subjects who filled a prescription for a benzodiazepine during 1989 (prevalent users) were excluded from the estimation of incidence rates. Incidence rates were estimated separately for men and women for the study period, January 1, 1990 to December 31, 1994 for overall benzodiazepine use and for individual products. Incidence rates per 1,000 person-years were reported for the five age groups. January 1, 1990 was considered to be time zero (T_0) for the calculation of the total person-time at risk. Since no prescription information was available during hospitalization, periods of hospitalization were temporarily censored and not included in the calculation of total person-time at risk. For the overall benzodiazepine incidence, the date of the first benzodiazepine prescription was considered to be the event of interest and the end of observation for that subject. For the individual product incidence, each subject was censored at the time of the first benzodiazepine prescription unless the first prescription was for the specific product. In all analyses, subjects were also censored when they died, moved out of the province, were institutionalized or at the end of the follow-up on December 31, 1994.

4.2.4.4 Predictors of Incidence

For all subjects except prevalent users, predictors of initiating benzodiazepine use for individual products were evaluated using Cox regression model for time-to-event analysis.[42] Starting time for the observation period (T_0) was January 1, 1990 and follow-up continued until December 31,1994 unless a subject was censored because of loss to follow-up due to death, moving away from Quebec, or institutionalization. Potential predictors were selected *a priori* from baseline characteristics measured in 1989. To assess if the role of potential predictors was the same for men and women, interaction terms were included for sex and

several baseline characteristics. Interaction terms were tested individually using a Wald test at 0.05 significance level. If a significant interaction was found between the binary variable, sex, and the continuous variable, age, the parameter estimate for sex would be meaningless since it would represent the effect of sex at age = 0. In order to avoid this problem, the age variable was transformed by subtracting a subject's age in 1989 from the median age of the cohort. Thus if a significant interaction was found between age and sex, the parameter estimate for sex would represent the hazard for men compared to women at the median age.

For baseline covariates of health care use, predictors that measured similar variables, i.e. number of physicians seen versus number of prescribing physicians, were modeled separately. The models were compared using Akaike Information Criterion (AIC) to select the optimal variable.[43] AIC is calculated as twice the sum of the negative log likelihood of the data under a given model and the number of parameters estimated in the model:

$$AIC = 2 \times (-\log L) + 2 \times (\text{number of parameters})$$

with the optimal model corresponding to the minimum AIC value.

To assess the time-dependence of the predictive ability of the baseline variables and to assess the plausibility of the proportional hazards assumption, two types of additional survival analyses were conducted. First, two separate Cox proportional hazard regression analyses were carried out for two mutually exclusive follow-up periods: i) restricting the follow-up to 1990 and ii) starting follow-up only in 1991. In the first analysis, only incident use in 1990 was considered an event, and all subjects who remained at risk on December 31, 1990 were censored at that time. In the second analysis, only incident use after 1990 was considered and T_0 began on January 1, 1991 and continued until the end of the study on

December 31, 1994. Comparison of the corresponding hazard ratios estimated for the two analyses allowed assessment of whether the baseline characteristics predicted equally well incident use over the longer periods as during the first year of follow-up. The second approach relied on the methods developed by Grambsch and Therneau (1994) using the Schoenfeld residuals and the standard Cox variance estimator for a global test of proportional hazards assumption as well as for testing the time-dependence of the predictive ability of the baseline measurements of individual covariates.[45]

Statistical analyses were conducted using SAS Systems 8.0 for Windows[46] and S-Plus 4.[47] Graphs and figures were constructed using Microsoft Excel.[48] To correct for the number of statistical tests, significance levels were set at 0.01.

4.3 RESULTS

4.3.1 Baseline Characteristics of Study Cohort

The average age of the cohort was 73.6 years (sd = 6.0) and 59% were women. Almost half of the study participants filled a benzodiazepine script in 1989 (45%), and two-thirds of this group were women. For the other subjects, 38% never filled a benzodiazepine script (51% women) and 17% went on to fill a benzodiazepine script sometime between January 1, 1990 and December 31, 1994 (56% women).

Based on the first prescription filled in 1989, the most common benzodiazepine for prevalent users was lorazepam (37%), followed by triazolam (13%), flurazepam (12%), oxazepam and diazepam (11% each). A somewhat different pattern was shown for incident users (filling the first script between 1990 and 1994) with the most common first script being filled for lorazepam (42%), followed by oxazepam (20%), flurazepam (7%), diazepam (6%), alprazolam and bromazepam (5% each). No prescriptions for clobazam, a new drug in the

Quebec formulary, were detected before 1992 and clorazepate prescriptions were not detected after1990 when the medication was excluded from the formulary.[49]

Table 4.1.a and 4.1.b compare the baseline characteristics represented, respectively, by continuous and categorical variables, among benzodiazepine non-users, incident users and prevalent users. All differences between groups were statistically significant ($p \leq 0.01$) except between the mean number of hospital discharges among non-users and incident users. The statistical significance of the differences partly reflected the very high statistical power due to the large sample size, and may not be clinically relevant.

Overall, prevalent users of benzodiazepines were much more likely to be taking other medications including non-benzodiazepine psychotropic medications, cardiac medications, anti-hypertensive agents, vasodilators, opiate agonists, partial opiate agonists, and diuretics than incident users and non-users. Prevalent users were also more likely to have impairments and disabilities, have a higher rate of co-morbidity, use more health care services and be more likely to live in an area that was not close to a teaching hospital than incident users and non-users of benzodiazepines. These differences were reflected in the Charlson Co-morbidity Index (CCI), where twice as many prevalent users than incident and non-users had a CCI ≥ 3 (Table 4.1.b). One of the most marked between-group differences was for filling at least one script for another psychotropic medication (20% of prevalent users versus 9% of incident users, 7% of non-users). Also, 59% of prevalent benzodiazepine users filled at least one script for medications that affect motor stability (cardiac drugs, anti-hypertensives, vasodialators, opiate and partial opiate agonists, non-thiazide diuretics) compared to 38% of non-users and 44% of incident users.

Table 4.1.a Means (standard deviations) of baseline (1989) characteristics among non-users (174,444), incident users (78,367), and prevalent users (209,732) of benzodiazepines among Quebec elderly.*

Type of Variable	Variable	Benzodiazepine Exposure		
		Non-Users	Incident	Prevalent
Age	Age in years	73.6 (5.9)	73.6 (6.1)	73.0 (5.7)
Measures of Health Care Use	No. Prescribing Physicians	1.8 (1.5)	2.1 (1.6)	3.0 (1.9)
	No. Physician Visits	3.8 (3.9)	4.3 (4.0)	5.9 (5.0)
	No. Days with Billings	8.5 (10.8)	9.7 (11.0)	15.0 (14.8)
	Total No. of Billings	9.7 (13.7)	11.0 (13.7)	17.1 (18.9)
	No. Hospital Discharges†	0.2 (0.7)	0.2 (0.6)	0.3 (0.8)
	No. Acute-Care Hospital Discharges†	0.2 (0.6)	0.2 (0.5)	0.3 (0.7)
Health Status	Charlson Co-morbidity Index‡	0.6 (1.3)	0.5 (1.2)	0.5 (1.1)

* All differences are statistically significant unless otherwise indicated based on multiple comparisons with ANOVA for continuous measures and chi-square for binary measures. Benzodiazepine use is based on any of the twelve available benzodiazepines. Midazolam was not available through community pharmacies and clobazam had no detected use before 1992.

† No statistically significant difference between non-users and incident users.

‡ Charlson Co-morbidity Index (CCI) is also shown as a binary variable in Table 4.1.b.

4.3.1.1 Frequency of Clinical Indications Among Incident Users

A diagnosis for at least one of the main therapeutic indications was detected in the year prior to the initial benzodiazepine script for only 4.3% of incident users. Anxiety was the most common diagnosis (3.2%), followed by seizure disorders (0.5%), alcohol abuse (0.3%) and finally insomnia and muscle spasticity (0.2% each)

Interestingly, two thirds of patients with a seizure disorder (n=9,451) had been prescribed a benzodiazepine but among incident users with a seizure disorder (n=1,407), 66% of the first prescriptions were for benzodiazepines not normally indicated as anti-convulsants (37% lorazepam, 22% oxazepam and 7% flurazepam). Benzodiazepines that are labeled for use as an anti-convulsant (clorazepate, clobazam and clonazepam) accounted for less than 5% of the incident benzodiazepine use by subjects with a seizure disorder.

4.3.2 Prevalence

Prevalence rates for benzodiazepine use in 1989 among men and women are shown by age group in Table 4.2. Overall, 51% of women filled at least one benzodiazepine script in 1989 compared to 37% of men. Lorazepam accounted for over one third of the prevalent use. Triazolam, oxazepam, diazepam and flurazepam all had similar prevalence rates and together accounted for almost half of the prevalent use. Each of the remaining benzodiazepines accounted for less than 2% of prevalent use.

For both men and women, the overall prevalence rate increased by age until 79 years and then decreased. The highest prevalence rates occurred in the 75-79 year age group with 54% of women and 39% of men filling a benzodiazepine script. This non-monotone effect of age on the overall use of benzodiazepines mostly reflected the pattern observed for the

Table 4.2 Estimated 1989 prevalence (percent) of benzodiazepine use for women and men by age group and type of benzodiazepine script first detected during the year.*

Elimination Half-life	Type of Benzodiazepine First Used	Sex	Age Groups					All Ages	Total
			66-69	70-74	75-79	80-84	85+		
	Any Benzodiazepine	Women	48.8	52.7	53.7	52.2	47.5	51.3	45.3
		Men	34.3	37.8	38.6	38.1	36.6	36.8	
Ultra-Short	Triazolam	Women	5.5	6.5	7.3	7.5	7.8	6.6	6.1
		Men	4.3	5.5	6.1	6.4	6.4	5.3	
Short-Intermediate	Temazepam	Women	0.6	0.8	0.8	0.8	0.7	0.7	0.7
		Men	0.5	0.6	0.7	0.8	0.7	0.6	
	Nitrazepam	Women	0.7	0.7	0.7	0.6	0.5	0.7	0.6
		Men	0.4	0.6	0.6	0.5	0.7	0.5	
	Alprazolam	Women	2.3	2.1	1.8	1.4	1.2	1.9	1.6
		Men	1.3	1.3	1.1	0.9	0.7	1.2	
	Oxazepam	Women	4.8	5.8	6.6	7.3	7.7	6.0	5.1
		Men	3.2	3.9	4.3	4.8	5.9	3.9	
	Bromazepam	Women	2.3	2.2	1.8	1.4	0.9	2.0	1.7
		Men	1.4	1.4	1.2	0.9	0.8	1.2	
	Lorazepam	Women	19.5	20.6	20.3	19.3	16.6	19.8	16.9
		Men	12.4	13.1	13.1	12.7	11.8	12.8	
Long	Clonazepam	Women	0.5	0.4	0.3	0.3	0.2	0.4	0.3
		Men	0.3	0.2	0.2	0.2	0.1	0.3	
	Flurazepam	Women	5.4	6.0	6.1	5.4	4.6	5.7	5.4
		Men	4.6	5.3	5.3	5.2	4.7	5.0	
	Chlordiazepoxide	Women	0.7	0.7	1.0	0.9	0.8	0.8	0.8
		Men	0.8	0.7	0.7	0.7	0.6	0.7	
	Diazepam	Women	5.3	5.6	5.9	6.1	5.7	5.6	5.1
		Men	4.2	4.5	4.7	4.3	3.5	4.4	
	Clorazepate	Women	1.2	1.2	1.1	1.0	0.7	1.1	0.9
		Men	0.7	0.7	0.6	0.6	0.5	0.7	

* Subjects who started simultaneously on more than one script (20) or had unknown type of first benzodiazepine (30) are excluded from the table (0.02% of prevalent users). Clobazam had detected use for only 2 subjects.

most popular drug, lorazepam, and was not consistent for individual products. Notably, for triazolam and oxazepam the prevalence rate continually increased with older age groups for both males and females. In contrast, for alprazolam, bromazepam, clonazepam and clorazepate, prevalence rates decreased in older age groups.

4.3.3 Incidence

Incidences per 1,000 person years of observation are shown in Table 4.3 by sex and age group. The overall incidence rate for filling a benzodiazepine script was 88.7 per 1,000 person-years. Again, this rate was higher for women (95.0 per 1,000 person-years) than men (81.8 per 1,000 person-years). As with prevalence, the overall incidence rate showed a non-monotone association with age, first increasing then decreasing. However, while the highest incidence rates for women were found in the 75-79 year age group (96.2 per 1,000 person-years), the highest rates for men were found in the 80-84 year age group (87.8 per 1,000 person-years). Lorazepam and oxazepam accounted for 62% of incident use (42% and 20% respectively). Temazepam, alprazolam, bromazepam, flurazepam and diazepam each accounted for about 5% of the incident use and the remaining five benzodiazepines accounted for less than 2%.

Approximately 1% of incident users started on more than one benzodiazepine. Incident use declined over time (34% in 1990, 23% in 1991, 17% in 1992, 14% in 1993 and 11% in 1994), as was expected given the fixed cohort design of our study.

4.3.4 Predictors of Incidence

At the first step of the multivariable Cox regression analyses, models containing alternative variables that measured similar characteristics, and therefore might cause near-

Table 4.3 Estimated incidence per 1,000 person-years for benzodiazepine use, 1990-1994, for women and men by age group and type of benzodiazepine first used (number of incident users).*

Half-life	Type of Benzodiazepine First Used	Sex	Age Groups					All Ages	Total
			66-69	70-74	75-79	80-84	85+		
Any Benzodiazepine	(78,367)	Women	94.98	96.62	96.15	92.67	87.86	95.03	88.70
		Men	77.04	82.70	86.19	87.81	86.77	81.76	
Ultra-Short	Triazolam	Women	2.43	2.70	2.69	2.13	2.77	2.53	2.58
	(2,282)	Men	2.20	2.76	2.86	3.30	3.11	2.62	
Short-Intermediate	Temazepam	Women	4.06	4.18	4.70	4.56	4.44	4.30	4.58
	(4,049)	Men	4.27	4.96	5.23	6.10	6.00	4.88	
	Nitrazepam	Women	1.51	1.71	1.75	1.73	1.79	1.66	1.65
	(1,458)	Men	1.45	1.68	1.78	1.87	2.07	1.64	
	Alprazolam	Women	6.11	5.79	4.22	3.79	3.47	5.22	4.48
	(3,959)	Men	3.98	3.63	3.57	3.35	2.07	3.68	
	Oxazepam	Women	15.92	18.83	20.89	22.57	23.07	18.95	17.65
	(15,600)	Men	13.15	16.08	18.94	22.43	22.14	16.24	
	Bromazepam	Women	5.97	5.60	4.85	3.70	2.61	5.18	4.39
	(3,877)	Men	3.71	3.69	3.04	3.11	3.70	3.52	
	Lorazepam	Women	42.04	41.51	41.37	39.98	37.99	41.29	37.20
	(32,822)	Men	31.64	33.15	34.47	32.44	33.83	32.78	
Long	Clonazepam	Women	2.35	2.11	2.02	2.36	1.75	2.18	2.04
	(1,800)	Men	2.04	1.71	1.96	1.76	1.41	1.88	
	Flurazepam	Women	5.60	5.48	5.15	4.62	3.04	5.22	6.14
	(5,425)	Men	6.99	7.50	7.03	6.93	6.37	7.13	
	Chlordiazepoxide	Women	0.96	0.94	0.88	0.92	0.66	0.91	1.00
	(887)	Men	1.32	0.94	1.15	0.77	0.52	1.10	
	Diazepam	Women	6.54	6.32	6.16	5.13	5.10	6.15	5.55
	(4,908)	Men	4.84	5.17	4.78	4.56	4.66	4.90	
Starting on more than one type of benzodiazepine		Women	1.18	1.19	1.20	1.00	0.97	1.15	1.17
		Men	1.23	1.22	1.23	1.02	0.59	1.19	

* No incidence rates were estimated for two of the benzodiazepines: clobazam, which had detected use only starting in 1992 and clorazepate, which had detected use only in 1990.

collinearity problems if included in the same model, were compared with respect to goodness-of-fit. Based on the minimum AIC value,[43] the following variables were kept for further analyses. The number of prescribing physicians (AIC = 1893346) was kept instead of the total number of billings (AIC = 1894320), the number of days with any billings (AIC =1894181) or number of physicians seen (AIC = 1894120). The number of acute-care hospital discharges (AIC = 1893346) was kept instead of total number of hospital discharges (AIC = 1893356) and the continuous version of the CCI (AIC = 1893331) was kept instead of the binary version (AIC = 1893346).

A further issue concerned the relationship between the two original variables representing the diagnosis of depression and the use of anti-depressant medication. Use of anti-depressant medication during 1989 was detected for 33% of the total cohort with a diagnosis of depression. However, only 30% of the subjects who filled at least one prescription for an anti-depressant had a diagnosis for depression. In order to separate the overlap between subjects filling prescriptions for anti-depressants and those subjects with a diagnosis of depression, a different coding was done. Any subject with a diagnosis for depression regardless of medication use was represented by the original variable for baseline depression. Then a new variable was created to identify only those subjects who filled a prescription for an anti-depressant but did not have a diagnosis for depression. Therefore this covariate, anti-depressant use, represented only those people using the medication without a recorded diagnosis of depression.

Table 4.4 compares estimated hazard ratios for incident use of any benzodiazepine, with p-values and 95% confidence intervals for the entire follow-up periods and for two

Table 4.4 **Estimated hazard ratios and 95% confidence intervals for predictors of starting on any benzodiazepine for all incident users (78,367 users), 1990 incident users only (26,637 users), and 1991-1994 incident users only (51,730 users).**

Predictor Class	Predictors	Total		1990 Only		1991-1994 Only	
		H.R. (P-VALUE)	95% CI	H.R. (P-VALUE)	95% CI	H.R. (P-VALUE)	95% CI
Patient Demographics*	Age for women (5 year increments) §	non-linear (0.004)		0.96 (<.0001)		non-linear (0.0003)	
	Age for men (5 year increments) §			1.02 (0.01)			
	Sex - Men vs Women‡	0.87 (<.0001)	0.86-0.89	0.79 (<.0001)	0.77-0.81	0.92 (<.0001)	0.90-0.94
	Peripheral Region	1.09 (<.0001)	1.07-1.11	1.04 (0.006)	1.01-1.08	1.11 (<.0001)	1.08-1.13
	Intermediate Region	1.16 (<.0001)	1.14-1.18	1.12 (<.0001)	1.08-1.16	1.18 (<.0001)	1.15-1.21
	Remote Region	1.25 (<.0001)	1.22-1.28	1.19 (<.0001)	1.14-1.24	1.28 (<.0001)	1.24-1.32
Health Care Utilization	No. Prescribing Drs.	1.09 (<.0001)	1.09-1.10	1.11 (<.0001)	1.10-1.12	1.08 (<.0001)	1.07-1.09
	No. Hospital Stays	0.95 (<.0001)	0.94-0.97	0.98 (0.09)	0.95-1.00	0.93 (<.0001)	0.91-0.95
Disabilities and Impairments	Any Injury (1989)	0.96 (0.02)	0.93-0.99	1.02 (0.53)	0.96-1.08	0.92 (0.0006)	0.88-0.97
	Visual Impairment	0.97 (0.0003)	0.95-0.99	0.98 (0.17)	0.95-1.01	0.96 (0.0008)	0.94-0.98
	Stroke	0.95 (0.03)	0.91-0.99	0.99 (0.73)	0.92-1.06	0.93 (0.01)	0.88-0.99
	Depression	1.35 (<.0001)	1.30-1.41	1.43 (<.0001)	1.34-1.52	1.31 (<.0001)	1.25-1.38
	Neurological Disorders	1.10 (<.0001)	1.05-1.15	1.09 (0.01)	1.02-1.17	1.10 (0.0008)	1.04-1.17
	Arthritis	1.08 (<.0001)	1.06-1.10	1.10 (<.0001)	1.06-1.14	1.06 (<.0001)	1.04-1.09
	Seizure	0.96 (0.19)	0.91-1.02	0.97 (0.45)	0.89-1.05	0.96 (0.21)	0.89-1.02
	Osteoporosis	0.99 (0.91)	0.90-1.10	0.93 (0.40)	0.80-1.10	1.04 (0.51)	0.92-1.18
	Misc. Impairments	1.01 (0.573)	0.98-1.05	1.02 (0.48)	0.96-1.08	1.00 (0.88)	0.96-1.05
	Alcohol Abuse	1.35 (<.0001)	1.18-1.54	1.62 (<.0001)	1.34-1.96	1.16 (0.10)	0.97-1.40
	Drug Abuse	1.18 (0.02)	1.03-1.37	1.12 (0.32)	0.89-1.41	1.23 (0.03)	1.02-1.48
	Charlson Co-morbidity Index	1.02 (<.0001)	1.02-1.03	1.04 (<.0001)	1.02 -1.05	1.01 (0.01)	1.00-1.02

* Region of residence is modeled as a dummy variable with the region containing a teaching hospital being the reference: "Region 1" is peripheral, "Region 2" is intermediate and "Region 3" is remote.

‡ Estimated for the effect of sex at median sample age (73.4 years) for men compared to women (reference group).

Table 4.4 Continued.

Predictor Class	Predictor	Total		1990 Only		1991-1994 Only	
		H.R. (P-VALUE)	95% CI	H.R. (P-VALUE)	95% CI	H.R. (P-VALUE)	95% CI
Medications Potentially Protective for Fractures	Estrogen	1.03 (0.76)	0.84-1.26	1.32 (0.07)	0.98-1.78	0.87 (0.33)	0.66-1.15
	Thiazide Diuretics	1.03 (0.0006)	1.01-1.05	1.04 (0.009)	1.01-1.07	1.03 (0.02)	1.00-1.05
Non-Benzodiazepine Medications Associated with an Increased Risk of Injury	Anti-Depressants	1.67 (<.0001)	1.61-1.74	1.72 (<.0001)	1.62-1.83	1.64 (<.0001)	1.56-1.72
	Anti-Psychotics	1.23 (<.0001)	1.16-1.31	1.31 (<.0001)	1.20-1.42	1.16 0.0001	1.08-1.26
	Sedatives	1.27 (<.0001)	1.23-1.32	1.23 (<.0001)	1.16-1.31	1.30 (<.0001)	1.25-1.36
	Lithium, L-tryptophan	1.26 (0.002)	1.09-1.46	1.05 (0.68)	0.82-1.35	1.41 0.0002	1.18-1.68
	Cardiac Drugs	1.05 (<.0001)	1.03-1.07	1.01 (0.34)	0.98-1.05	1.07 (<.0001)	1.04-1.09
	Anti - Hypertensives	1.06 (<.0001)	1.04-1.08	1.05 (0.006)	1.01-1.09	1.07 (<.0001)	1.04-1.09
	Vasodilators	1.17 (<.0001)	1.15-1.20	1.24 (<.0001)	1.19-1.28	1.14 (<.0001)	1.11-1.17
	Opiate Agonists	1.14 (0.0008)	1.06-1.23	1.28 (<.0001)	1.14-1.44	1.05 (0.35)	0.95-1.16
	Partial Opiate Agonists	1.11 (0.31)	0.91-1.34	1.25 (0.13)	0.94-1.67	1.03 (0.84)	0.79-1.33
	Non-Thiazide Diuretics	1.08 (<.0001)	1.06-1.11	1.12 (<.0001)	1.07-1.16	1.05 (0.0008)	1.02-1.08

separate analyses restricted, respectively, to 1990 incident use and 1991-1994 incident use. Most variables showed a very small difference between the two period-specific hazard ratios, and also showed confidence intervals that usually overlapped considerably. Variables that showed a larger change in hazard ratios with no overlap in 95% confidence intervals (i.e. the use of opiate agonists in 1989) were investigated further. When these covariates were modeled using a program specifically designed to evaluate the time-dependence of covariates in survival analysis,[50] none of the changes were statistically significant (data not shown). The test of the proportional hazards assumption was conducted on a random sample of the cohort (n=25,264) for all the covariates. The proportional hazards hypothesis was not rejected at the 0.05 level for any of the individual predictors (data not shown). Overall, the results of these analyses indicated that the predictive ability of baseline characteristics remains approximately constant over five years of follow-up. Therefore, all incident use occurring between 1990 to 1994 was combined for the remaining analyses.

Tables 4.5.a, 4.5.b, and 4.5.c compare the estimated hazard ratios with p-values and 95% confidence intervals for predictors of incident use of individual benzodiazepines grouped by three classes of half-life. Each of the three tables focuses on a different subset of potential predictors even though all the results related to a given benzodiazepine in the three tables were obtained from the same multivariable Cox model. Use of clobazam and clorazepate was not analyzed since these drugs were not listed in the provincial formulary for the full observation period. The analysis for use of more than one benzodiazepine was not conducted because this only occurred with 1,027 subjects (1.3% of incident users) and the results would be difficult to interpret because of different subjects starting on different combinations of two

Table 4.5.a Estimated hazard ratios (p-value) and 95% confidence intervals for patient demographics and baseline health care use (1989) as predictors of incident benzodiazepine use (1990-1994).*

Half - life	Type of Benzodiazepine First Used	Patient Demographics†						Baseline Health Care Use	
		Age (5 yr increment)‡		Sex Men/Women§	Region of Residence			No. of Prescribing Doctors	No. of Hospital Stays
		Women	Men		Peripheral	Intermediate	Remote		
Ultra - Short	Triazolam	0,99 (0,66)	1,08 (0,02)	1,05 (0,29) 0,96-1,14	1,19 (0,04) 1,00-1,25	1,58 (<,0001) 1,42-1,76	1,66 (<,0001) 1,45-1,90	1,06 (<,0001) 1,03-1,09	0,94 (0,25) 0,86-1,04
Short - Intermediate	Temazepam	1,03 (0,18)	1,09 (<,0001)	1,18 (<,0001) 1,10-1,25	1,17 (<,0001) 1,09-1,27	1,32 (<,0001) 1,21-1,43	1,28 (<,0001) 1,14-1,42	1,06 (<,0001) 1,04-1,08	1,01 (0,63) 0,96-1,06
	Nitrazepam	1,04 (0,21)	1,09 (0,007)	1,00 (0,96) 0,90-1,11	1,37 (<,0001) 1,20-1,56	1,66 (<,0001) 1,45-1,91	2,26 (<,0001) 1,93-2,65	1,06 (0,001) 1,03-1,11	0,86 (0,03) 0,76-0,99
	Alprazolam	0,84 (<,0001)	0,92 (0,0005)	0,72 (<,0001)¶ 0,67-0,77	1,02 (0,70) 0,94-1,10	1,21 (<,0001) 1,11-1,32	1,50 (<,0001) 1,35-1,67	1,10 (<,0001) 1,07-1,12	0,81 (<,0001) 0,75-0,89
	Oxazepam	non-lin. (0,01)	non-lin. (0,008)	0,89 (<,0001)¶ (0,85-0,93)	1,35 (<,0001) 1,30-1,41)	1,14 (<,0001) 1,09-1,19	1,16 (<,0001) 1,09-1,23	1,09 (<,0001) 1,07-1,10	0,98 (0,24) 0,95-1,01
	Bromazepam	0,84 (<,0001)	0,93 (0,003)	0,70 (<,0001)¶ 0,65-0,75	1,31 (<,0001) 1,21-1,41)	0,94 (0,23) 0,86-1,04	1,43 (<,0001) 1,28-1,59	1,10 (<,0001) 1,08-1,13	0,90 (0,02) 0,83-0,98
	Lorazepam	0,97 (<,0001)	0,99 (0,66)	0,80 (<,0001)¶ 0,78-0,82	0,95 (0,0009) 0,93-0,98	1,14 (<,0001) 1,11-1,17	1,20 (<,0001) 1,15-1,25	1,10 (<,0001) 1,09-1,10	0,96 (0,001) 0,93-0,98
Long	Clonazepam	0,93 (0,02)	0,93 (0,04)	0,92 (0,09) 0,83-1,01	0,95 (0,43) 0,85-1,07	0,85 (0,02) 0,74-0,97	1,19 (0,04) 1,01-1,41	1,12 (<,0001) 1,09-1,15	0,91 (0,10) 0,82-1,02
	Flurazepam	0,91 (<,0001)	0,97 (0,06)	1,32 (<,0001) 1,22-1,42	1,18 (<,0001) 1,10-1,26	1,39(<,0001) 1,29-1,49	1,68 (<,0001) 1,54-1,83	1,08 (<,0001) 1,06-1,10	1,01 (0,58) 0,97-1,06
	Chlordia-zepoxide	0,99 (0,78)	0,85 (0,0008)	1,12 (0,11) 0,97-1,29	1,19 (0,04) 1,01-1,40	1,14 (0,16) 0,95-1,37	1,23 (0,08) 0,97-1,56	1,07 (0,005) 1,02-1,12	0,95 (0,57) 0,81-1,12
	Diazepam	0,92 (<,0001)	0,94 (0,008)	0,82 (<,0001) 0,77-0,87	0,89 (0,002) 0,83-0,96	0,95 (0,23) 0,88-1,03	0,76 (<,0001) 0,67-0,85	1,13 (<,0001) 1,11-1,15	0,85 (<,0001) 0,79-0,91

* Adjusted for baseline impairments and other medication use.

† Region of residence is modeled as a dummy variable with the region containing a teaching hospital being the reference: "Region 1" is peripheral, "Region 2" is intermediate and "Region 3" is remote. Women are the reference group for sex.

‡ A quadratic function was used to test the non-linearity of age.

§ Estimated for the effect of sex at median sample age (73,4 years).

¶ Statistically significant interaction between sex and age (p-value≤0,01).

Table 4.5.b Estimated hazard ratios (p-value) and 95% confidence intervals for baseline disabilities and impairments[†] (1989) as predictors of incident benzodiazepine use (1990-1994).[*]

Half - life	Type of Benzodiazepine First Used	Injuries Related to Falls	Depression	Visual Impairment	Neurological Disorders	Arthritis	Seizure Disorders	Alcohol Abuse	Drug Abuse	Charlson Comorbidity Index
Ultra - Short	Triazolam	1.07 (0.52) 0.88 – 1.30	1.14 (0.29) 0.89-1.46	0.93 (0.15) 0.84 - 1.03	1.15 (0.28) 0.89 1.47	1.19 (0.003) 1.06 - 1.33	1.13 (0.40) 0.85 - 1.51	1.74 (0.08) 0.93 - 3.25	1.786(0.09) 0.91 - 3.41	1.04 (0.07) 1.00 - 1.08
Short - Intermediate	Temazepam	0.98 (0.77) 0.84 – 1.14	1.22 (0.03) 1.02-1.46	0.85 (<.0001) 0.79 – 0.92	1.28 (0.006) 1.07 - 1.53	1.04 (0.43) 0.95 - 1.13	0.97 (0.78) 0.77 - 1.22	1.53 (0.10) 0.92 - 2.54	1.13 (0.70) 0.61 - 2.11	1.02 (0.13) 0.99 - 1.05
	Nitrazepam	1.01 (0.96) 0.78 – 1.29	1.53 (0.003) 1.16-2.01	0.93 (0.26) 0.82 - 1.06	1.25 (0.14) 0.93 - 1.69	1.16 (0.04) 1.01 - 1.34	1.37 (0.06) 0.98 - 1.90	1.52 (0.36) 0.63 - 3.67	2.08 (0.08) 0.93 - 4.70	1.00 (0.96) 0.94 - 1.06
	Alprazolam	0.96 (0.61) 0.82 – 1.12	2.02 (<.0001) 1.75-2.34	0.95 (0.21) 0.88 - 1.03	0.92 (0.47) 0.74 - 1.15	1.06 (0.19) 0.97 - 1.16	0.86 (0.26) 0.67 - 1.11	0.68 (0.40) 0.28 - 1.65	1.30 (0.43) 0.67 - 2.51	1.00 (0.93) 0.97 - 1.04
	Oxazepam	0.99 (0.78) 0.92 – 1.07	1.23 (<.0001) 1.12-1.34	1.01 (0.73) 0.97 - 1.05	1.26 (<.0001) 1.14 - 1.38	1.07 (0.002) 1.03 - 1.12	1.04 (0.48) 0.93 - 1.17	1.57 (0.001) 1.20 - 2.07	1.13 (0.47) 0.81 - 1.56	1.04 (<.0001) 1.02 - 1.05
	Bromazepam	0.91 (0.24) 0.77 – 1.07	1.50 (<.0001) 1.27-1.77	0.97 (0.43) 0.90 - 1.05	0.86 (0.20) 0.68 - 1.09	1.23 (<.0001) 1.13 - 1.34	0.82 (0.15) 0.63 - 1.07	0.83 (0.65) 0.37 - 1.86	2.40 (.0008) 1.44 – 4.01	0.93 (0.0005) 0.89 - 0.97
	Lorazepam	0.94 (0.02) 0.89 - 0.99	1.29 (<.0001) 1.22-1.37	0.99 (0.52) 0.97 - 1.02	0.97 (0.43) 0.90 - 1.04	1.06 (0.0001) 1.03 - 1.09	0.87 (0.002) 0.80 - 0.95	1.08 (0.49) 0.86 - 1.37	1.14 (0.27) 0.90 - 1.43	1.03 (<.0001) 1.02 - 1.04
Long	Clonazepam	0.87 (0.24) 0.69 - 1.10	2.44 (<.0001) 2.03-2.94	0.94 (0.29) 0.84 - 1.05	2.29 (<.0001) 1.88 - 2.78	1.30 (<.0001) 1.15 - 1.46	1.38 (0.02) 1.05 - 1.82	0.22 (0.13) 0.03 - 1.55	0.44 (0.25) 0.11 - 1.78	1.05 (0.04) 1.00 - 1.10
	Flurazepam	1.02 (0.78) 0.90 - 1.16	1.26 (0.003) 1.08-1.46	0.90 (0.002) 0.84 - 0.96	1.18 (0.04) 1.01 - 1.37	1.04 (0.31) 0.96 - 1.12	1.02 (0.88) 0.84 - 1.23	1.48 (0.07) 0.97 - 2.25	1.00 (1.00) 0.59 - 1.69	1.04 (0.0008 1.02 - 1.07
	Chlordiazepoxide	1.32 (0.06) 0.99 - 1.75	1.63 (0.005) 1.16-2.30	1.01 (0.90) 0.86 - 1.19	1.08 (0.74) 0.70 - 1.65	0.87 (0.18) 0.72 - 1.06	1.01 (0.96) 0.62 - 1.65	12.91 (<.0001) 8.58 - 19.42	1.12 (0.85) 0.35 - 3.53	0.95 (0.20) 0.88- 1.03
	Diazepam	0.87 (0.06) 0.75 - 1.00	1.27 (0.002) 1.09-1.48	0.96 (0.25) 0.90 - 1.03	0.87 (0.16) 0.71 - 1.06	1.13 (0.001) 1.05 - 1.22	0.97 (0.81) 0.79 - 1.21	0.95 (0.87) 0.49 - 1.83	1.16 (0.65) 0.62 - 2.16	0.97 (0.14) 0.94 - 1.01

[†] Results for stroke are not shown since this disability is included as part of the Charlson Comorbidity Index. Osteoporosis and other miscellaneous impairments were not shown since all hazard ratios were non-significant. For osteoporosis this may have been due to the small number of cases (0.5% of all incident users, 0.4% of non-users).

[*] Adjusted for baseline patient characteristics, health care use and other medication use.

Table 4.5.c Estimated hazard ratios (p-value) and 95% confidence intervals for non-benzodiazepine baseline medication (1989) use as predictors of incident benzodiazepine use (1990-1994).*

Half-life	Type of Benzodiazepine First Used	Protective for Fractures[¶]	Associated with an Increased Risk for Injuries									
		Thiazide Diuretics	Anti-Depressants	Anti-Psychotics	Other Sedatives	Lithium, L-tryptophan	Cardiac Drugs	Anti-Hypertensive	Vasodi-lators	Opiate Agonists	Partial Opiate Agonists	Non-Thiazide Diuretics
Ultra-Short	Triazolam	1.11 (0.04) 1.01 - 1.23	1.83 (<.0001) 1.48-2.27	0.93 (0.69) 0.64 - 1.34	1.24 (0.04) 1.01 - 1.54	1.27 (0.59) 0.53 - 3.08	1.02 (0.71) 0.92 - 1.13	1.07 (0.26) 0.95 - 1.22	0.95 (0.43) 0.83 – 1.08	1.45 (0.07) 0.97 - 2.16	2.48 (0.02) 1.18 - 5.22	1.09 (0.19) 0.95 - 1.25
Short/ Inter-mediate	Temazepam	1.14 (0.0008) 1.06 - 1.23	2.16 (<.0001) 1.85- 2.52	1.71 (<.0001) 1.38 - 2.11	1.69 (<.0001) 1.47 - 1.94	2.09 (0.004) 1.27 - 3.43	1.04 (0.28) 0.96 - 1.13	1.08 (0.12) 0.98 - 1.19	1.05 (0.31) 0.95 - 1.16	1.43 (0.02) 1.05 – 1.94	0.82 (0.69) 0.31 - 2.19	1.13 (0.02) 1.02 - 1.25
	Nitrazepam	1.04 (0.44) 0.92 - 1.19	2.49 (<.0001) 1.96 – 3.16	1.43 (0.06) 0.99-2.08	1.40 (0.008) 1.09 - 1.80	1.32 (0.58) 0.49 – 3.56	0.90 (0.11) 0.78 - 1.02	1.05 (0.56) 0.89 - 1.23	1.18 (0.04) 1.01 - 1.38	1.35 (0.27) 0.79 - 2.29	1.69 (0.37) 0.54 - 5.27	1.23 (0.01) 1.04 - 1.46
	Alprazolam	1.00 (0.97) 0.92 - 1.08	2.29 (<.0001) 1.96 - 2.67	1.01(0.94) 0.77 - 1.33	1.37 (<.0001) 1.18 - 1.60	0.97 (0.92) 0.50 – 1.87	1.05 (0.25) 0.97 - 1.13	1.04 (0.46) 0.94 - 1.14	1.16 (0.002) 1.06 - 1.28	0.84 (0.42) 0.56 - 1.27	1.35 (0.46) 0.60 - 3.02	1.02 (0.68) 0.92 - 1.14
	Oxazepam	1.02 (0.28) 0.98 - 1.06	1.68 (<.0001) 1.54 - 1.83	1.19 (0.008) 1.04 - 1.35	1.32 (<.0001) 1.22 - 1.42	1.26 (0.19) 0.89 - 1.78	1.07 (0.0004) 1.03 - 1.12	1.14 (<.0001) 1.09 - 1.19	1.21 (<.0001) 1.16 - 1.27	1.24 (0.009) 1.06 - 1.47	1.16 (0.49) 0.76 - 1.76	1.16 (<.0001) 1.10 - 1.22
	Bromazepam	1.00 (0.91) 0.92 - 1.08	1.84 (<.0001) 1.56 – 2.18	0.98 (0.91) 0.73 - 1.32	1.26 (0.005) 1.07 - 1.48	0.98 (0.95) 0.48 – 1.96	1.02 (0.62) 0.94 - 1.11	1.06 (0.24) 0.96 - 1.17	1.03 (0.53) 0.93 - 1.14	1.07 (0.71) 0.74 - 1.56	0.69 (0.51) 0.22 - 2.13	1.02 (0.72) 0.91 - 1.14
	Lorazepam	1.03 (0.01) 1.01 - 1.06	1.45 (<.0001) 1.36 - 1.55	1.02 (0.70) 0.92 - 1.12	1.18 (<.0001) 1.12 - 1.25	0.75 (0.06) 0.55 - 1.01	1.06 (<.0001) 1.03 - 1.09	1.05 (0.003) 1.02 - 1.09	1.20 (<.0001) 1.16 - 1.24	1.04 (0.58) 0.91 - 1.18	0.92 (0.64) 0.66 - 1.29	1.04 (0.03) 1.01 - 1.08
Long	Clonazepam	0.85 (0.01) 0.76 - 0.96	3.07 (<.0001) 2.54 – 3.70	2.30 (<.0001) 1.82 – 2.89	1.22 (0.07) 0.98- 1.52	5.19 (<.0001) 3.60 – 7.46	1.12 (0.06) 1.00 - 1.26	1.03 (0.68) 0.89 - 1.19	0.99 (0.859) 0.856 - 1.14	1.29 (0.28) 0.81 - 2.03	1.02 (0.97) 0.33 - 3.19	1.20 (0.02) 1.03 - 1.39
	Flurazepam	1.01 (0.74) 0.94 - 1.08	1.68 (<.0001) 1.46 - 1.95	2.09 (<.0001) 1.76 - 2.49	1.53 (<.0001) 1.36 - 1.73	2.41(<.0001) 1.64 - 3.54	1.02 (0.55) 0.95 - 1.09	1.06 (0.16) 0.98 - 1.15	1.29(<.0001) 1.19 - 1.40	1.15 (0.34) 0.86 - 1.52	1.92 (0.02) 1.11 - 3.31	1.15 (0.001) 1.06 - 1.26
	Chlordiaz.	1.04 (0.64) 0.88 - 1.24	2.03 (<.0001) 1.42 - 2.89	1.10 (0.74) 0.62 – 1.95	1.01 (0.96) 0.68 - 1.47	- [§]	0.96 (0.62) 0.80 - 1.14	1.03 (0.78) 0.83 - 1.28	0.95 (0.64) 0.76 - 1.18	1.34 (0.42) 0.66 - 2.69	- [§]	0.83 (0.15) 0.64 - 1.07
	Diazepam	1.05 (0.16) 0.98 - 1.13	1.24 (0.02) 1.04 - 1.47	1.40 (0.003) 1.12 - 1.75	1.12 (0.12) 0.97 - 1.30	0.61 (0.23) 0.27 - 1.37	1.03 (0.34) 0.96 - 1.11	0.93 (0.10) 0.85 - 1.01	1.16 (0.0007) 1.06 - 1.26	1.19 (0.27) 0.87 - 1.62	0.88 (0.78) 0.37 - 2.13	1.01 (0.75) 0.92 - 1.12

* Adjusted for baseline patient characteristics, health care use and disabilities.

[¶] Hazard ratios for estrogen could not be estimated because of the small number of occurrences (0.1% for incident users and non-users).

[§] Hazard ratios not estimated due to the small number of incident users.

Figure 4.1 Estimated change in hazard ratio with age for incident oxazepam use in men and women, adjusted for all other covariates.

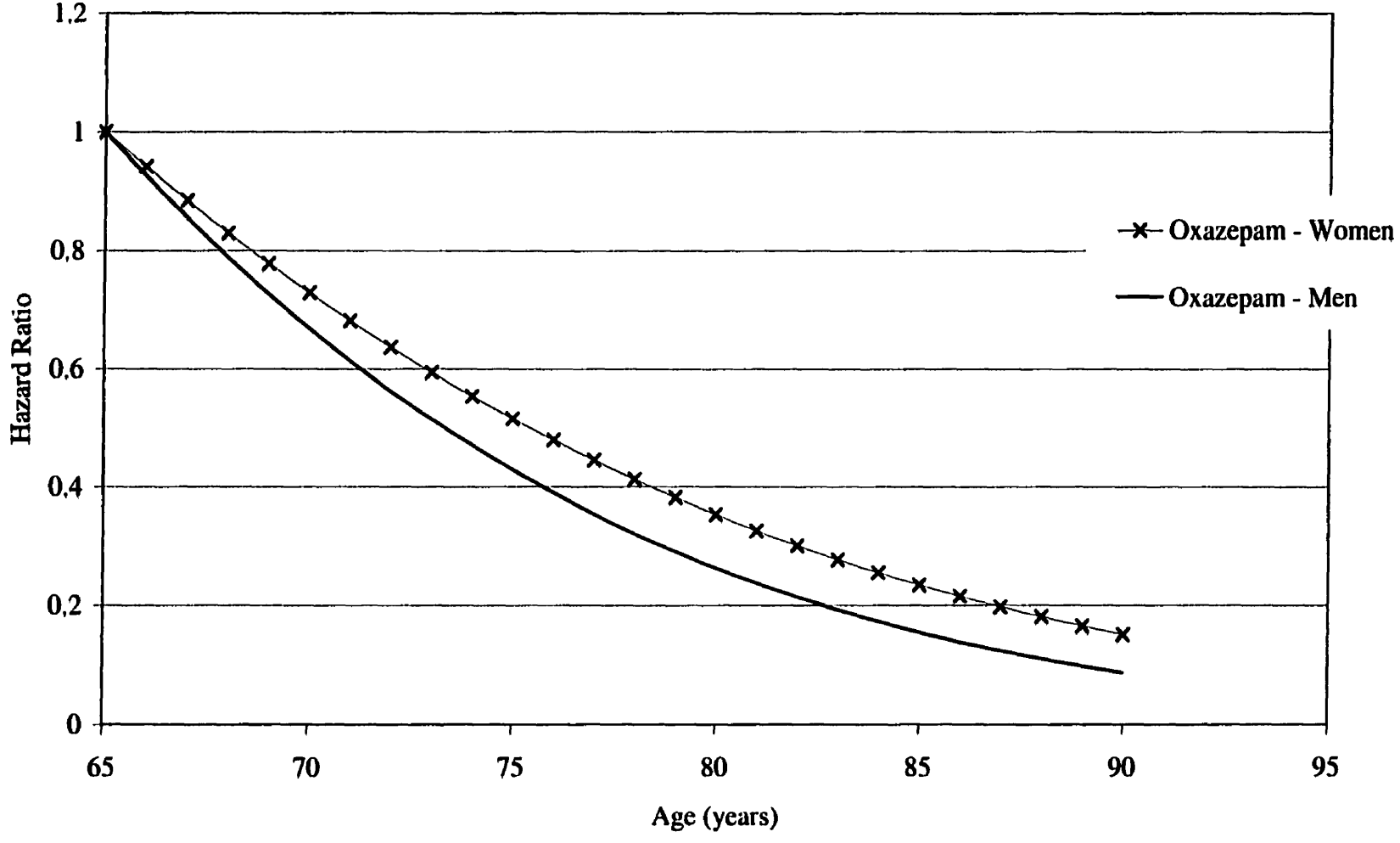
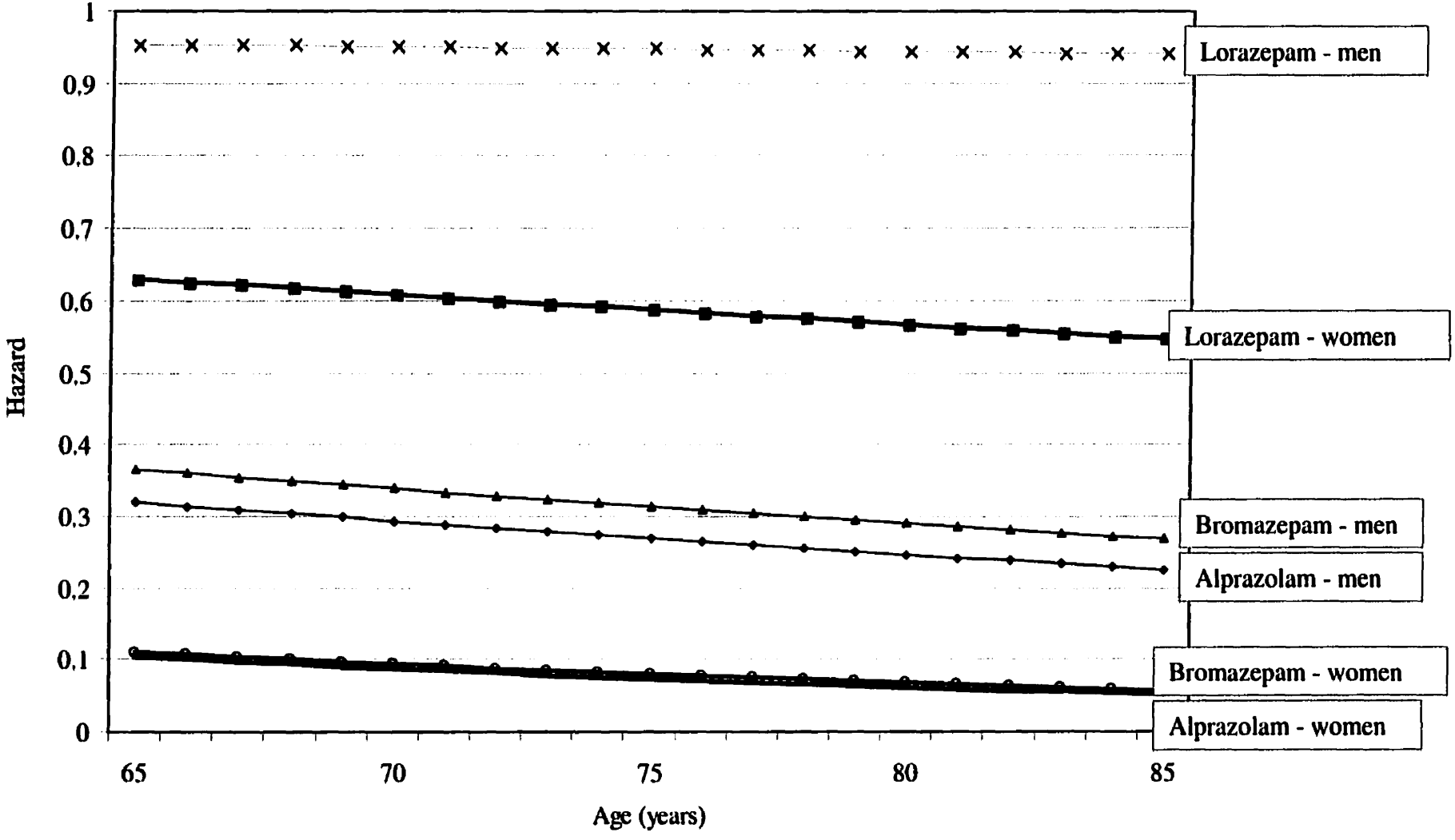


Figure 4.2 **Estimated change in hazard ratio with age for men compared to women for incident benzodiazepine use in models with statistically significant interactions, adjusted for all other baseline characteristics.**



benzodiazepine in the next five years, there was a slightly decreased probability for lorazepam (HR=0.94, p=0.02) and an increased probability for chlordiazepoxide (HR=1.32, p=0.06). A diagnosis for depression during the baseline year was strongly associated with an increased hazard for subsequent incident use of all the benzodiazepines. This increase in probability was particularly strong for alprazolam (HR=2.02, p<0.0001) and clonazepam (HR=2.44, p<0.0001). A weaker but consistently positive association was found between arthritis and incident benzodiazepine, although the statistical significance varied between drugs. There were also several strong, positive associations between certain impairments and incident use of specific benzodiazepines. These included the association between neurological disorders (included dementia and Parkinson's disease) and clonazepam (HR=2.29, p<0.0001); alcohol abuse and both oxazepam (HR=1.57 p=0.001) and chlordiazepoxide (HR=12.9, p<0.0001); as well as drug abuse with bromazepam (HR=2.40, p=0.0008).

Associations between other types of disabilities and incident benzodiazepine use were specific to the type of benzodiazepine and demonstrated no discernable pattern between drugs with similar elimination half-lives. For example, for every increase of one point in the Charlston Co-morbidity Index, the hazard for starting on bromazepam significantly decreased by 7% while the hazard for starting on other intermediate half-life benzodiazepines, such as oxazepam and lorazepam, significantly increased by 3-4%.

4.3.4.4 Other Medication Use

Like disabilities, the significant predictors for starting benzodiazepine use among medications considered in our analyses were quite different across specific benzodiazepines. Overall, the associations between the use of cardiac drugs, anti-hypertensives and non-

thiazide diuretics were very weak for all the benzodiazepines. Contrasting associations were found for use of certain medications and different benzodiazepines. For example, the use of thiazide diuretics was associated with a significant increase in probability for temazepam use (HR=1.14, p=0.0007) but with a decrease in probability for clonazepam use (HR=0.85, p=0.01).

The strongest and most consistent associations were seen for use of anti-depressants as well as other psychotropic medications (anti-psychotics and non-benzodiazepine sedatives, lithium or l-tryptophan). For a subject without a detected diagnosis of depression, filling a prescription for an anti-depressant significantly increased the hazard of starting any particular benzodiazepine, but the strength of the association varied from a 24% increase for diazepam to more than tripling the probability for clonazepam. For use of anti-psychotics, other sedatives, and lithium or l-tryptophan, the statistically significant hazard ratios were greater than 1.0 but, again, the strength of the associations varied considerably across products. For example, the use of anti-psychotics more than doubles the probability of incident clonazepam and flurazepam use ($p<0.0001$) and the use of lithium or l-tryptophan increases the probability of clonazepam use by over five times (HR=5.19, 95% CI 3.60-7.46).

4.4 DISCUSSION

4.4.1 Summary

As with the findings of other studies that have examined the characteristics of elderly, prevalent users of benzodiazepines,[2;3;51;52] we found that elderly patients who filled a benzodiazepine prescription in 1989 were generally more likely to be women, to have poorer health and to be taking more medication. The relatively high prevalence rates of 37% for men

and 51% for women agreed with the results of an earlier study by Tamblyn et al (1994) of Quebec elderly. Despite the fact that these rates were relatively high compared with similar studies, given the large size of the Quebec elderly population compared to other regions that have universal health coverage, the yearly prevalence rates of benzodiazepine use in our study should still have been an accurate reflection of benzodiazepine consumption in elderly populations.

The most common drug for prevalent users in our study was lorazepam, followed by oxazepam. This high prevalence of lorazepam was also found in a database study of Nova Scotia seniors[21] but was not noted in other studies of benzodiazepine prevalence.[2;5;51] However the difference in rates of use may reflect the availability of the medications or possible shifts in prescribing patterns over time. We were unable to find any published studies that provide incidence rates for individual benzodiazepines. We also found that lorazepam was the most common drug for first-time prescriptions, followed by oxazepam. A comparison of incident rates between our study and other published estimates is difficult since many of the incidence rates are reported as percentages and not in terms of person-years of observation. The overall incident rate of 88.7 per 1,000 person-years can be roughly translated to 8.9% per year. Using this figure, our rates were significantly higher than the 2.5% reported by Taylor et al (1998) for an elderly cohort in England.[4] Since Taylor's study uses an age-gender stratified sample of people living in the Liverpool region and relies on self-reported medication use at two different interview periods, we expected this rate to be an underestimation of the true incidence of benzodiazepine use due to inadequate ascertainment of exposure.[4]

While the characteristics of prevalent benzodiazepine users clearly indicated that this group had a higher risk profile, due to the cross-sectional nature of the data we were unable to determine if any or all of these conditions occurred before, or after initiating benzodiazepine treatment. This limitation was overcome in our analysis of the predictors of incident use. By measuring these factors in a group of elderly who did not use benzodiazepines for at least one year, we were able to determine that many of the pre-existing conditions had a significant effect on the probability of initiating benzodiazepine treatment in the next five years. This confirmed the importance of including these factors in any study that evaluates the adverse effects, such as risk of falls or injuries, associated with benzodiazepine use.

Nelson and Chouinard (1999), in their guidelines for clinical use of benzodiazepines, comment that the sensitivity to the adverse effects of benzodiazepines that elderly people experience may only occur with specific products.[11] This specificity is related to the unique pharmacokinetic and pharmacodynamic profile of each benzodiazepine.[11;17;20] Therefore, initial research into risks associated with benzodiazepine use in the elderly population should first establish if there are any discrepancies among the rates of individual benzodiazepine use as well as the characteristics of the users of specific products. In our study, we found that not only did the rates of use vary, but also the factors associated with new benzodiazepine use varied greatly among the individual benzodiazepines. If there were only certain benzodiazepines that posed specific risks, the distribution of benzodiazepine use among the different products could have been a crucial factor in comparing the results of studies assessing the overall impact of benzodiazepine use in different populations. Furthermore,

there were significant differences among the characteristics of elderly people who started using any of the benzodiazepines compared to those elderly who never filled a benzodiazepine script as well as significant differences among incident users depending on which benzodiazepine was first used.

In order to properly assess the risk of adverse effects associated with benzodiazepine use, the presence of pre-existing risk factors must be examined. If these factors are not included in a model used to estimate the risk of falls associated with benzodiazepines, the results will be biased due to a classical confounding factor.[53] According to Rothman and Greenland, there are three criteria for a confounding factor: (i) the factor must be a risk factor for outcome of interest, (ii) the factor must not be affected by the exposure or the outcome of interest, and (iii) the factor must be associated with the main exposure in the source population.[53] Most of the predictors of incident use that we included in our study met these requirements. Part of the basis for the selection of our predictors was that the factor had to be identified in at least one published study as a risk factor for injuries from falls, thereby meeting Rothman and Greenland's first criterion for confounding. By employing a prospective study design that only included incident use of benzodiazepine and measured characteristics a year before possible exposure to benzodiazepines, we ensured that these pre-existing factors were not affected by the exposure, benzodiazepine use, or the outcome, injuries from falls, which ensures the second criterion. Finally, our study was unique in that it provided confirmation of the association between these factors and the exposure, benzodiazepine use, thereby demonstrating that many of these factors met, as well, the third criterion for confounders. Therefore, our study provided conclusive evidence for including

these variables in any analysis of the impact of benzodiazepine use on the risk of adverse events in order to avoid potential spurious associations due to confounding.

It is possible that some of the previous studies showing that benzodiazepine use is associated with higher risk of injuries from falls, but did not control for these subject characteristics, may have overestimated the impact of the benzodiazepines.[24] For example, our study found a very strong association between the use of anti-depressant medication in 1989 and the increased probability of incident benzodiazepine use in the next five years. A strong relationship was also found by other investigators between the use of anti-depressants and falls.[36;54] Yet several of the studies reporting high associations between benzodiazepine use and injuries from falls do not control for anti-depressant use.[13;24;35;37]

Moreover, the fact that the predictors of incident use, and the strength of their effects, varied considerably between individual benzodiazepines, indicated that it was essential to adjust for these characteristics when comparing the impact of different products on the risk of injuries from falls. Although many of the more recent studies that examine the risks associated with benzodiazepine use attempt to control for medication use and health status in the elderly,[13-16;35] none of these studies measure health care utilization. In our study, one of the most consistent predictors of subsequent benzodiazepine use was the number of prescribing physicians in the baseline year. The interpretation of this association is not straightforward. While the estimate is adjusted for the use of many medications, and illnesses that are associated with falls, our list of predictors was not exhaustive. The number of prescribing physicians may have been an indication of other aspects of health status, not reflected by the variables included in our analyses. There was also the possibility that this

predictor was a measure of a patient's tendency to higher utilization of the health care system, independent of the patient's actual health status. Within the context of a database study, it is impossible to make this distinction but the conjecture that this association may have partly reflected "doctor shopping" behaviour was supported by the fact that the association persisted even after adjusting for several measures of the patient's health status.[55;56] This was consistent with the previous finding that the risk of potentially inappropriate drug combinations increased with number of physicians involved in the medical management of an elderly patient.[56]

Despite the obvious lack of some details on the patients' health status, the use of administrative databases offered several advantages for our study. The main advantage was in sample size resulting in high statistical power and precision of the estimation. We had a large enough sample size to examine different, detailed aspects of individual benzodiazepine use with a prospective cohort design. Even for drugs such as chlordiazepoxide, with a very small market share, significant predictors were detected. Although the differences in statistical significance of some of the predictors among the individual benzodiazepines may have been partly due to power considerations for the less frequent benzodiazepines, these considerations affected only very weak associations (hazard ratios between 0.8 and 1.2). However, comparing the significant predictors for the two most common incident benzodiazepines, lorazepam and oxazepam, shows quite different profiles (Table 4.5). This disparity of strength and magnitude for the predictors of incident use among the different benzodiazepines reinforced the fact that analyses of the impact of benzodiazepines on risks of adverse effects such as injurious falls must be by individual products.

estrogen use and subsequent incident benzodiazepine use. The small number of detected osteoporosis diagnoses and estrogen use, likely due to under-reporting, did not allow us to explore the role of these factors as predictors. Also, certain conditions such as anxiety and insomnia were often not coded in the billing databases making it difficult to assess the association between these variables and benzodiazepine use.[62] While benzodiazepines may often be prescribed for inappropriate reasons,[22;58;62-64] the lack of sensitivity in the diagnostic codes for billing databases may partly have accounted for our finding that only a very small proportion of incident users were diagnosed with any of the conditions corresponding to the labeled uses of benzodiazepines.

Furthermore, there was no prescription information available during hospitalization. Although we adjusted our estimates of incidence rates accordingly, by removing periods of hospitalization from the total person-years calculation, the lack of this information may have accounted for the apparent lack of effect of the number of acute care hospital stays in the baseline on subsequent incident benzodiazepine use. Grad et al (1999) found that recent hospitalization increases the risk of incident benzodiazepine use out of hospital in community-dwelling elderly people of Quebec.[65]

Finally, in our study we only evaluated the first new benzodiazepine script filled. We did not go on to look at subsequent use, so we were not able to say, for example, whether lorazepam remained a popular drug after initiation of therapy or to comment on different aspects of patterns of use such as switching or adding benzodiazepines, duration of use and changes in the dose of the subsequent prescriptions.

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5.0 PREFACE TO MANUSCRIPT 2

This is the second article in a series of four that addressed specific components of the overall thesis objective of assessing the risk of injuries from falls associated with patterns of benzodiazepine use in community-dwelling elderly people. This article is a logical continuation of the research described in the first manuscript. The first article estimated the level of benzodiazepine consumption in an elderly population and examined the characteristics of subjects who initiated therapy using different benzodiazepines. The second manuscript continued with the next step in that research by investigating patterns of benzodiazepine use that occurred after the first prescription. This investigation was motivated by the expectation that some aspects of time-dependent changes in the exposure to benzodiazepines may be important to identify more precisely the mechanisms by which they affect the risks of injuries from falls.

In order to achieve the specific objective of describing, among new users of benzodiazepines, initial and evolving patterns of use over time, the manuscript evaluated such aspects as duration of uninterrupted use, changes in dosage, switching or adding of prescriptions, and assessed how these aspects of patterns of use related to specific benzodiazepines and patient characteristics.

The results of this article were then used to guide the next steps of the thesis research. Specifically, based on the finding of complex patterns of benzodiazepine use that change over time, the next article focused on the methodological issues involved in modeling this level of complexity in exposure. The results from this article confirmed the necessity of utilizing carefully defined time-dependent covariates to represent different aspects of

exposure to benzodiazepines in all subsequent analyses. Information from the characterization of these patterns was the basis for the selection of the variables that were constructed in Manuscript 3 and that were included in the final analyses of risk associated with benzodiazepine exposure in Manuscript 4 (Chapters 6 and 7, respectively).

MANUSCRIPT 2: Patterns of Benzodiazepine Use in the Elderly

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Abstract

Background Given the widespread use of benzodiazepines in elderly patients, there are concerns about duration of use, the choice of benzodiazepine, and the increased risk of physiological dependence. Only limited information is available about patterns of benzodiazepine use and their evolution over time.

Objectives To characterize different aspects of the patterns of benzodiazepine use in an elderly cohort including the choice of specific products, switching or adding medications, changes in duration and dosage over time, evidence of dependence through increasing dosage or duration of use, and to develop new approaches to summarize these complex patterns.

Methods Using information from provincial administrative databases, 78,367 community-dwelling Quebec residents over the age of 65 classified as incident users(no benzodiazepine prescription for one year) were followed for five years. Time-dependent covariates representing different aspects of benzodiazepine exposure and summary measures of change in dosage, switching or adding were constructed and compared between patients and specific products. Dose was standardized using recommended maximum adult daily doses. In order to identify patterns suggesting possibly increasing drug dependency, Spearman's rank correlation coefficients were calculated to assess strengths and direction of association between duration of use or current dose, and time. Multiple logistic regression models evaluated subject characteristics associated with extreme positive correlations considered a proxy measure for dependence.

Results The median duration for uninterrupted periods of use was 31 days (mean=75.5 days, sd=137.2). The mean daily dose was almost half the recommended maximum adult daily

5.0 PATTERNS OF BENZODIAZEPINE USE IN THE ELDERLY (MANUSCRIPT 2)

5.1 INTRODUCTION

With the well-documented widespread consumption of benzodiazepines in community dwelling elderly (see Chapter 4.0), many investigators and clinicians have focused on the non-optimal use of these medications. Several studies have been published on duration of use, the choice of benzodiazepine product, usually in terms of length of elimination half-life, and non-optimal prescribing.[1-5] Non-optimal prescribing may include exceeding the recommended duration or dosage for specific benzodiazepines, potentially inappropriate drug combinations or providing a benzodiazepine for no acceptable reason.[1;2;6] While the recommended duration of use for many benzodiazepines is 30 days,[7-9] published studies estimate that approximately 20-30% of the elderly using benzodiazepines exceed this time and almost 10% exceed 90 days.[12,2,30] Furthermore, investigators estimate that 10-15% of these patients are taking more than one benzodiazepine at the same time.[2;10] Although there is evidence that many prescriptions are given with instructions to be taken *pro re nata* (as needed) and that many elderly report taking lower doses than prescribed,[10;11] researchers suggest that many benzodiazepine prescriptions still appear to exceed the recommended daily maxima.[12]

Since factors such as the presence of other illnesses, increased length of elimination half-life, higher dose level, and increased duration contribute to the likelihood of developing of benzodiazepine dependence,[7;13-16] the non-optimal use of benzodiazepines may make elderly patients particularly susceptible to this problem.[7;8;16;17] Dependence occurs with

chronic exposure to benzodiazepines that causes physiological alterations in a patient so that abrupt termination of the medication is associated with uncomfortable or painful withdrawal symptoms.[7;18-20] Withdrawal symptoms can include depressed mood (dysphoria), depersonalization, loss of appetite, headache, nausea, fatigue, nausea, weakness, dizziness, muscle aches and twitches, and perceptual disturbances.[7;8;20;21] Researchers believe that the majority of benzodiazepine dependence, unlike dependence on other sedatives, occurs with little, if any, dosage increase,[19]however very few studies have investigated changes in benzodiazepine dosage over time.

Despite these concerns, we were unable to identify any studies that have comprehensively examined the patterns of benzodiazepine use in the elderly over a long period of time. The objective of this study is to characterize different aspects of the patterns of benzodiazepine use in an elderly cohort including the choice of specific products, switching or adding medications, changes in duration and dosage over time and evidence of dependence through increasing dosage or duration of use.

5.2 METHODS

5.2.1 Data Source and Study Population

A cohort of elderly Quebec residents were studied for the period, January 1, 1989 to December 31, 1994, using information from provincial administrative health databases. Details of the cohort and the available subject information are provided in Chapter 4.0. Since no information on benzodiazepine use was available before January 1, 1989, only subjects who did not fill a benzodiazepine prescription during this year were eligible to be included in the study. Furthermore, subjects for whom the first detected benzodiazepine

prescription during the study period, January 1, 1990 to December 31, 1994, was a refill were also excluded (n=209,732). The remaining subjects were included in the study if a record for at least one new benzodiazepine prescription was detected during the study period. Thus, all new incident users of benzodiazepine were assessed.

For the final cohort, data was retrieved on several baseline characteristics including age, sex, area of residence, disabilities, co-morbidity, hospitalization, health care use, use of other selected prescription drugs and diagnosis for fractures and soft tissues injuries. Further details are provided in Chapter 4.0. This study was conducted in accordance with the ethical standards of the McGill Faculty of Medicine Institutional Review Board for research involving human subjects.

5.2.2 Measurement of Benzodiazepine Exposure

In order to discriminate between prevalent use of benzodiazepines and new use, the active follow-up was restricted from 1990 to 1994 while 1989 was considered a baseline period. All subjects were followed until the end of the study at Dec. 31, 1994 or until lost to follow up due to death, moving out of the province or institutionalized.

Information on benzodiazepine use included start and end dates for each uninterrupted period of exposure; exact drug type; dosage; and hospitalization information for each prescription. To facilitate between drug comparisons, a standardized daily dose was calculated for each prescription according to the following formula:

$$\left(\frac{\text{total number of pills}}{\text{duration of prescription in days}}\right) \times \left(\frac{\text{dosage per pill in mg}}{\text{WHO recommended adult daily dosage in mg}}\right)$$

where the first term represented the average number of pills per day and the second term converted a given dosage into the percent of the World Health Organization (WHO) recommended adult daily dose[22] for the respective drug (see Appendix III). If the prescribed dose was close to the recommended daily dose for this specific product then the standardized dose would be close to 1.0.

In addition, several time-dependent covariates representing different aspects of benzodiazepine exposure were constructed. January 1, 1990 was considered the start of the observation period for the time-dependent covariates. Since benzodiazepine exposure would be affected by the length of observation, January 1, 1990 was also used as time zero (T_0) for the calculation of the total person-time of observation. No prescription information was available during hospitalization so periods of hospitalization longer than seven days were temporarily censored and not included in the calculation of total person-time of observation or in the construction of the time dependent covariates. Cumulative exposure to benzodiazepines was calculated as the sum of all daily doses since the beginning of the follow-up period, January 1, 1990, until censoring occurred from loss-to-follow-up or due to the end of the study on December 31, 1994. Cumulative duration of benzodiazepine exposure was also calculated as the sum of all time intervals since the beginning of the follow-up period until censoring occurred. These summary measures were created for overall benzodiazepine exposure, i.e. cumulative dose and duration across different products, as well as for exposure to individual benzodiazepines. Given that most elderly may occasionally forget to take a pill, may reduce their dosage, or may have difficulty seeing their physician to obtain a refill prescription, we felt that periods of less than two weeks between

consecutive prescriptions were unlikely to be "true" periods of non-use. To avoid under-estimating the cumulative duration of uninterrupted use, periods of less than 15 days between two consecutive benzodiazepines prescriptions were considered as continued use at the dosage of the earlier prescription. This rule did not apply if the period of interruption was due to hospitalization.

Summary measures were also made for changes in dosage, the number of times a subject switched to a different benzodiazepine or added an additional benzodiazepine. Again, to avoid bias by over-estimating how often a subject was filling more than one benzodiazepine prescription at a time, when the period of time where there was a record for more than one benzodiazepine prescription was less than five days, the overlap was ignored and the overlap period was assumed to reflect only information from the earlier prescription. The period of five days was chosen based on the distribution of the duration for period overlaps between more than one benzodiazepine within the study. This rule was applied whether the later prescription was for the same benzodiazepine as the earlier prescription or for a different type. For the analyses of changes in dosage over time, periods were considered uninterrupted as long as the subject did not change the dose of the medication (either by changing the dose of the currently prescribed medication or by adding or switching to another benzodiazepine).

5.2.3 Statistical Analyses

Frequency distributions of categorical benzodiazepine exposure variables were reported and the means, standard deviations (sd) and ranges were reported for continuous variables. Chi-square tests and one-way analysis of variance using Tukey-Kramer tests for

multiple comparisons[23;24] were used to compare the distribution of categorical and continuous variables, respectively.

Spearman's rank correlation coefficients were calculated, for each subject with 3 or more distinct periods of use, to assess strengths and direction of association between duration of uninterrupted periods of benzodiazepine use and time. Time was represented by an ordinal variable reflecting rank order of subsequent periods of use. Subjects were then categorized based on the distribution of the correlation coefficients with high positive correlations indicating increasing durations of use with consecutive time periods. Subjects were categorized using a cut-off corresponding to 90th percentile of the sample distribution of Spearman's correlation coefficients as having "increasing duration." Multiple logistic regression modeling was used to identify baseline subject characteristics that were associated with "increasing" duration. The same approach was employed to identify "increasing" dosage, and to assess its correlates.

Potential predictors were identified *a priori* from baseline characteristics measured in 1989. However, age was included as age at time of first benzodiazepine prescription. To assess if the role of potential predictors was the same for men and women, interaction terms were included for sex and several baseline characteristics. Interaction terms were tested individually using a Wald test. If a significant interaction was found between the binary variable, sex, and the continuous variable, age, the parameter estimate for sex would be meaningless since it would represent the effect of sex at age = 0. In order to avoid this problem, the age variable was transformed by subtracting a subject's age in 1989 from the median age of the cohort. Thus, if a significant interaction was found between age and sex,

the parameter estimate for sex represented the hazard for men compared to women at the median age. Significant predictors were selected using automated stepwise procedures.

Statistical analyses were conducted using SAS Systems 8.0 for Windows[25] and S-Plus 4.[26] Graphs and figures were constructed using Microsoft Excel.[27] To correct for the number of statistical tests, significance levels were set at 0.01.

5.3 RESULTS

Of the 252,811 elderly subjects who did not fill a benzodiazepine prescription in 1989, 30% went on to fill at least one during the study period (n=78,367). The baseline characteristics of these subjects are reported in Chapter 4.0 (see incident users, Table 4.1). The average age of subjects in the study when they filled their first benzodiazepine prescription was 75.5 years (sd=5.8) with no clinically significant differences between men (75.1 years) compared to women (75.7 years). Fifty-six percent of the subjects were hospitalized at least once for a period greater than seven days during the follow-up (n=43,683). Significantly more men were hospitalized compared with women (63% versus 50%, $p<0.0001$). However, among these subjects, the average duration of hospitalization (excluding stays of one week or less) was slightly longer for women (54.5 days) compared to men (51.1 days, $p<0.0001$).

5.3.1 Duration of Benzodiazepine Use

Table 5.1 reports the descriptive statistics for the distribution of duration of subject observation and for benzodiazepine exposure. After filling their first prescription for a benzodiazepine, elderly subjects spent an average of 34% (sd=35.1) of their time on benzodiazepines. Only one subject spent the entire 1,826 days of follow-up using benzodiazepines. However, 11% of the elderly patients spent all of their non-hospitalized

Table 5.1 Description of study observation time* and periods of benzodiazepine exposure for 78,237 incident users over 5 years of follow-up.†

Variable	No. of Subjects	Mean (sd)	Median	Range
Observation time (days)	78,367	1,625.1 (407.0)	1826	10 - 1,826
Duration of hospitalization periods‡ (days)	43,683	53.6 (58.8)	34	8 - 1,306
Duration of hospitalization periods as a fraction of total observation time	78,367	0.03 (0.06)	0.06	0 -0.996
Observation time excluding periods of hospitalization (days)	78,367	1,595.2 (420.8)	1809	1 - 1,826
Observation time after first benzodiazepine script (days)	78,367	915.7 (568.1)	927	1 - 1,826
Observation time after first benzodiazepine script excluding periods of hospitalization (days)	78,367	896.5 (570.2)	904	1 - 1,826
Total duration of benzodiazepine use (days)	78,367	228.6 (327.3)	83	1 - 1,826
Duration of benzodiazepine use as a fraction of observation time since first benzodiazepine script excluding hospitalization	78,367	0.34 (0.35)	0.18	0.0005 - 1.0
Number of periods of uninterrupted benzodiazepine use	78,367	3.2 (3.3)	2	1 - 32
Average duration of uninterrupted periods of benzodiazepine use (days)	78,367	75.5 (137.2)	31	1 - 1,826
Average duration of interruption between periods of benzodiazepine use¶ (days)	42,219	187.1 (239.9)	95.6	15 - 1,773

* The observation period starts on January 1, 1990 (Day 0) and continues until the end of the study on December 31, 1994 (Day 1826).
† Based on exposure to any of the 13 benzodiazepines available in community-based pharmacies in Quebec.
‡ Among subjects hospitalized at least once for more than 7 days, only hospital stays longer than 7 days were considered resulting in an inflation of the mean and median duration.
¶ Calculated only with those benzodiazepine users who had two or more distinct periods of use.

observation time after filling their first prescription on benzodiazepines, and 15% of the sample spent 90% or more of their time since the first prescription on benzodiazepines. The average duration of uninterrupted benzodiazepine use was greater than 35 days for 45% of the subjects (n=35,442). Among the subjects whose average duration of use exceeded 35 days, 20.1% of the subjects had an average duration of use between 36-65 days, 7.6% between 66-95 days, 9.0% between 96-185 days and 8.5% exceeded 185 days. Although subjects who were followed for less than one year had somewhat shorter average periods of benzodiazepine use, Figure 5.1 shows that overall the duration of uninterrupted benzodiazepine use was not significantly affected by the amount of time that a subject was observed. Furthermore, Figure 5.2 shows that men and women had very similar distributions for the average duration of use even if women contributed on average over four months more to the observation time after filling their first prescription compared to men (951.4 versus 814.9 days, $p<0.0001$).

When the duration of uninterrupted use was examined by the number and order of distinct intervals, 40.9% of the subjects had only one period of use (53.0% of women). The overall mean duration of the first period of use was 69.7 days (sd=147.2 days). Table 5.2 compares the average duration of the first period of use for women and men, by the type of benzodiazepine listed on the first prescription. Table 5.2 shows that whereas overall, men had slightly longer mean durations of use for the first period, this difference was only statistically significant for triazolam (17.7 days longer for men) and lorazepam (4.5 days). By contrast, women had a significantly longer average duration of first use for two long elimination half-life benzodiazepines, flurazepam (14.3 days) and chlordiazepoxide (15.7).

Figure 5.2 Distribution of mean duration of uninterrupted benzodiazepine use for men and women.

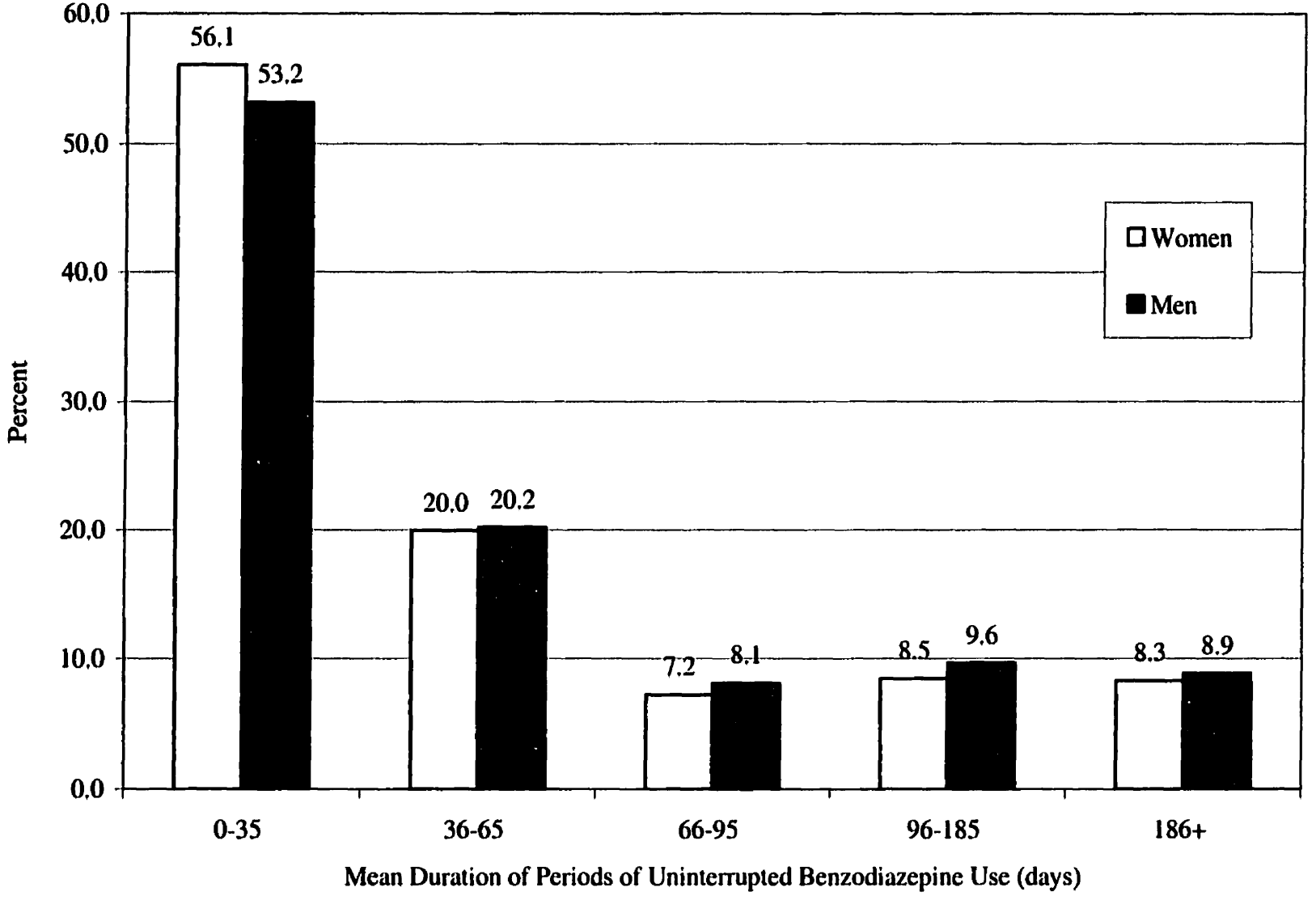


Table 5.2 **Average duration of first period of uninterrupted benzodiazepine exposure for women compared to men by type of first prescription and by year first prescription was filled.**

Elimination Half-Life	Year or Type of Benzodiazepine First Used	No. of Subjects (% women)	Mean Duration of First Period of Uninterrupted Use in Days* (sd)		Difference for women compared to men (p-value)
			Women	Men	
Short	Triazolam	2,282 (51.2)	71.3 (152.5)	89.0 (186.4)	-17.7 (0.01)
Intermediate	Temazepam	4,049 (48.8)	98.8 (213.3)	89.5 (185.7)	-9.3 (0.14)
	Nitrazepam	1,458 (52.3)	82.3 (188.7)	82.4 (174.2)	-0.1 (0.99)
	Alprazolam	3,959 (60.5)	61.0 (130.7)	65.6 (125.1)	-4.6 (0.27)
	Oxazepam	15,600 (55.8)	79.3 (161.6)	78.9 (153.5)	0.48 (0.85)
	Bromazapam	3,877 (61.4)	53.5 (119.6)	50.3 (105.3)	-2.1 (0.57)
	Lorazepam	32,882 (57.6)	66.0 (141.8)	70.5 (141.3)	-4.5 (0.004)
Long	Clonazepam	1,800 (55.6)	72.6 (149.9)	73.4 (150.5)	-11.3 (0.11)
	Clobazam†	28 (35.7)	81.6 (70.6)	128.2 (251.4)	-46.6 (0.57)
	Flurazepam	5,425 (44.2)	68.1 (164.6)	53.8 (117.6)	14.3 (0.0003)
	Chlordiazepoxide	887 (47.3)	54.2 (120.9)	38.5 (75.4)	15.7 (0.02)
	Diazepam	4,908 (57.6)	40.6 (79.6)	42.5 (86.0)	-1.9 (0.41)
	Clorazepate‡	177 (62.1)	36.7 (30.5)	36.0 (29.1)	0.6 (0.88)
More than one type		1,035 (51.2)	120.9 (216.0)	130.6 (225.9)	-9.73 (0.47)
Any Benzodiazepine§	1990	26,637 (58.2)	77.0 (184.1)	78.1 (174.7)	-1.1 (0.62)
	1991	17,826 (55.4)	69.8 (148.8)	76.1 (154.1)	-6.3 (0.006)
	1992	13,527 (55.2)	68.1 (134.6)	72.4 (140.2)	-4.3 (0.07)
	1993	11,422 (53.2)	64.4 (108.3)	65.6 (108.9)	-1.2 (0.53)
Total		78,367 (55.7)	68.7 (149.1)	70.8 (144.7)	-2.1 (0.04)

* If a subject switches or adds another benzodiazepine after the first prescription, this will count as a period of uninterrupted use as long as the prescriptions are filled without any time in between.
† Clobazam has detected use only after 1992.
‡ Clorazepate has detected use only in 1990.
§ Average duration was not calculated for subjects who started benzodiazpine use in the last year of the study period (1994).

Figure 5.3 Average duration of the first five periods of uninterrupted benzodiazepine use for men and women among subjects with more than one period of use (46,282).

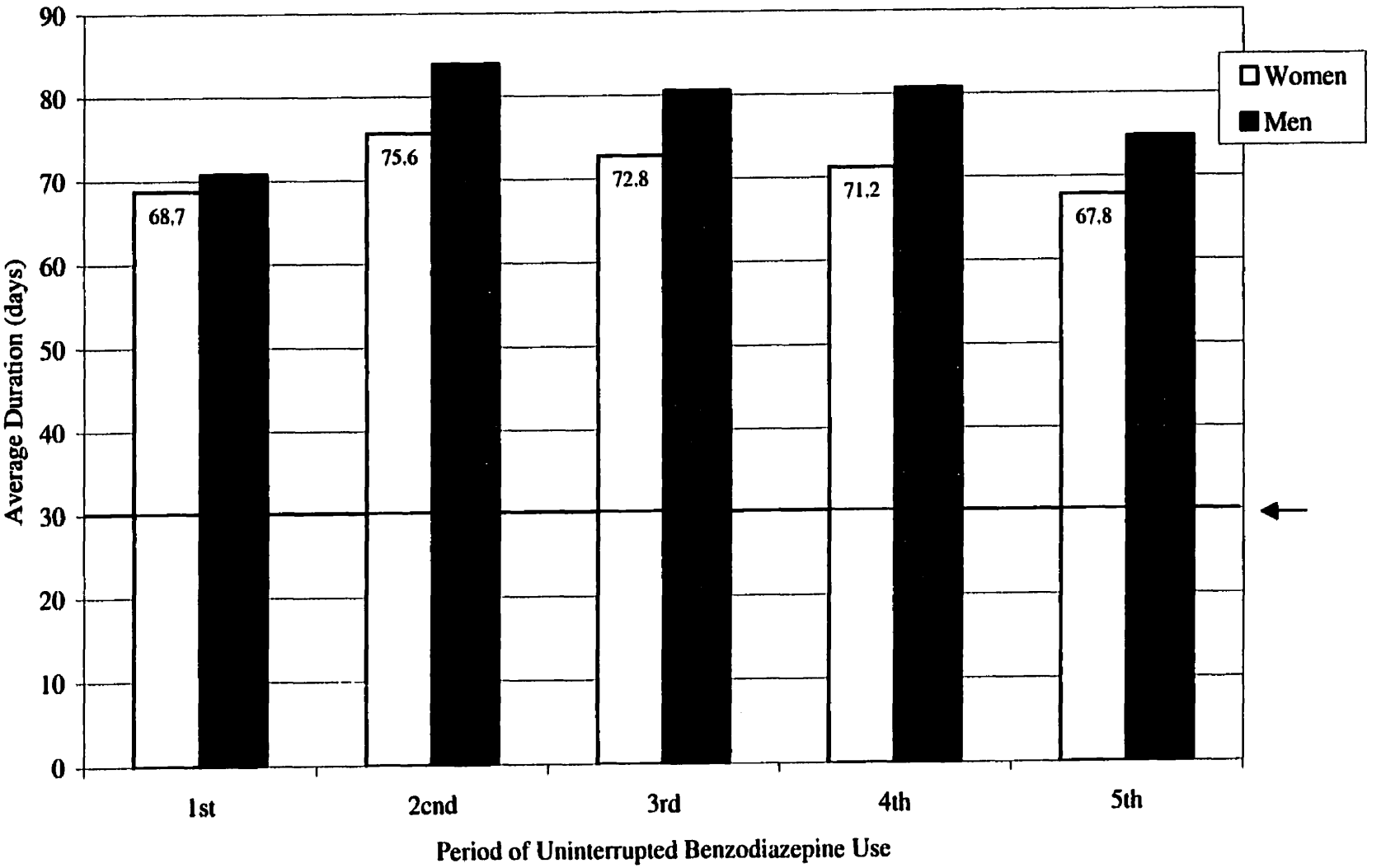
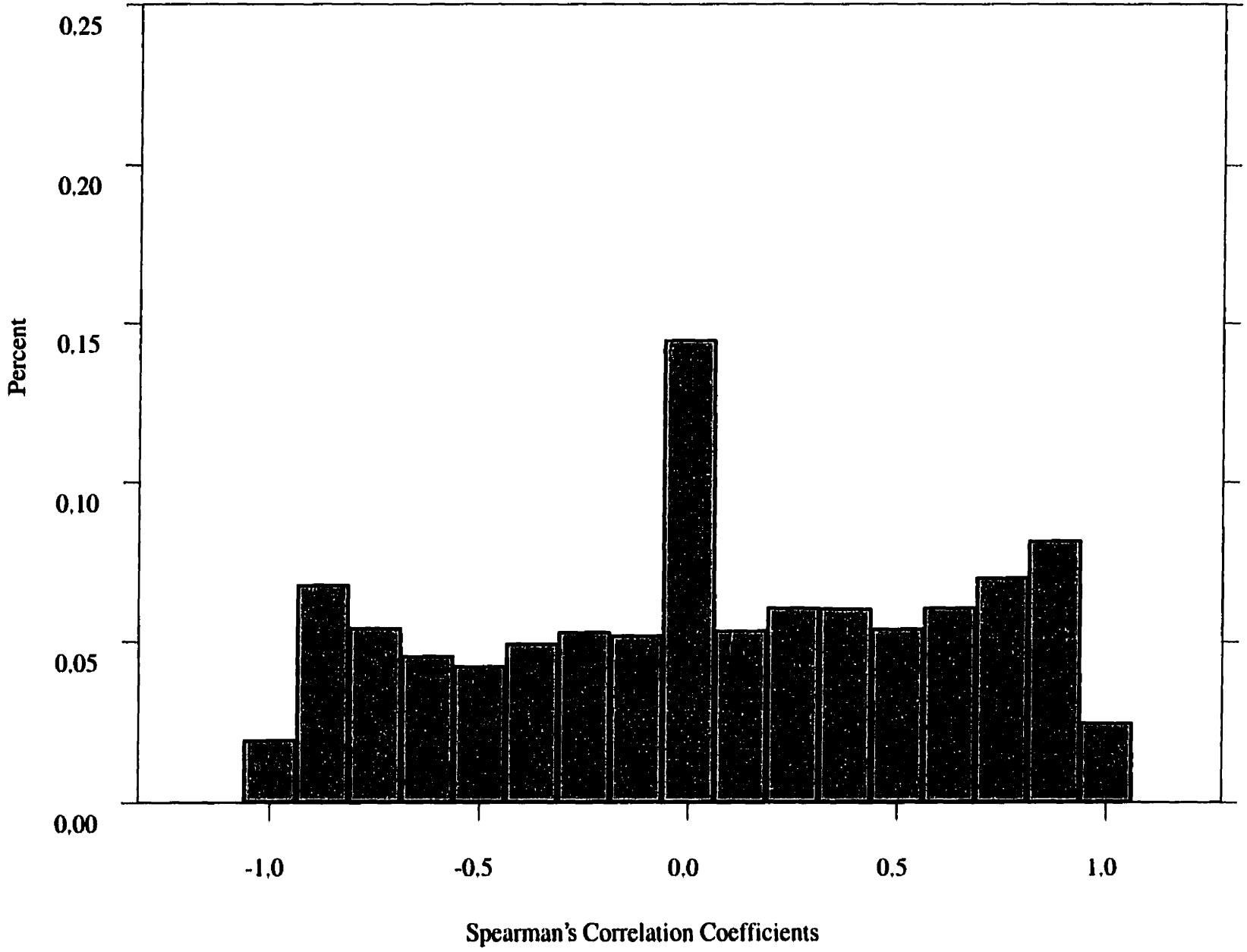


Figure 5.4 **Frequency distribution of Spearman's rank correlation coefficients between duration of subsequent periods of benzodiazepine use and their ranking in time for subjects with 3 or more distinct periods of use (31,800).**



for -1 and +1. The 90th percentile was 0.83, with about 3,800 subjects beyond the cut-off. Subjects above these cutoffs were categorized with having a strong tendency for increasing duration of use with subsequent periods of use.

Table 5.3 presents the results of the forward model selection of the predictors of increased duration of use over time, based on the multiple logistic regression analyses. Age at date of first prescription was very statistically significant ($p<0.0001$), with about 2% increase in risk of increasing duration of benzodiazepine use over time with every year increase in age at the time of first prescription (OR=1.02, 95% CI 1.01-1.03). This represented an increase of 10% for an increase in age of five years at date of first prescriptions (OR=1.10) and 22% for an increase in age of 10 years (OR=1.22). Men were more likely to show a trend toward increasing duration compared to women (OR=1.14, 95% CI 1.05-1.23). Among the different benzodiazepines used with the first prescription only, subjects initially prescribed temazepam had a significant increase in risk (OR=1.30, 95% CI 1.07-1.52) compared to users of lorazepam.

5.3.3 Predictors of Increasing Benzodiazepine Dosage

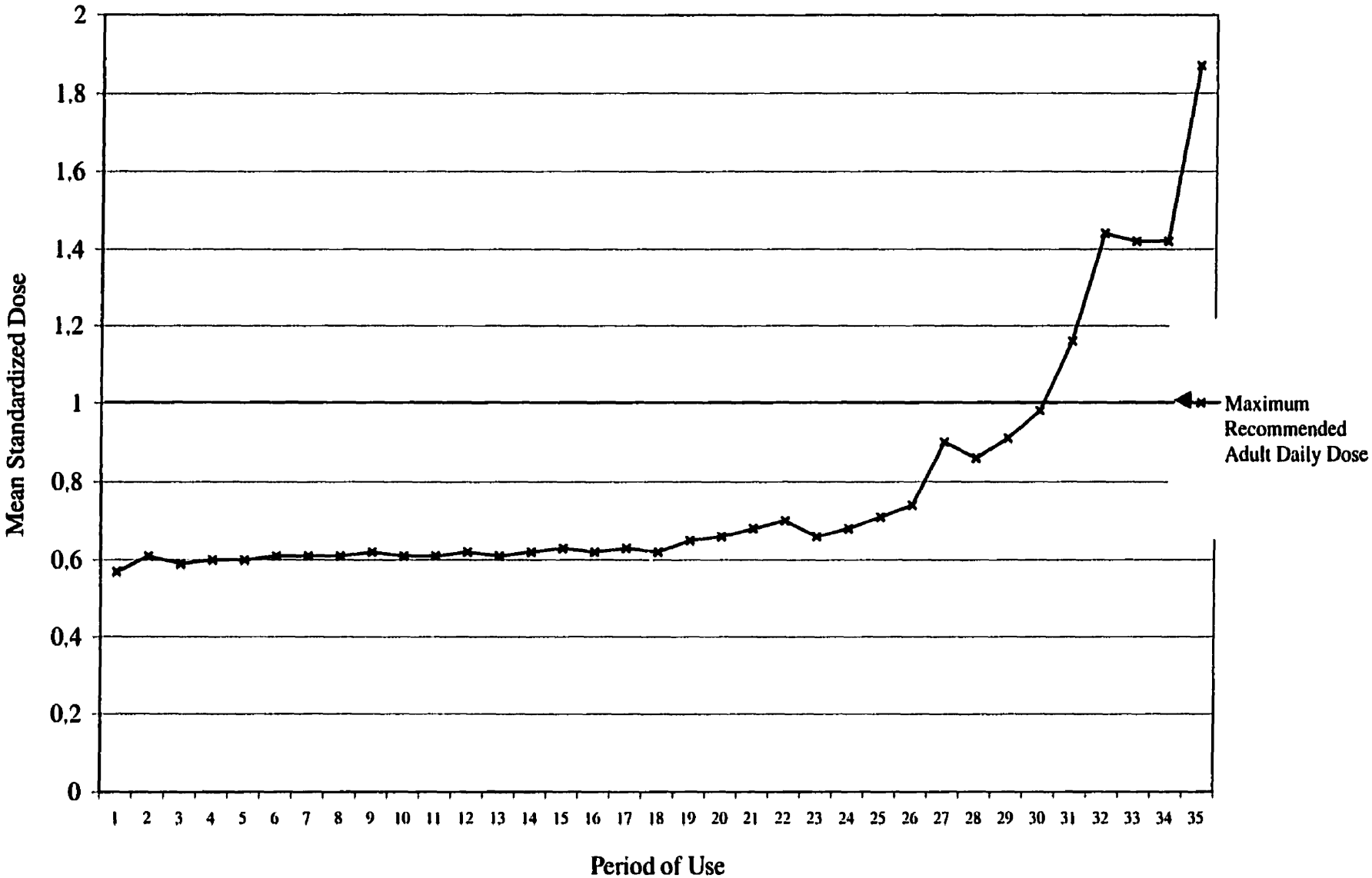
The average standardized dose for all subjects was 0.57 (sd=0.37) corresponding to just over one-half of the recommended maximum daily adult dose, with a median dose of 0.48 (range from 0.01-11.0). Men had a slightly higher average standardized dose (0.61) compared to women (0.54, $p<0.0001$). A value of 1.0 was equal to the WHO recommended maximum adult daily dose, and the average daily dose exceeded this value for 8.6% of the elderly subjects. A similar proportion of men (3.9%) exceeded the maximum daily dose, on average, as women (4.7%, $p=0.45$).

The average number of distinct periods of benzodiazepine use, defined as a period with no interruption in use and no change in dosage, was 3.75 per subject (sd=3.8) with a median value of 2.0 (range of 1 - 35). Figure 5.5 shows how average dose changed with subsequent periods of use. The average dose remained stable for the fist 20 periods and while it increases in the upper tail of the Figure 5.5, this apparent increase is based on few subjects. Accordingly, there was no significant overall trend for average dose to increase or decrease with subsequent periods of use.

Figure 5.6 shows the distribution of the Spearman's rank correlation coefficients between dose and ranking of subsequent periods, among the 35,941 subjects with 3 or more intervals of distinct benzodiazepine use. While the most frequent correlations clustered around zero, the distribution was not as uniform as the distribution of correlations with duration (see Figure 5.4). The cut-off for the 90th percentile was 0.87 and included 3,666 subjects.

The results for the forward model selection of predictors of increased dosage with duration of use over time are shown in the bottom half of Table 5.3. As with duration, age at date of first prescription was again statistically significant ($p<0.0001$), with the same increase in risk of 2% for increasing dosage over time with every year increase in age at time of first prescription (OR=1.02, 95% CI 1.01-1.03). Also similar to duration, men were more likely to show a trend to increasing dosage than women (OR=1.17, 95% CI 1.08-1.25). For the different benzodiazepines used with the first prescription, alprazolam, oxazepam, and clonazepam were all associated with a statistically significant increase in the risk of increasing dosage over time compared to the reference group of lorazepam users. Subjects who started on diazepam were less likely than lorazepam users to increase dosage over time

Figure 5.5 Mean standardized dose for each period of distinct use.



(OR=0.76, 95% CI0.64-0.91). Also, taking medications that affected motor stability in 1989 reduced the probability of increasing dosage by almost 10% (Table 5.3).

5.3.4 Switching or Adding Benzodiazepines

Among incident users, 28.8% switched at least once from the initial type of benzodiazepine to another product and/or added a different benzodiazepine to the current prescription. Of these subjects, 71.5% only switched benzodiazepines and did not add an additional prescription. On average, subjects who never switched or added benzodiazepines were one year older at the time of first benzodiazepine prescription compared to those who did add or switch ($p<0.0001$). The same proportions of men and women switched benzodiazepines.

Among subjects who switched at least once, the average number of switches from one to another benzodiazepine was 1.9 (sd=1.7) with a median of 1 (range 1 - 26). When the number of switches was adjusted for the total observation time since the first script excluding periods of hospitalization, there was an average of 1.0 switches per person-year of observation (sd=1.9) with a median value of 0.5 switches per person-year (range 0.2-73.0). Figure 5.7 shows that the distribution of the number of switches per subject did not differ depending on the benzodiazepine used in the first prescription. However, Figure 5.8 shows that the majority of the first switches, regardless of the initial prescription, were to lorazepam (33.4%). The next most popular drug for the first switch was oxazepam (17.6%). In order to ensure that these high proportions did not simply reflect higher market share of these two products, we also estimated, separately, for each benzodiazepine, what proportion of the first users represented subjects who switched from another benzodiazepine. The proportion of subjects using a given drug for the first time who previously filled a prescription for another

Figure 5.7 Comparison of the distributions of numbers of switches from one benzodiazepine to another among subjects who have switched benzodiazepines at least once, for subjects who started with particular products.

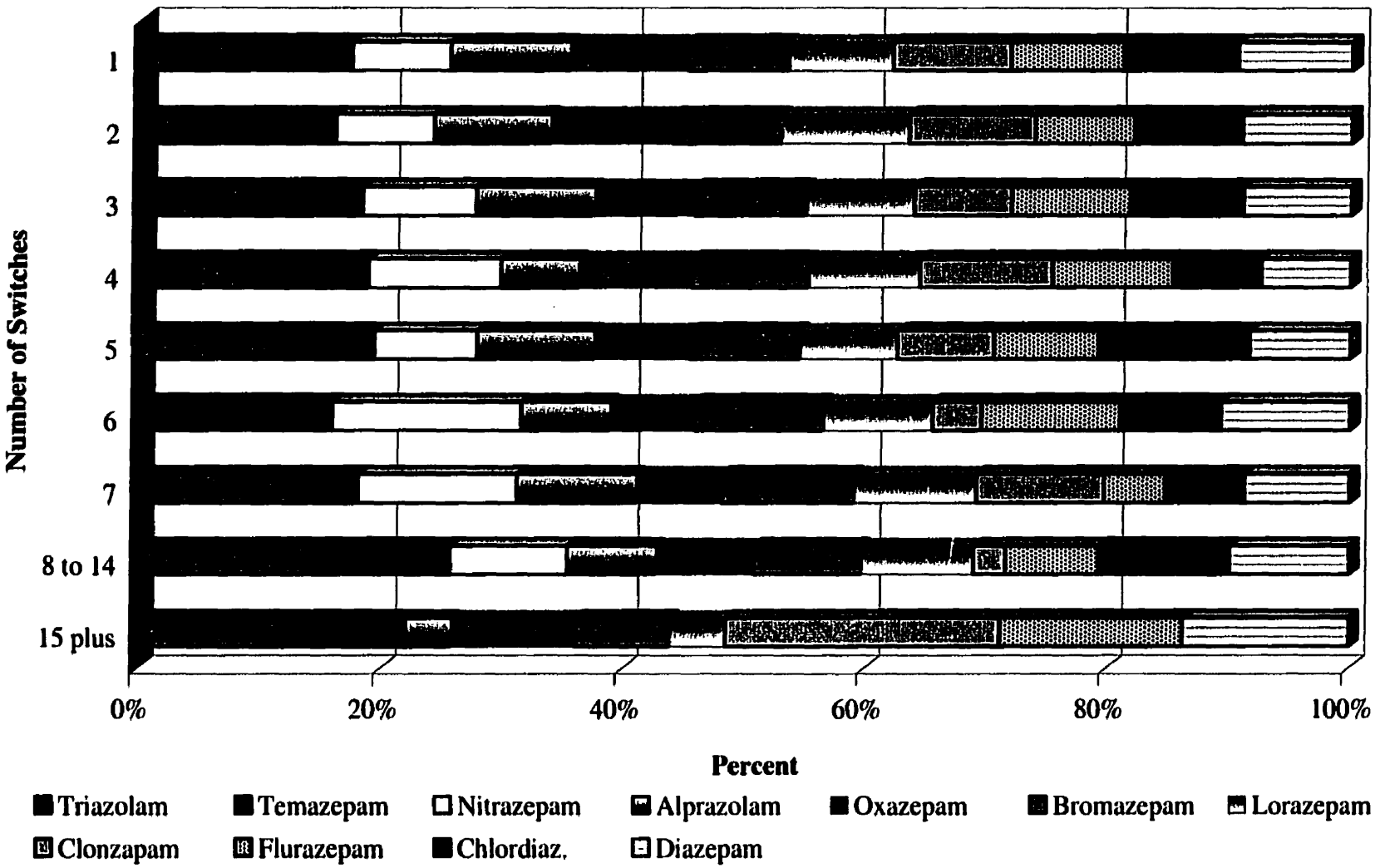
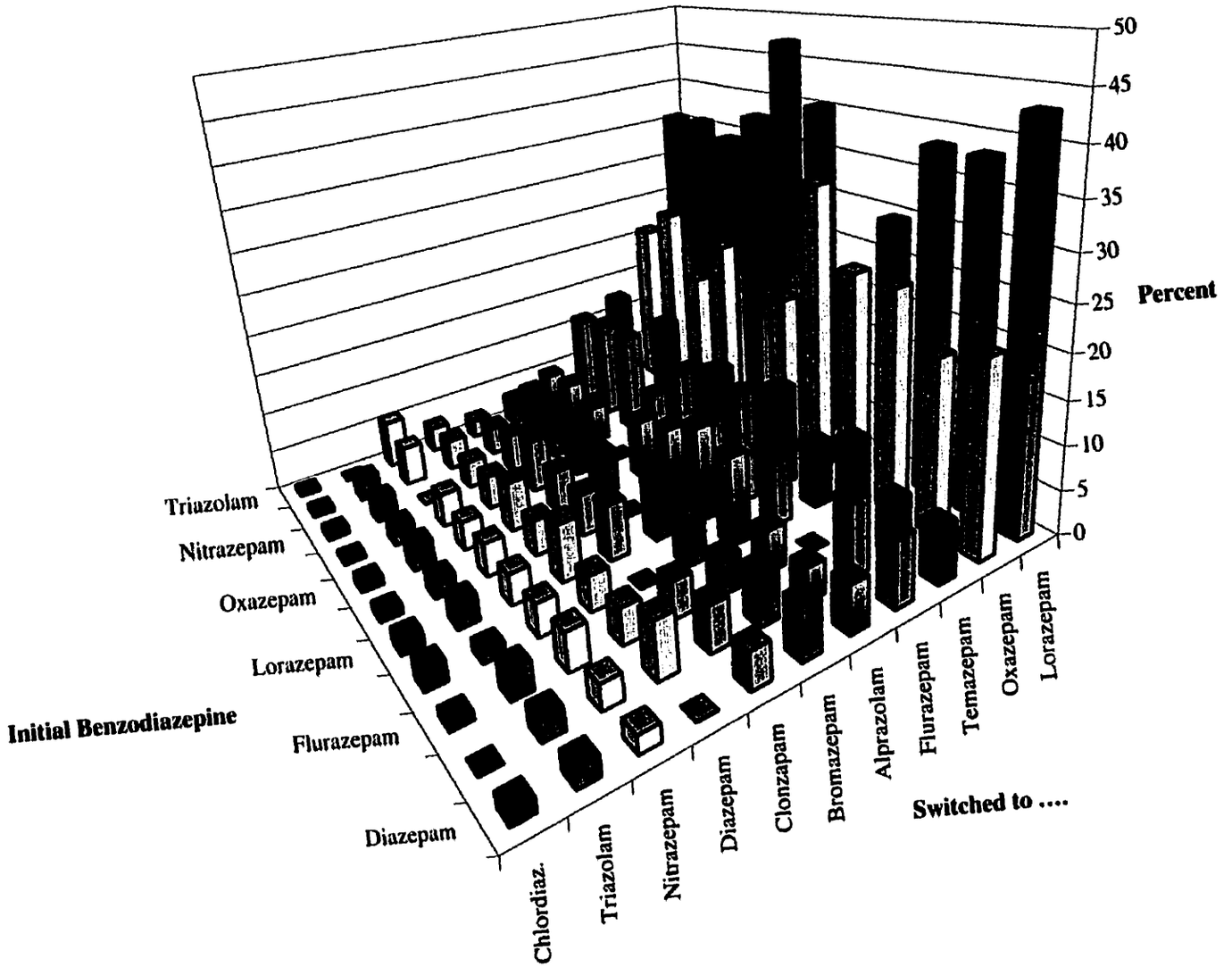


Figure 5.8 Distribution of benzodiazepine chosen for first switch.

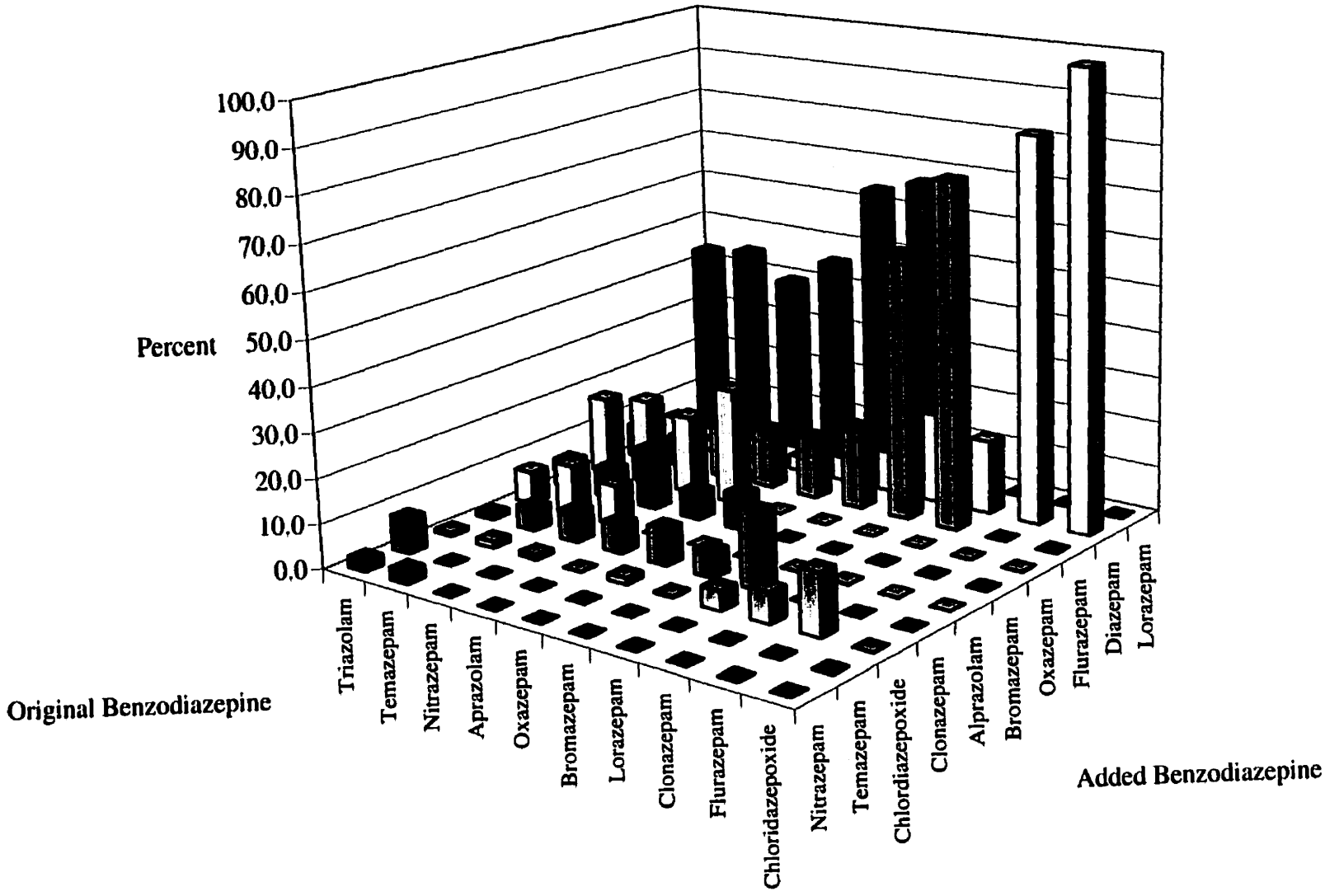


benzodiazepine was the highest for lorazepam (21.6%) and for oxazepam (19.7%). The proportion of switchers among first users of all other benzodiazepines was much lower, ranging from 6.3% for nitrazepam to 15.3% for bromazepam. This indicated clearly that lorazepam and oxazepam were the favorite benzodiazepines for subjects who had switched from another benzodiazepine.

Subjects who added an additional benzodiazepine (n=6,424) did so an average of 1.3 times (sd=0.80) during the study period with a median value of 1 (range1-14). Figure 5.9 shows the distribution of the benzodiazepines that were added for the first time. Again, lorazepam was by far the most frequently added drug (41.6% of first additions) with diazepam (8.5%) and flurazepam (20.2%) being the only other relatively popular drugs. For these subjects, 82.5% added a single benzodiazepine for only one period during the observation. An additional 10.1% had at least two occasions where they added one extra benzodiazepine prescription. The remaining 7.3% added more than one additional benzodiazepine (maximum of 5) on different occasions with a maximum of 14 distinct occasions for using two or more different benzodiazepines.

When relevant data on consecutive or simultaneous use of different benzodiazepines were combined, 4.0% of the subjects had both average duration of uninterrupted benzodiazepine exposure greater than 35 days and an average standardized dose greater than 1.0. Among subjects exceeding 35 days average duration of use, 7.0% had a strong trend for increasing dose over time as indicated by a strong positive correlation compared to 1.5% of short-term (average duration of use less than 35 days) users ($p<0.0001$). This was very similar for strong positive correlations with increasing duration of use (5.5% versus 1.6%,

Figure 5.9 Distribution of the first addition of a benzodiazepine among those who added an extra benzodiazepine prescription at least once (6,425).



p<0.0001). Almost twice as many subjects who exceeded the recommended 35 days of use switched drugs at least once compared to short-term users (17.5% vs 10.0%, p<0.0001).

5.4 DISCUSSION

Overall we found that the majority of the new benzodiazepine users were filling prescriptions that followed the guidelines of providing elderly patients with doses that are half of the recommended adult daily dose,[7-9;16;28;29] with only a small proportion of the subjects exceeding the maximum daily dose. Moreover, with many benzodiazepine prescriptions being given on a *pro re nata* basis, the average daily doses may have been overestimated for elderly patients only filling one prescription (41% of subjects) or if there were long periods between prescriptions.

On the other hand, although the average duration of use for most of the sample was less than 90 days, almost half of the new users exceeded 35 days for duration of uninterrupted use.[9] Our finding that 16.8% of women and 18.5% of men whose average duration of uninterrupted use exceeded 90 days was almost twice that found in a later study of Nova Scotia seniors (9.6% in 1995/96 fiscal year)[12] but was slightly lower than the 19.8% found by Egan et al (2000) among Quebec participants of the Canadian Study of Health and Aging.[30] When the average duration for the first period of uninterrupted use was examined by the calendar year in which the first prescription was filled, we found a mean decrease of almost two weeks between 1990 and 1993. Some of this decrease may have been due to the fact that our study used a closed cohort of subjects, however this would not entirely explain the findings. The decrease may have reflected a heightened awareness of the problems associated with long-term use in the elderly. Despite this decrease, the average duration for the first period of use still exceeded 60 days in 1993.

suggested the presence of dependence with escalating dose and raised the question about possible predictors of such patterns of use. Our finding that older age at the time of the first benzodiazepine prescription was a significant predictor for both increasing duration and dosage confirmed that older subjects were more likely to become dependent on benzodiazepines. Since these analyses were restricted to subjects with extensive benzodiazepine exposure of more than three periods of distinct use or increases in dose, it was unlikely that actual benzodiazepine use in those subjects was overestimated based on the information on prescriptions available in our database. A patient who was a chronic user, i.e. filled subsequent prescriptions, was unlikely to be using the benzodiazepine at a reduced dosage or not at all.

Benzodiazepines appeared to be misused in a small proportion of subjects. These patients not only exceeded both the recommended duration of use and the maximum recommended adult daily doses, but were also more likely to be using at least two benzodiazepines at the same time. Although we estimated that almost 10% of elderly patients filled at least two benzodiazepine prescriptions at the same time, most of these subjects had only one period of overlap between their prescriptions. Given that almost a third of the study cohort switched from one type of benzodiazepine to another at least once, it was likely that elderly patients with apparent overlap between prescriptions for two different benzodiazepines actually switched to another medication due to uncomfortable side-effects or a lack of therapeutic effect with the original medication. The popularity of lorazepam in our cohort and the number of subjects who switched to this medication supports this conjecture and suggested that these benzodiazepines probably had relatively few unpleasant or unwanted side effects.[11] The phenomenon of drug discontinuation and

medication switching in the elderly is documented with other types of medication.[11;33-35] However, using database records, we had no way of assessing whether a patient stopped taking the original prescription before starting a second prescription and therefore actually switched medications instead of adding an additional prescription. Despite this limitation, the identification of subjects who had periods of use when more than three benzodiazepine prescriptions were filled simultaneously, with repetition of this pattern, provided strong evidence for misuse of benzodiazepines in a small number of elderly (0.5%).

5.4.1 Conclusion

In our study, we looked at the patterns of benzodiazepine use in an elderly cohort over time. The methods we developed to assess different aspects of these patterns could be useful for studies of other types of medication. We found that the majority of benzodiazepine use in the elderly patients followed clinical guidelines, however there was definite evidence for tolerance and dependence with dose escalation over time. A small proportion of elderly patients appeared to misuse benzodiazepines, and periods of use greater than 60 days were still quite common. The next step of our research will be to account for the relevant aspects of longitudinal patterns of benzodiazepine use when evaluating the risk of injury associated with these medications.

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6.0 PREFACE TO MANUSCRIPT 3

This is the third article in a series of four that addressed specific components of the overall thesis objective of assessing the risk of injuries from falls associated with patterns of benzodiazepine use in community-dwelling elderly people. This article dealt with some of the methodological issues that required in-depth investigation based on the findings from the first two articles in this series. The research contained in this manuscript is a logical continuation of the research conducted in the first two manuscripts and a necessary step in order to proceed with the final analyses contained in the fourth manuscript.

The first manuscript concluded that predictors of incident use in the elderly vary substantially across different products resulting in different patterns of potential confounding. This reinforced the need to evaluate risks associated with benzodiazepines by individual products. Moreover, the finding that characteristics of incident benzodiazepine users differ systematically from those of non-users, suggested that it is important to reduce the risk of residual confounding which could occur. Specifically, in the analyses in which the periods of non-current benzodiazepine exposure is represented by a time-dependent covariate, it was important to develop methods to separate periods of non-use among incident users from the "permanent" non-exposure among non-users. The second manuscript showed that the patterns of benzodiazepine use are very complex and, again, varied across individual products. The conclusion from these findings was that in order to explore the mechanisms by which benzodiazepine use may affect risks of injuries from falls, the effects of current dose, duration of past exposure or cumulative dose have to be disentangled. However, the methods necessary for evaluating various time-varying aspects of exposure for eleven

different benzodiazepines while ensuring validity and comparability of results have not previously been explored.

The specific objective of this manuscript was to address several of the above methodological issues related to assessment of complex benzodiazepine exposure. The findings of this article were the basis for the selection of the methods used in Manuscript 4 to analyze the risk of injuries from falls associated with benzodiazepine exposure in elderly patients.

MANUSCRIPT 3: Methodological Issues in Modeling the Impact of Benzodiazepine Use on Risk of Injuries

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Abstract

Background Benzodiazepine use in the elderly is complex and varies across individual products. The methods necessary for evaluating various aspects of exposure to several different benzodiazepines while ensuring validity and comparability of results need to be evaluated.

Objectives To address methodological issues related to assessment of the role of different aspects of time-varying benzodiazepine exposure. Specifically, (i) to assess the impact of changing the start of the observation period and of the inclusion of non-users in one analysis; (ii)to analyze the time-dependence of the effect of benzodiazepine exposure to determine if the risks change with time since first use; and (iii) develop new methods to model the impact of cumulative dose and duration for exposure with differential weighting of past exposures.

Methods The four sub-cohorts of elderly incident users of four particular benzodiazepines, with a random selection of non-users matched on age and sex, were observed for a five year period or until the time of a fall-related injury. Cox proportional hazards (PH) regression was used to model the risk of injury with two different starting dates, including and excluding non-users. The time-dependence of exposure was analyzed with the piecewise time-stratified Cox PH model and a flexible generalization of this model. Five alternate versions of Cox PH model, representing different aspects of benzodiazepine exposure, including duration or cumulative dose, were estimated using two different functions to weight past exposure, and negative log likelihoods were compared.

Results Using the start of the study period instead of the date of first prescription lead to a significant over-inflation of the risk of injuries associated with benzodiazepine exposure. The risk was overestimated, due to residual confounding, when non-users were included

unless a separate covariate was introduced to separate ever-users from non-users. The hazards associated with the binary classification of exposure were non- proportional during follow-up(p=0.0004). The best fitting models for estimating the impact of benzodiazepine exposure on risk of injuries varied between products, but always included a measure of weighted cumulative duration or cumulative dose.

Conclusions Analyses that were restricted to incident users were able to focus on in-depth evaluation of the impact of different aspects of exposure. Using alternative representations of cumulative dose and duration allowed for the selection of the model that best fits the data and provided insight into the mechanisms behind the risk associated with individual benzodiazepine exposure among users of these medications.

6.0 METHODOLOGICAL ISSUES IN MODELING THE IMPACT OF BENZODIAZEPINE USE ON RISK OF INJURIES (MANUSCRIPT 3)

6.1 INTRODUCTION

Many studies report an increased risk of injuries from falls associated with benzodiazepine use, however the findings for the strength and magnitude of the association are not consistent.[1-6] A review of these studies reveals that classification of exposure has become more sophisticated with time, and this may explain some of the discrepancies (Chapter 2.0). Earlier studies simply look at any benzodiazepine use while later studies examine risk associated with use of benzodiazepines with similar elimination half-lives or clinical indications.[1;2;6-9] The most recent studies attempt to look at individual products, and suggest that the impact of individual benzodiazepines may be quite different.[3-5] Findings from Tamblyn et al (1998), in one of the few studies of individual benzodiazepine use that adjusted for current dose, further suggest that the apparent differences in impact may simply reflect the typical doses at which the products are prescribed.[4]

Our previous research showed that patterns of benzodiazepine use in the elderly were very complex and varied across individual products (Chapter 5.0). In order to explore the mechanisms by which benzodiazepine use may affect risks of injuries from falls, the effects of current dose, duration of past exposure or cumulative dose may have to be disentangled. When using cumulative dose, how to account for variation over time in the daily dose must be determined and the clinically relevant window of past exposure must be decided. Moreover, it is unclear if the relative risks associated with current exposure change with duration of use. In order to accurately assess the risk of injury associated with

benzodiazepine use, this complexity must be taken into account. It may be that these different aspects of patterns of use are more relevant for establishing the reasons for the increased risk of injury than the simple fact of using a benzodiazepine.

In addition, previous research shows that risks associated with individual benzodiazepines may be quite different,[2-5;9] which suggests that the various aspects of patterns of use should also be assessed separately for each benzodiazepine. This necessity is further reinforced by our previous findings that predictors of incident use vary substantially across different products (Chapter 4.0) resulting in different patterns of potential confounding.

Yet, it is not completely clear how to evaluate various aspects of exposure to eleven different benzodiazepines while ensuring validity and comparability of results. Simultaneous modeling of several aspects of exposure creates modeling challenges even in the case of one type of exposure,[10] and simultaneous modeling of many aspects of exposure for each of the eleven drugs would be impossible, especially given the need to represent many of these aspects by time-dependent covariates.

Furthermore, it is unclear how to best assess the impact of an individual benzodiazepine in a prospective cohort study. Although it seems natural to limit such analysis to actual users of a particular benzodiazepine, a difficulty is that individual subjects become "users" only some time after the beginning of follow-up, so that on January 1, 1990 we do not know who will later become a "user." While the obvious solution may be to "look back in the data" from the end of the study on December 31, 1994 to determine a person's status, using retrospective information on exposure, outcome, or both exposure and outcome has been demonstrated to induce bias in Cox regression analysis of time-to-event.[11]

A related issue concerns the question of whether non-users should be included in the analysis of the impact of a particular product. On one hand, many exposure-related variables, such as cumulative or current dose, can be meaningfully defined only for actual users. Moreover, inclusion of non-users makes it difficult to separate the effect of a time-dependent binary variable (on/off), indicating the relative risks associated with current use, from possible systematic differences between non-users and users that may persist even when the latter are not exposed. On the other hand, an important advantage of including non-users in the separate analyses focusing on individual benzodiazepines is that this group would then provide a common reference for assessing relative risks associated with different products. In the absence of such a common reference group, each of these separate analyses will assess only the risks associated with periods of use versus periods of non-use among users of a particular product, raising concerns about comparability of the estimates.

In this article, we address several of the above methodological issues related to a comprehensive assessment of the impact of various aspects of patterns for use of individual benzodiazepines. Specifically, we focus on the following issues: (i) assessing the impact of changing the start of the observation period and the inclusion of non-users; (ii)analysis of the time-dependence of the effect of benzodiazepine exposure in order to determine if the risks change with time since first use; and (iii) estimating cumulative dose and duration for benzodiazepine use and assessing the sensitivity of these analyses with respect to differential weighting of past exposures.

6.2 GENERAL METHODS

Data for the analyses were selected from a cohort of Quebec elderly who did not fill a benzodiazepine prescription in the baseline year, 1989 (n=252,811). Subjects who went

generated for each subject with the date at which the first distinct injury occurred. Since both hospitalization databases and medical billing data were used, to obtain this information, some of the injuries may have occurred after hospitalization (i.e. falls from hospital beds). In order to exclude these events and to take into account the imprecision of administrative dates, only injuries recorded in the first five days of hospitalization were considered as an outcome for our study and observation for these subjects was stopped at the time of the event. If there was an event, the subject was not recorded as being hospitalized for these five days. Due to the absence of data on benzodiazepine exposure during hospitalization, a subject with an event that occurred more than five days after hospital admission but before hospital discharge was permanently censored at that time as lost to follow-up, i.e. these events were not used in the analyses.

For this study, the date of the first injury in the study period was determined to be the end of the observation for that subject. Subjects who did not have any injury during the study period were censored at the end of the five year follow-up (December 31, 1994)or if the subject was lost to follow-up caused by placement in a nursing home, a long term care facility or by death. For analyses that were restricted to users of specific benzodiazepine products, subjects were censored at the time of a switch to a different type of benzodiazepine or the addition of a new one. Furthermore, since no prescription information was available during hospitalization, temporary censoring was applied during each distinct hospital stay longer than five days. These periods of hospitalization were subtracted from the total observation time for all subjects.

Most analyses in this article relied on time-to-event methods, and specifically on conventional Cox regression model[13] or its flexible generalization.[14] In all models, the

variables related to benzodiazepine use were adjusted for a set of *a priori* selected baseline covariates. Measured in 1989, there characteristics included patient demographics, health care utilization, history of injuries related to falls, other non-benzodiazepine medication use, and baseline illness and impairments (see Chapter 4.0 for details). Methods specific to each analysis are described in Sections 6.3, 6.4 and 6.5. Statistical analyses were conducted using SAS Systems 8.0 for Windows[15] and S-Plus 4.[16] Graphs and figures were constructed using Microsoft Excel.[17]

6.3 ASSESSING THE IMPACT OF CHANGING TIME ZERO AND INCLUDING NON-USERS OF BENZODIAZEPINES

The selection of the time for starting observation for a cohort study (time zero) may introduce bias in the estimate of risk especially if there is an "immortal-time" included in the cohort.[18] "Immortal time" refers to periods in the follow-up where subjects cannot experience the event of interest. This is not because the cohort has become physically immune to the outcome of interest, in this case injuries from falls, but because the selection criteria for entry into the study cohort excludes subjects who have experienced an event before being exposed.

Assume, for example, that we were interested in comparing the risk of injuries in incident benzodiazepine users, thus restricting the analysis to users. Exposure would be assessed by periods of use and non-use among these subjects and subjects who experienced an event before filling their first benzodiazepine prescription would be excluded from the cohort. Thus, subjects who were retained in the cohort would be artificially "protected" until filling their first benzodiazepine prescription. This would under-estimate the incidence rate and other indices of absolute risk.[18] The impact of such a restriction on *relative* risk estimates is less clear and in this section we will attempt to explore this issue.

6.3.1 Methods

The four different cohorts corresponding to the users of a particular benzodiazepine were used for these analyses. All incident users of the specific benzodiazepine were included in the cohort and subjects were censored at the day they switched to, or added, a different type of benzodiazepine. Non-users were included in a separate cohort. Each of the four cohorts of users were analyzed separately with or without non-users.

Two different methods were used to establish time-zero (T_0). The first was to set T_0 to the start of the follow-up period, January 1, 1990. The second method was to set T_0 to the date of the first benzodiazepine prescription for the incident users. When the T_0 was adjusted based on the first benzodiazepine prescription, randomly selected non-users were individually matched to the incident users on age and sex. Then, the non-user was given the same T_0 as the matched benzodiazepine user. This process was repeated for the four types of incident benzodiazepine users and randomization of non-users was carried out separately for each sub-cohort of users, with a new seed number each time.

Periods of benzodiazepine use were represented by a binary time-dependent covariate, later referred to as "on/off" variable, with on/off = 1 for the periods the subject where the subject filled a benzodiazepine prescription, and 0 in the remaining time periods. In addition to the time-dependent benzodiazepine on/off variable, a binary covariate (later referred to as "group") was constructed to indicate if a subject was a non-user (group=0) or a benzodiazepine user (group=1). Cox proportional hazards regression[13] was used to model the risk of injury. Three different models were constructed for each of the four different benzodiazepines. A different T_0 was provided for selected models for a total of twenty models. The first model evaluated the risk of injury based on periods of use and non-

use among incident benzodiazepine users only. The second model was similar, except that non-benzodiazepine users were included in the analysis. The only difference between the second and third model was that the latter additionally included the variable indicating whether a subject was an incident user or non-user (group).

The main focus of the comparison between the three models was on hazard ratios (HR) for the on/off variable, i.e. on the estimate of the impact of current use of a given benzodiazepine. The HR for the group variable was considered a measure of residual confounding. Our reasoning was that this reflected the additional risk among users, relative to non-users, that could not be explained by either the current exposure to the benzodiazepine (on/off) or other covariates in the model.

6.3.2 Results and Discussion

The hazard ratios with p-values and 95% confidence intervals (CI) for the different models are presented in Table 6.1. Whether non-users were included (Model II) or excluded (Model III), starting the period of observation at January 1, 1990 almost doubled the hazard ratios for benzodiazepine exposure across all drugs compared to the models that use the date of the first prescription as T_0. Because events that occurred among incident users before the first prescription were excluded, and given the fact that most benzodiazepine prescriptions were filled for at least thirty days, almost all the events that occurred early in the observation period would have been among subjects exposed to benzodiazepines. This artifact would have led to the inflation of the relative risk of injury for benzodiazepine exposure when T_0 was set to January 1, 1990 (Models I and II). These biases were minimized by shifting the T_0 so that observation of each subject only began at the time when the first benzodiazepine

Table 6.1 Comparison of three models of benzodiazepine use using two different methods for starting the observation period (T_0).*

Model	Variable†	No. of Events	T_0	Hazard Ratio (p-value)	95% CI
I. Only Incident Temazepam Users	Temazepam Exposure	255	Jan. 1, 1990	2.67 (<.0001)	2.03 - 3.50
		255	First Script	1.29 (0.08)	0.97 - 1.71
II. Incident Temazepam Users and Non-Users	Temazepam Exposure	475	Jan. 1, 1990	3.02 (<.0001)	2.36 - 3.84
		475	First Script	1.71 (<.0001)	1.33 - 2.20
III. Incident Temazepam Users and Non-Users	Temazepam Exposure	475	First Script	1.23 (0.14)	0.93 - 1.62
	Type of User (group)			1.71 (<.0001)	1.40 - 2.10
I. Only Incident Nitrazepam Users	Nitrazepam Exposure	116	Jan. 1, 1990	1.71 (0.01)	1.11 - 2.64
		116	First Script	1.10 (0.66)	0.71 - 1.72
II. Incident Nitrazepam Users and Non-Users	Nitrazepam Exposure	205	Jan. 1, 1990	2.27 (<.0001)	1.52 - 3.38
		205	First Script	1.43 (0.08)	0.95 - 2.16
III. Incident Nitrazepam Users and Non-Users	Nitrazepam Exposure	205	First Script	1.00 (0.99)	0.65 - 1.55
	Type of User (group)			1.91 (<.0001)	1.41 - 2.58
I. Only Incident Lorazepam Users	Lorazepam Exposure	2,345	Jan. 1, 1990	1.83 (<.0001)	1.67 - 2.01
		2,345	First Script	1.02(0.66)	0.92 - 1.13
II. Incident Lorazepam Users and Non-Users	Lorazepam Exposure	4,303	Jan. 1, 1990	2.11(<.0001)	1.93 - 2.30
		4,299	First Script	1.31(<.0001)	1.20 - 1.43
III. Incident Lorazepam Users and Non-Users	Lorazepam Exposure	4,299	First Script	1.03(0.52)	0.94 - 1.14
	Type of User (group)			1.50(<.0001)	1.41 - 1.61
I. Only Incident Flurazepam Users	Flurazepam Exposure	391	Jan. 1, 1990	3.08 (<.0001)	2.43 - 3.89
		391	First Script	1.60 (0.0006)	1.22 - 2.08
II. Incident Flurazepam Users and Non-Users	Flurazepam Exposure	726	Jan. 1, 1990	3.63 (<.0001)	2.91 - 4.52
		725	First Script	2.18 (<.0001)	1.72 - 2.76
III. Incident Flurazepam Users and Non-Users	Flurazepam Exposure	725	First Script	1.65 (0.0001)	1.28 - 2.12
	Type of User (group)			1.64 (<.0001)	1.40 - 1.92

* All models are adjusted for baseline characteristics including age, sex, use of non-benzodiazepine medications, disabilities, impairments, Charlson Comorbidity Index, number of prescribing physicians, number of short hospital stays and region of residence.

† Benzodiazepine exposure is a time-dependent "on/off" variable.

prescription was filled eliminating the pre-exposure periods when the subsequent users appeared to be "protected."

Another methodologically important finding of the analyses summarized in Table 6.1 concerned the impact of including non-users on the estimated effect of the on/off time-dependent variable representing current exposure. Even when using the appropriate T_0, corresponding to the time of the first prescription, the estimates from Model II that included non-users were systematically higher, for all four products, than those from Model I which relied on users only. Moreover, in the case of lorazepam this difference induced an important change in the final conclusion, as the effect of exposure was practically nil (HR=1.02; 95% CI, 0.92-1.13; p=0.66) in Model I but became statistically very significant in (HR=1.31; 95% CI, 1.20-1.43; p<0.0001) in Model II. Results of our Model II provided an explanation of these discrepancies.

By adjusting the effect of the on/off variable for another variable "group" discriminating between subjects who had used benzodiazepines at least once from those who never used a benzodiazepine during the study period, the two effects were separated, thus ensuring that the effect of current exposure was estimated only among actual users (group=1). Accordingly, Model II demonstrated that being currently on or off lorazepam did not affect the risks among users (HR=1.03; 95% CI, 0.94-1.14; p=0.52), which was consistent with the results of Model I, based on users only (with T_0 set to the date of the first prescription).

In contrast, Model III indicated clearly that there was a systematic and very significant increase of risk among subjects who were ever exposed to lorazepam before regardless of whether they were on or off the drug at the time (HR=1.50; 95% CI, 1.41-1.61;

$p<0.0001$). The most likely explanation for this systematic effect of the "group" variable was related to residual confounding. It appeared that subjects ever prescribed lorazepam before have higher risks of injuries from falls for reasons not captured by their exposure status or by the baseline covariates taken into account in our analyses. Similar results were obtained for the three other benzodiazepines, since in each case Model III revealed a significant increase in risks for "group" variable (Table 6.1) In contrast, Model II that included only the on/off variable, was unable to separate the effects of potential residual confounding between ever users and non-users of benzodiazepines from the actual impact of being currently exposed. The reason was that in Model II, both a user who had not filled a benzodiazepine prescription and a non-user were assigned the same value (0) for the only benzodiazepine-related variable (on/off). As a consequence, the estimated effect of the on/off variable in Model II represented a compound of the two separate effects leading to a substantial inflation of the relative risks and possible incorrect conclusions about the statistical significance of the impact of current exposure for certain benzodiazepines, such as lorazepam. For example, the estimated hazard ratio from Model II for current exposure to flurazepam (2.18) was close to the product of the two relevant estimates from Model III for current use (1.65) and type of user (1.64).

Results from this section of the study suggest that if only users are included in an analysis evaluating risk of injury, it is essential that the period of observation starts at the date of the first prescription in order to avoid overestimating the impact of benzodiazepine exposure. If this time zero is used, estimates of the impact of current exposure to specific benzodiazepines can be explored in a cohort restricted to users of that specific product. In addition, if non-users are included in the analyses, the model should include two separate

variables, as in our Model III, in order to separate the actual effects of current use of a given product from the systematic differences in risk profile between subjects ever prescribed a specific benzodiazepine and non-users. Otherwise, residual confounding between users and non-users may result in a considerable over-estimation of the impact of current exposure to benzodiazepines.

6.4 ANALYSIS OF TIME-DEPENDENCE OF THE EFFECT OF BENZODIAZEPINE EXPOSURE

Many previous studies of benzodiazepine use have modeled the risk of injuries using multiple logistic regression.[2;3;5;6;9] However, the logistic regression model ignores the aspect of time to event. For example, an event that occurs two days after the start of the observation period will be considered equivalent to an event that occurs three years after the start of the follow-up. Moreover, variation in duration of follow-up is not accounted for in the logistic regression model.[19] In addition, the exposure in logistic regression analyses is typically represented by a fixed-in-time variable. Since logistic regression does not allow for time-dependent changes in benzodiazepine exposure, a subject who has filled only one benzodiazepine prescription for a five day period will be considered the same as a subject that continually filled benzodiazepine prescriptions for most of the follow-up period. Given that an exposure such as benzodiazepine prescriptions is characterized by periods of use and non-use (Chapter 5.0), we would expect that this over-simplification would lead to missclassification and possible bias in the estimates of association.

To overcome this limitation, survival analytical methods, such as the Cox proportional hazard model, can be used.[3] One of the advantages of utilizing this method in modeling benzodiazepine exposure is that it takes into account the variation in follow-up

duration and the timing of the events (injuries from falls).[3] Nonetheless, the Cox model imposes *a priori* the proportional hazards assumption which dictates that the relative risk associated with a given independent variable remains constant over the entire follow-up duration.[13] If this is a correct assumption, it facilitates the interpretation of the results since the impact of the risk factor can be summarized by a single parameter, the adjusted hazard ratio. On the other hand, in many studies there may not be sufficient substantive justification for imposing the proportional hazards assumption.[14] This is relevant for benzodiazepine use since there is some evidence that elderly people gradually develop a tolerance to the psychomotor effects of benzodiazepines so the impact on risks may change with duration of exposure.[20-22] It is also possible that the risks will increase with longer duration of exposure due to accumulation caused by incomplete or impaired elimination of the benzodiazepine.[21;23;24]

If the proportional hazards assumption is incorrect, then neither the relative risk estimates yielded by the proportional hazards model nor the inference about these estimates are valid.[14;25-27] For example, if the predictive ability of the binary measure of benzodiazepine exposure decreases with increasing duration of follow-up, then the results of the conventional proportional hazard analyses may underestimate the initial impact on risk of injuries from falls because the proportional hazards estimate will represent the average-over-time of the time-dependent effects.[14;28] Moreover, in such a case, the comparison of relative risks associated with different benzodiazepines may be confounded by differences in the mean duration of their use (Chapter 5.0). Products with longer use may show lower risk even if the actual risks, at a fixed duration, are identical for the two products. In order to obtain unbiased estimates of the evolution of relative risks over time, flexible modeling of time-

dependent hazard ratio would be necessary.[14:26:29] Moreover, the estimation of a function describing the pattern of such changes over time may provide insights into what measures of benzodiazepine exposure are more relevant and whether further investigation into time-dependence of the benzodiazepines effects is warranted.[14]

6.4.1 Methods

For this part of the study, we selected all incident flurazepam users. For some of the analyses involving a novel software that restricts the maximum sample size, a smaller, random sample of 1,200 flurazepam users and 1,200 subjects who never filled a benzodiazepine prescription was used. To illustrate the relevant methodological issues, the benzodiazepine found in previous analyses to have the strongest association with injuries in the elderly, flurazepam, was chosen.[3] The non-benzodiazepine users were randomly selected and then matched with flurazepam users based on age and sex. The non-users had to be alive and injury-free at the time of initial flurazepam prescription for the benzodiazepine users. Time zero was set at the date of the initial flurazepam prescription for each flurazepam user and their matched control was given the same time zero. All analyses were adjusted for baseline (1989) characteristics of the subjects. The outcome of interest was a detection of an injury due to falls and the exposure was a binary group variable.

The impact of flurazepam use on risk of injuries from falls was analyzed using the Cox proportional hazards model[13] and a new flexible generalization of this model.[14] Accordingly, the hazard ratio was used as a measure of the strength of association between flurazepam use and the risk of injuries from falls. Whereas the hazard ratio was restricted to remain constant over the entire follow-up period for the proportional hazards model, the flexible model allowed the hazard ratio for flurazepam use to change over time, according

to an arbitrary function, the shape of which is estimated from the data using a 5 degrees of freedom (df) regression spline, i.e. a piecewise quadratic polynomial with three pieces. The 4-df likelihood ratio test, comparing the fit of the conventional 1-df proportional hazards model and the flexible 5-df regression spline model, was used to verify the null hypothesis that the hazard ratio between users and non-users did not change with increasing time since beginning of use. All hypothesis were tested at the 0.05 significance level.

Using simulations, Abrahamowicz et al (1996) show that this model-based test is powerful against a wide range of alternatives and offers better power than some popular conventional tests.[14] This is particularly relevant when the pattern of time-dependent changes may be complex and when it is difficult to restrict the pattern to a specific class of functions *a priori*. If the constant hazard ratio hypothesis is rejected, the model will provide a reliable estimate of the pattern of changes, together with point-wise confidence intervals. Non-parametric estimation of the time-varying hazard ratio, using regression spline technique, ensures recovery of a broad range of patterns of changes in relative risks with increasing time since first exposure.

When using the time-varying model, we *a priori* assumed that the effects of the other risk factors met the proportional hazards assumption and focused on the stability of the predictive ability of flurazepam use. Such an approach, consistent with the objectives of this study and the results of Chapter 4.0, was necessary given that the number of events in this data set did not exceed 200. Simultaneous estimation and testing of the time-varying effects of several risk factors would have undermined the accuracy of the estimates and of inferential statistics.[14] In order to corroborate the results in a larger sample, methods developed by Grambsch and Therneau (1994) using the Schoenfeld residuals and the standard Cox

variance estimator were also used as a global test of proportional hazards and to test individual covariates.[31] This test was conducted on the full cohort of incident flurazepam users with a matched, random sample of non-users.

6.4.2 Results and Discussion

2,400 elderly subjects were followed for a median time of 936 days (standard deviation = 560) with 193 injuries (8% of sample). Although the likelihood ratio test of time-dependence was statistically non-significant ($p>0.20$), the relatively low number of events should be taken into account when interpreting the results, as it reduced the statistical power of the hypothesis testing. This lack of power was seen in the non-significance of the association for flurazepam ($p=0.23$). The pattern for the hazard ratio over-time is shown in Figure 6.1. It suggested that the risks among flurazepam users compared to non-users may increase with long-term exposure. However, the small number of events did not allow us to estimate the short-term changes in risks over the first two months after the first prescription.

To avoid the restrictions on sample size, we re-ran the time-dependent analyses using Grambsch and Therneau's (1994) method in a large sample with all incident users of flurazepam and the matched non-users.[31] This sample of 10,193 elderly was observed for an average of 832 days (standard deviation= 571) with 291 injuries (2.8% of sample). Grambsch and Therneau's test of the non-proportionality[31] of the effect of flurazepam exposure with this sample of flurazepam users was statistically significant ($p=0.0004$) although none of the other hazards for the covariates or the global test were significantly non-proportional. The estimated pattern of non-proportional changes in hazard ratio over time is shown in Figure 6.2. This figure shows that the impact of flurazepam exposure decreased

Figure 6.1 Time-dependence of log hazard ratio with 95% confidence bands for a sample of incident users of flurazepam compared to matched non-benzodiazepine users (2,400).

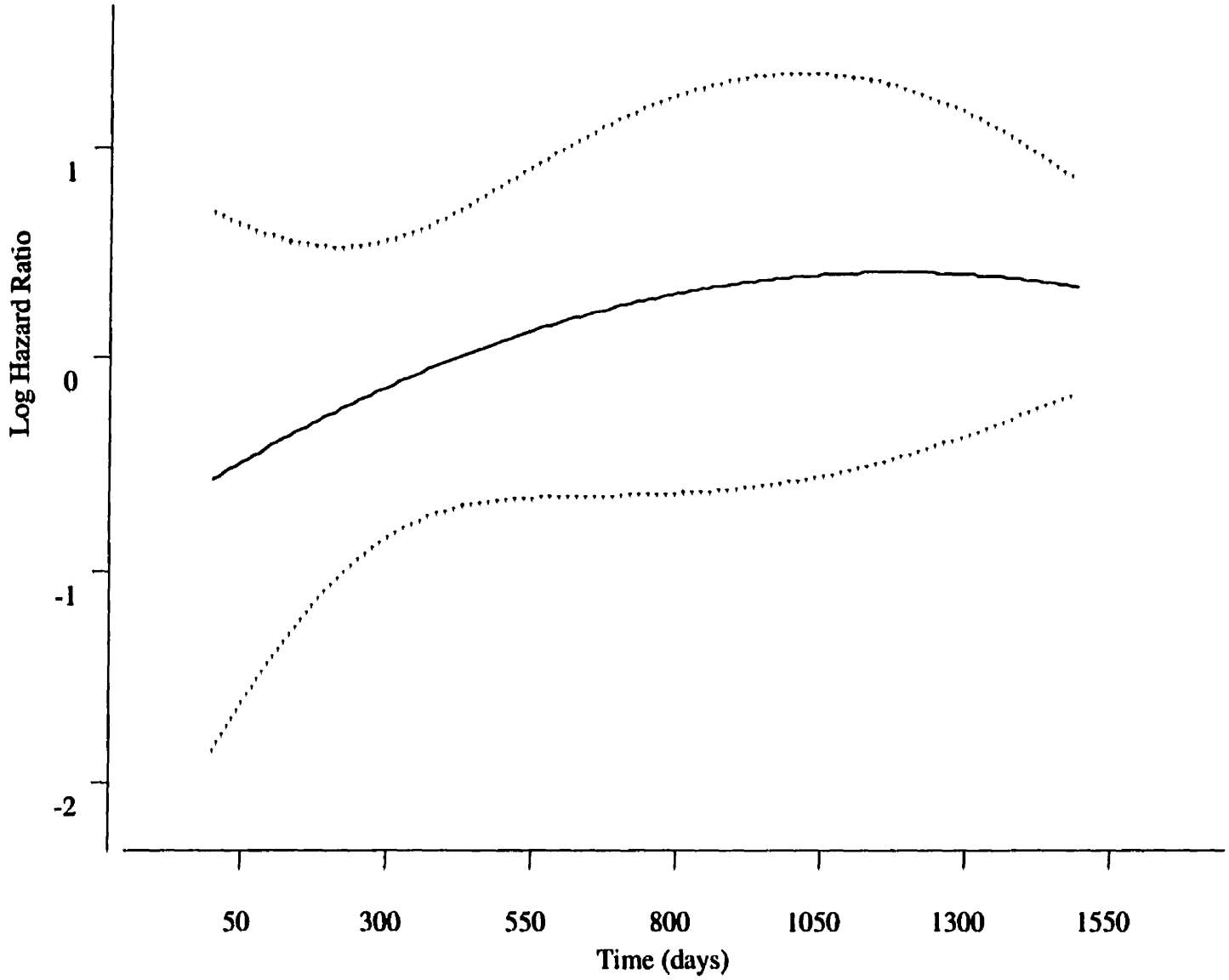
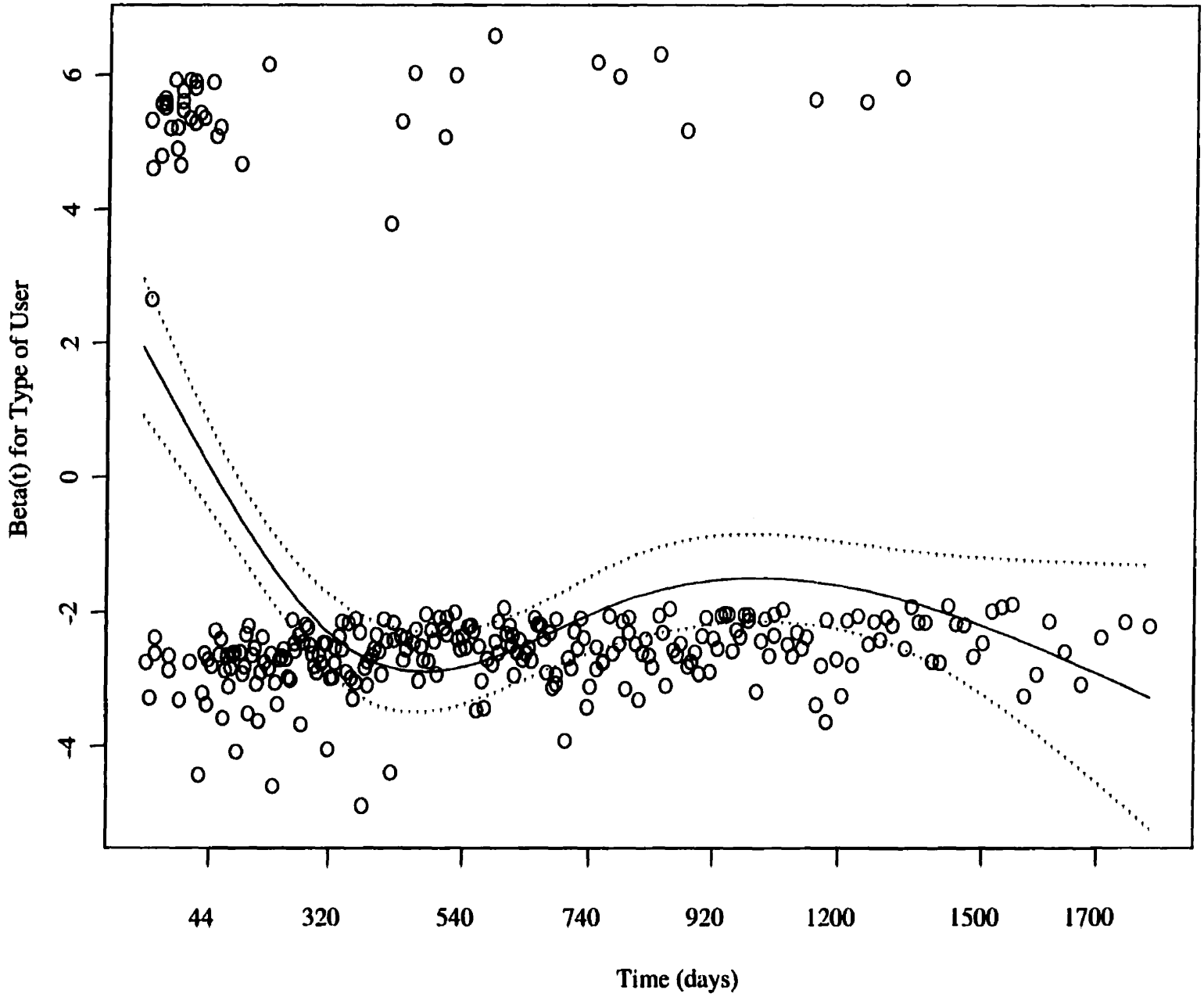


Figure 6.2 **Results from test of proportional hazards for categorization of all incident flurazepam users versus a matched sample of non-users with 95% confidence bands (p=0.0004).**



rapidly in the first few months after filling the first prescription but tended to increase with long-term exposure, the latter finding being consistent with Figure 6.1.

Based on these preliminary results, any modeling of benzodiazepine exposure should utilize time-dependent covariates. A fixed, binary representation of type of benzodiazepine user would cause bias from missclassification of exposure. This finding has important implications for the results of previously published studies that rely on such a classification to assess benzodiazepine risk. Furthermore, the hazards associated with the binary classification of exposure may not have been proportional for the entire period of follow-up. The sharp initial decrease in relative risks was consistent with expectations that the risks may have been highest right after initial exposure while the risks decreased with gradual development of tolerance to psychomotor effects.

6.5 ESTIMATING THE IMPACT OF CUMULATIVE DOSE AND DURATION OF BENZODIAZEPINE USE

Previous analyses of the impact of particular benzodiazepines were mostly restricted to a simple binary indicator of current use and sometimes included current dose,[2;3;5;6;9] In some studies, these indicators are represented by time-dependent covariates but this left open the question of what happens if the impact increases with increasing duration of medication use, with increasing cumulative dose, or with both. In order to respect the temporal sequence of exposure and outcomes, it is essential to represent both duration and cumulative dose by time-dependent covariates so that at any time during follow-up only previous exposure will be considered.[32] Because of frequent interruptions between subsequent periods of benzodiazepine use and changes in the dose (Chapter 5.0), a clinically meaningful

representation of both duration and cumulative dose requires a careful definition of the corresponding time-dependent variables.

Assume, for example, that Subject A was taking lorazepam between days 26 and 75 of the follow-up period while Subject B was exposed to lorazepam between days 71 and 120. If total exposure is assessed at day 125, both A and B will be assigned 50 days duration of past exposure. Yet from a clinical perspective, the exposure of Subject B is likely to be much more relevant because of the recency.[3]

A similar consideration applies to cumulative dose. Subject C who had a dose of 0.5 mg of lorazepam between days 51 and 80 and 1.0 between days 81 and 110 would have total cumulative dose of 45 mg for 60 days (30*0.5 + 30*1.0). However, Subject D who had a dose of 1.0 mg earlier in the observation period (days 51 to 80) and 0.5 mg later (days 81 to 100) would also have a total cumulative dose of 45 mg for 60 days (30*1.0 + 30*0.5). However, one would expect a higher impact in the case of Subject C, who was more recently exposed to a larger dose.

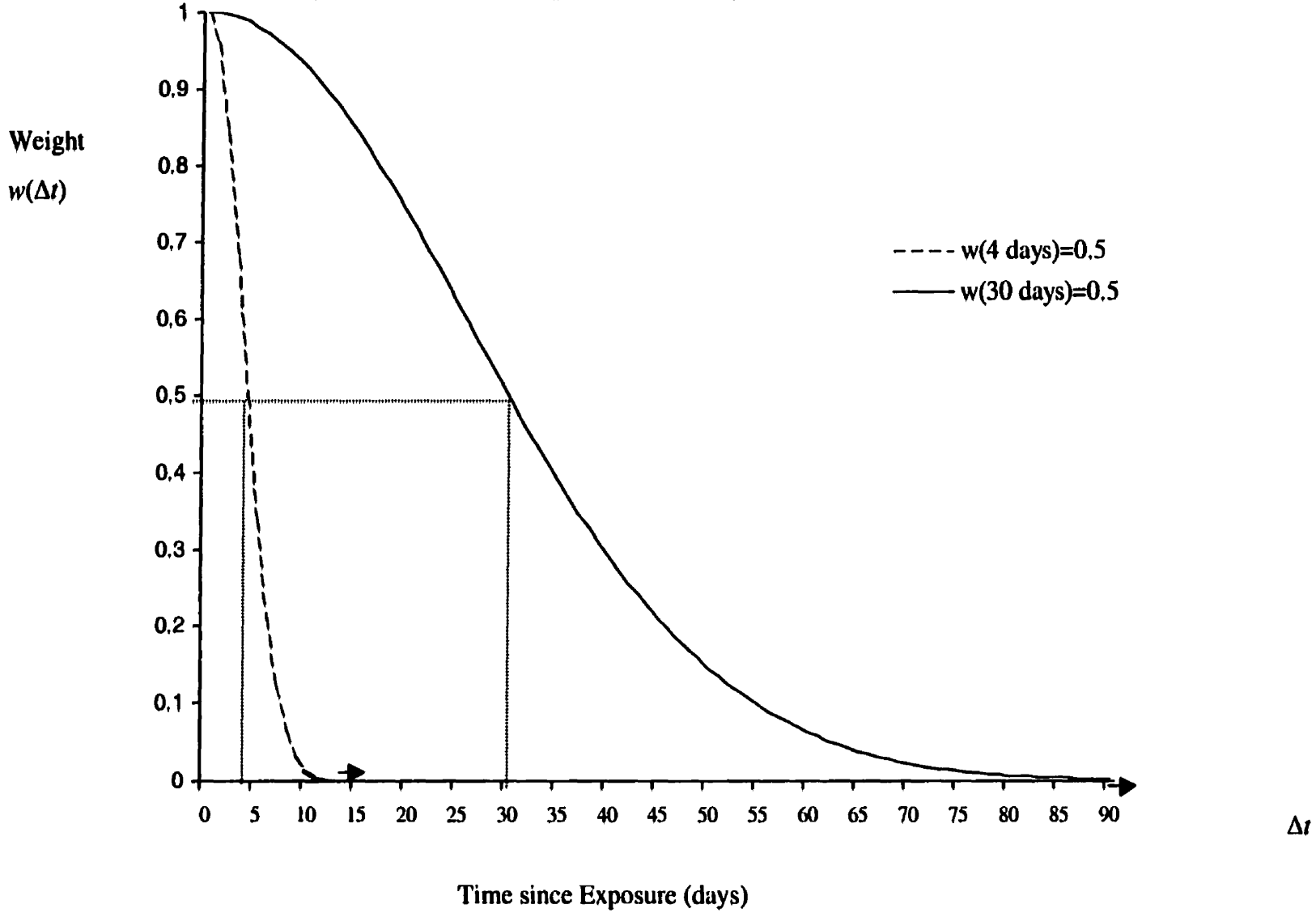
6.5.1 Representation of Cumulative Dose and Exposure

These considerations suggest that the operational definition of both duration of past benzodiazepine use and cumulative dose should incorporate weighting by recency.[32] This requires an *a priori* choice, based on substantive knowledge, of an appropriate weight function that assigns numerical weights for the difference in time between the time of exposure and the current time:[33]

$$w(\Delta t) = f(t_{\text{current}} - t_{\text{exposure}})$$

where $\Delta t = (t_{current} - t_{exposure})$ denotes time elapsed since exposure. Within a wide range of therapeutic plasma concentrations, the elimination of benzodiazepines follows first order

Figure 6.3 **Two Gaussian weight functions; used to weight past exposure as a function of time elapsed since exposure (Δt). Note that the time axis is reversed, with the origin Δt=0 corresponding to present time, and increasing Δt corresponding to more distant past. Both functions assign the highest weight of 1.0 to present exposure and they decrease to half the present weight (0.5) at 30 days (solid curve) and 4 days (dashed curve), respectively, in the past.**



Once the weight functions have been defined, the time-dependent covariates, representing past duration of use and past cumulative dose, are calculated. Specifically, the weighted duration is calculated by first multiplying the binary indicator of benzodiazepine use for a given day by the value of the weight function $w(\Delta t)$ corresponding to the distance between this day and present (Δt). The resulting products are summed across all days from time zero (T_0) to present day ($t_{current}$):

$$duration(t_{current}) = \sum_{t \leq t_{current}} I(t) * w(t_{current} - t)$$

where $I(t) = 1$ if the subject was using the drug on day t and $I(t) = 0$ otherwise.

Similar calculations define the time-dependent weighted cumulative dose:

$$cum.dose(t_{current}) = \sum_{t \leq t_{current}} dose(t) * w(t_{current} - t)$$

where $dose(t)$ indicates the dose prescribed at day t, with $dose(t) = 0$ on days when the subject was not using a benzodiazepine.

Figure 6.4 illustrates the implications of using the proposed weight functions. Figure 6.4a shows the pattern of benzodiazepine use by a hypothetical subject, with the horizontal axis representing the time since January 1, 1990 (t) and the vertical axis representing daily dose $d(t)$. The time axis is truncated at 320 days when the subject is assumed to have an event (injury from fall). The subject started using a benzodiazepine at the daily dose of 0.3 mg on day 120. On day 150 the dose was increased to 0.5 mg, but at day 180 the subject stopped using benzodiazepines until day 201, when a second period of exposure with a dose of 0.8 mg began. Figure 6.4a also implies that $I(t) = 1$ for time intervals 120 to 180 and 200 to 260 days, when the subject was exposed to a benzodiazepine. Figure 6.4b shows the

Figure 6.4.a Hypothetical Subject

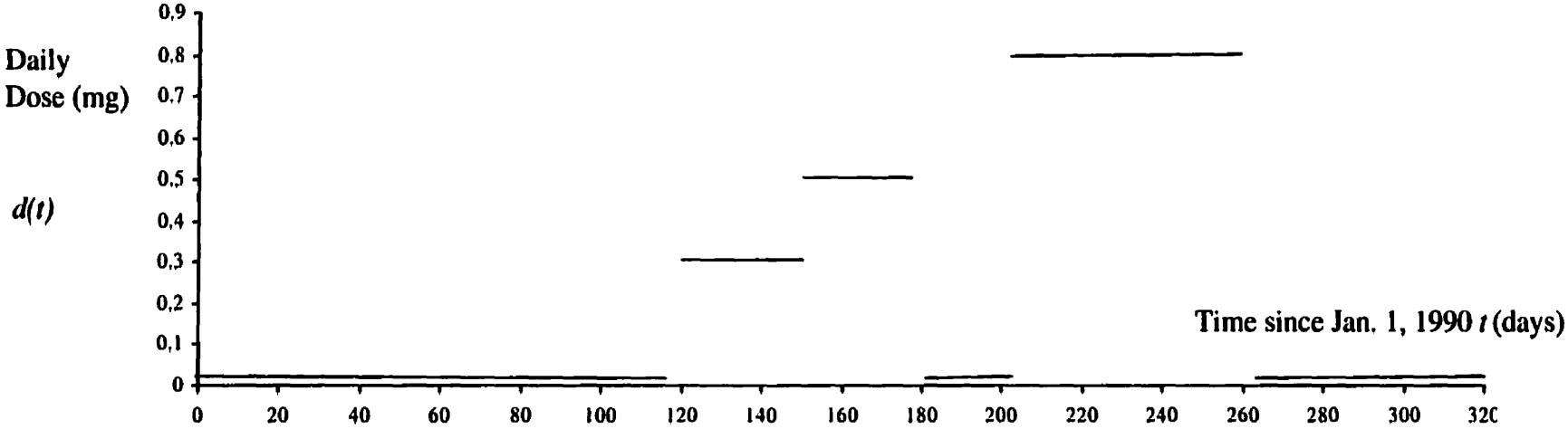
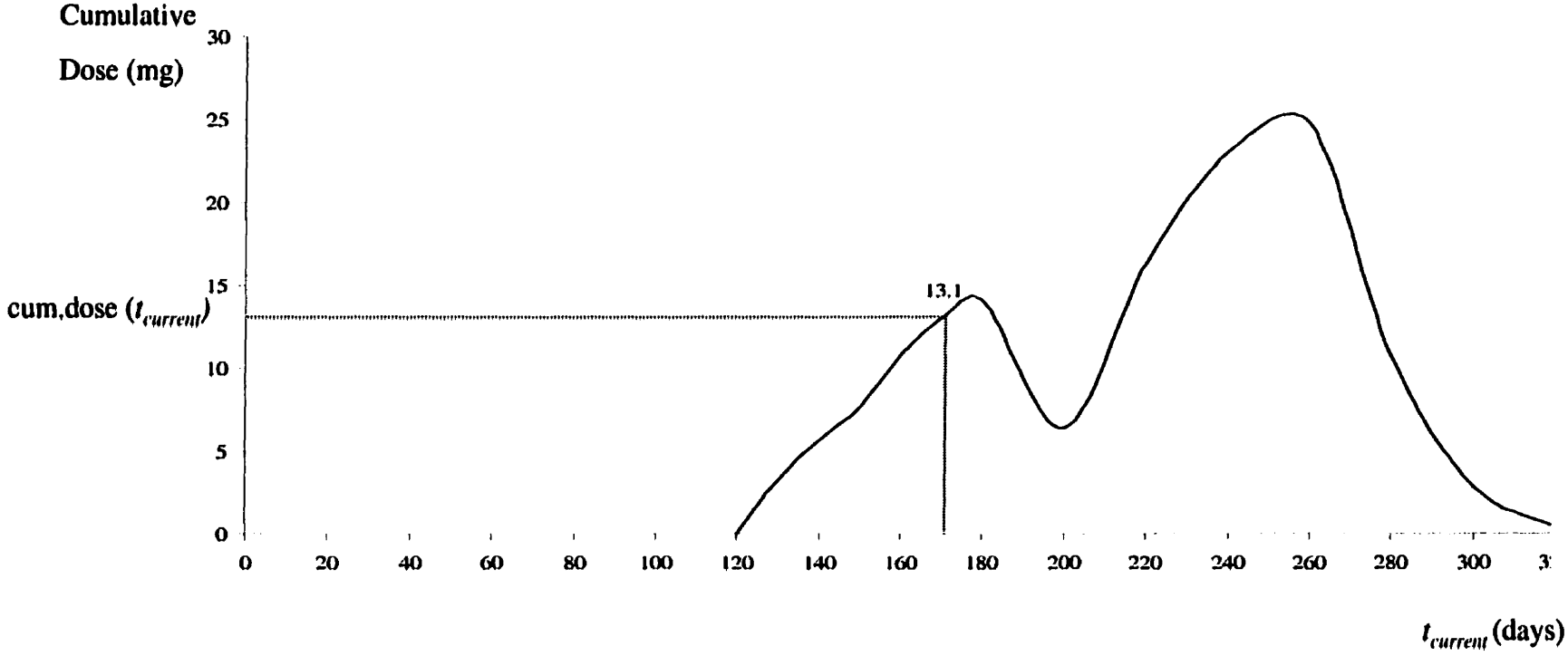
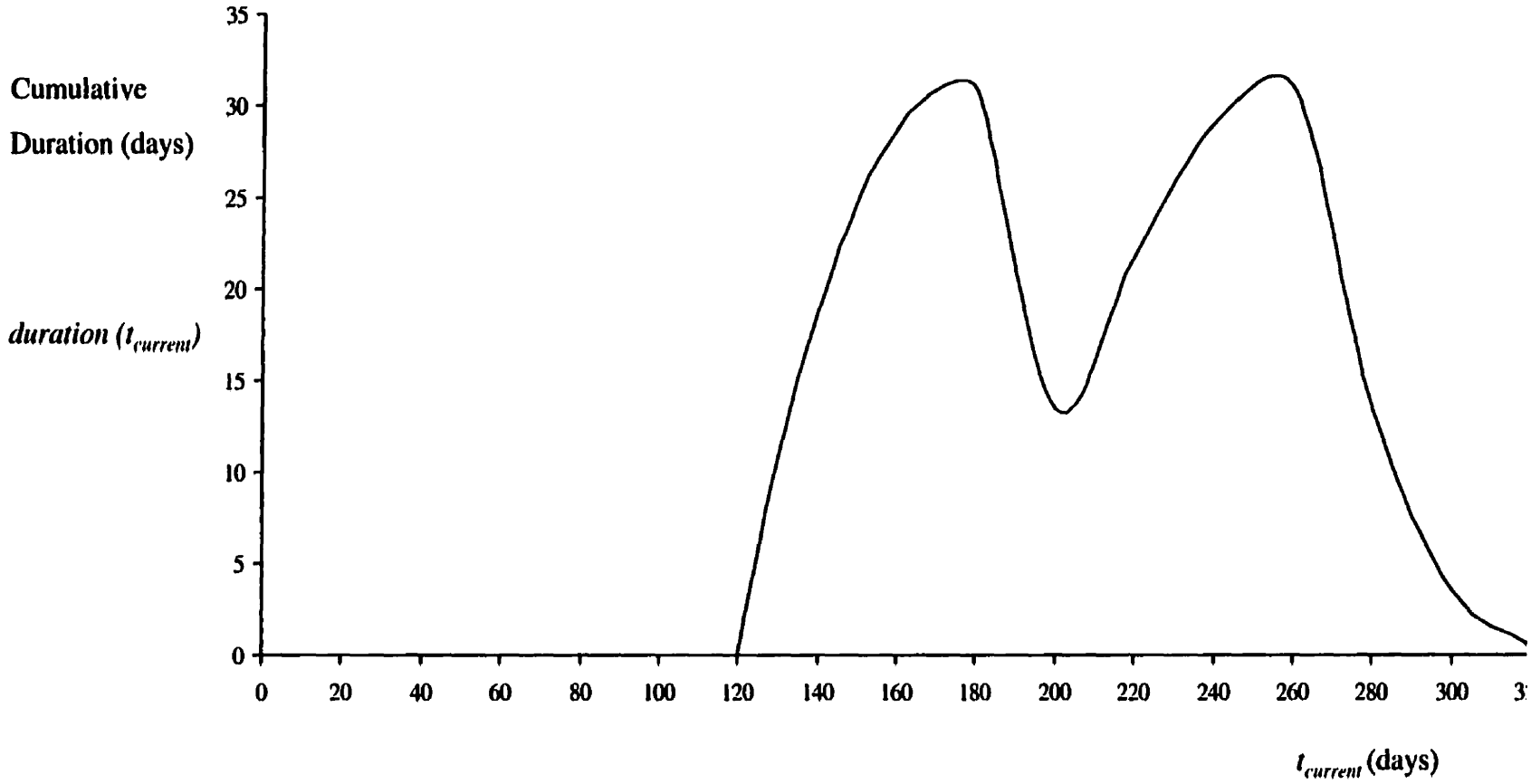


Figure 6.4.b Time-dependent covariate representing past cumulative dose*, as a function of current time ($t_{current}$), for the hypothetical subject shown in Figure 6.4.a.



* using weight function with $w(30 \text{ days}) = 0.5$

Figure 6.4.c **Time-dependent covariate representing past cumulative duration, as a function of current time ($t_{current}$), for the hypothetical subject shown in Figure 6.4.a.**



the intensity of the computational resources necessary to generate the cumulative exposures, all models were adjusted only for age, sex and history of injury in 1989 and incident users of lorazepam were not included in this analyses. Based on results from Section 6.3, T_0 was set to date of first prescription. Furthermore, since non-users do not provide information on dose or duration of use, the analyses were restricted to users of a specific product only.

In the first model, a binary, time-dependent reprcsentation of current dose was included. In order to compare our results with previous analyses, the second model included an on/off variable of benzodiazepine exposure. In the third model, the benzodiazepine effect was represented only by a time-dependent covariate indicating weighted duration while the fourth model included only the time-dependent covariate representing weighted cumulative dose. A comparison between the log likelihoods of these two models allowed us to assess if the additional information on variation in dose improved prediction. To further explore the relative importance of dose versus duration of use, we have also estimated a fifth model which included two benzodiazepine related time-dependent covariates, one representing weighted cumulative duration, $duration(t_{current})$, and a second representing current dose, $t_{current}$. Notice that such modeling avoids the near collinearity problem that would occur if we included both cumulative dose, $cum.dose(t_{current})$, and cumulative duration, $duration(t_{current})$, in the same model. All three models that included duration or cumulative dose were estimated twice, using two different functions to weight past exposure, and the log likelihood of the corresponding models were compared to gain some insight into the clinical relevance of past exposure.[33]

6.5.3 Results

Table 6.2 shows the estimated hazards ratios for the different exposure variables and the negative log likelihood for the five different models of benzodiazepine exposure for three different groups of incident users. Using the minimum values for the negative log likelihood as a measure of goodness-of-fit, the best modeling of exposure was different for each benzodiazepine (these models are indicated by the symbol, §, in Table 6.2). The best model for nitrazepam included weighted cumulative duration, $duration(t_{current})$ where $w(4)=0.5$ days, and current dose, $t_{current}$. The hazard ratio for cumulative duration was difficult to interpret since it represented an increase in a summed weight, however we could say that the the recent exposure to nitrazepam seemed to play an important role in increasing risk of injury among users of this drug (HR=1.31, p=0.0004). There was also a non-significant increase in risk associated with an increase of one standardized unit of current nitrazepam dose.

While the same model also provided the best fit for temazepam, the "optimal" weight function was different with $w(30)=0.5$ days, suggesting that a window of clinically relevant past exposure was longer for temazepam than for nitrazepam. In this case longer periods of exposure were associated with an increased risk of injury among temazepam users (HR=1.03, p=0.0002). Interestingly, once adjusted for the duration, an increased current dose of temazepam was associated with a decreased risk of injury (HR=0.60, p=0.02). Similar results were obtained using a more steeply weighted function for duration. These results helped explain why the current dose of temazepam did not have a significant impact on risk (Model Ib) and suggested that the marginally significant effect of cumulative dose (Model II) was due to increasing duration rather than increasing dose. Finally, the best-fitting models helped in detecting a statistically significant ($P<0.01$) impact of increasing duration of

Table 6.2 Comparison of models of benzodiazepine dose and duration of exposure using two different weight functions.*

Benzodiazepine (half-life)	Model†	Variable	$w(\Delta t)$=0.5 (days)	Hazard Ratio (p-value)	95% CI	-2 Log Likelihood§
Nitrazepam (20-40 hrs)	Ia	nitrazepam exposure	n.a.	4.51 (<.0001)	2.84-7.16	1154.99
	Ib	current dose	n.a.	2.31 (<.0001)	1.82-2.93	1160.81
	II	cumulative duration	4	1.41 (<.0001)	1.27-1.56	1149.68
n=1,385			30	1.04 (<.0001)	1.03-1.06	1172.69
	III	cumulative dose	4	1.21 (<.0001)	1.15-1.27	1156.38
			30	1.03 (<.0001)	1.02-1.03	1174.67
	IV	cumulative duration	4	1.31 (0.0004)	1.13-1.51	1147.78§
		current dose		1.34 (0.16)	0.89-2.01	
		cumulative duration	30	1.02 (0.05)	1.00-1.04	1156.80
		current dose		1.93 (<.0001)	1.42-2.62	
Temazepam (8-24 hrs)	Ia	temazepam exposure	n.a.	1.23 (0.12)	0.94-1.61	3625.05
	Ib	current dose	n.a.	1.10 (0.39)	0.87-1.41	3626.64
	II	cumulative duration	4	1.06 (0.03)	1.01-1.13	3622.62
n=3,797			30	1.01 (0.004)	1.00-1.02	3619.26
	III	cumulative dose	4	1.04 (0.14)	0.99-1.09	3625.22
			30	1.01(0.04)	1.00-1.02	3623.59
	IV	cumulative duration	4	1.22 (0.002)	1.08-1.39	3616.91
		current dose		0.50 (0.02)	0.27-0.91	
		cumulative duration	30	1.03 (0.0002)	1.01-1.04	3613.47§
		current dose		0.60 (0.02)	0.39-0.92	
Flurazepam (40-100 hrs)	Ia	flurazepam exposure	n.a.	1.73 (<.0001)	0.52-0.78	5859.81
	Ib	current dose	n.a.	2.12 (<.0001)	1.61-2.78	5854.10
	II	cumulative duration	4	1.15 (<.0001)	1.09-1.21	5850.81
n=5,111			30	1.02 (<.0001)	1.01-1.03	5856.45
	III	cumulative dose	4	1.20 (<.0001)	1.13-1.27	5845.48§
			30	1.03 (<.0001)	1.01-1.04	5851.13
	IV	cumulative duration	4	1.11 (0.05)	1.00-1.24	5850.29
		current dose		1.26 (0.47)	0.68-2.33	
		cumulative duration	30	1.01 (0.12)	1.00-1.02	5851.75
		current dose		1.64 (0.02)	1.06-2.53	

* Adjusted for age, sex and previous history of injury. Time zero is date of first benzodiazepine script. Dose is standardized and truncated at 3.0.

† Model I includes (a) a binary time-dependent representation of benzodiazepine exposure and (b) a continuous time-dependent representation of the current dose; Model II includes weighted cumulative duration; Model III includes weighted cumulative dose; Model IV includes weighted cumulative duration and current dose.

§ Indicates the best fitting model using the minimum negative log likelihood to measure of goodness-of-fit.

While temazepam is not known to be susceptible to accumulation through impaired elimination due to a different pathway of metabolism, the shortness of the half-life (8-24 hours) may increase the likelihood of elderly experiencing physiological dependence.[21;24] With repeated exposure of more than four weeks, tapering of dosage instead of abrupt termination is recommended in order to avoid withdrawal symptoms.[21;24] If withdrawal occurs with an abrupt discontinuation of the medication or with the termination of a course of therapy, the elderly patient may be at greatest risk of injury from falls due withdrawal symptoms such as dizziness and impaired coordination.[21] This theory was supported by our estimate of the best fitting model, with increased risks for longer cumulative duration but decreased risks for higher current dose. This exposure pattern implied that risks continued to increase if the patient was exposed to benzodiazepine for an extended period of at least thirty days. If the patient experienced an event soon after finishing a therapeutic course of temazepam, then at that point the cumulative exposure would still have been high but the current dose would have been zero. The latter explains why we found that higher current dose (specifically, current dose greater than zero) provided a protective effect, reflecting the additional risk due to recent discontinuation. Although this was a plausible explanation for our findings, we were not able to state this conclusion with certainty since the information on benzodiazepine prescriptions was only a proxy measure of actual benzodiazepine use.

Flurazepam is a benzodiazepine with a long elimination half-life (40-100 hours) that is metabolized through oxidation, thus being particularly susceptible to accumulation through prolonged use. However, the slow elimination of flurazepam due to the increased half-life actually acts a "self-tapering" mechanism that reduces the withdrawal and rebound symptoms that occur with discontinuation of treatment.[21] This may explain why, in our results, the

short-term cumulative dose predicted events better than the duration of exposure. Overall, the results for the three selected benzodiazepines demonstrated potential additional insights from careful modeling of cumulative dose and duration of individual drugs. The results also suggested that the impact of specific aspects of exposure may be different for individual benzodiazepines.

6.6 CONCLUSION

The investigation of the methodological issues addressed in this article confirmed our expectations that an in-depth and unbiased examination of the risk of injuries associated with benzodiazepine use must be evaluated with time-dependent measures of exposure. Based on our findings of the importance of specific aspect of benzodiazepine exposure that were relevant only to users and the finding that unbiased estimates of risk can be obtained in cohorts that exclude non-users, the analyses may be restricted to only incident users for each benzodiazepine and focus on in-depth evaluation of the impact of different aspects of exposure. Given the results of our previous research (Chapter 4.0 and 5.0), and the finding that the impact of specific aspects of exposure may be different for individual benzodiazepines, this type of analysis should be modeled separately for each benzodiazepine product. An additional reason for focusing on each product separately was the very substantial computational resources needed to represent several continuous-in-time, time-dependent covariates for each benzodiazepine. Starting observation for these analyses at the time of filling the first benzodiazepine prescription avoided an artificial inflation of relative risks. Finally, given that there was no one common model of time-dependent benzodiazepine dose and duration of exposure that best fit the effects of different products, different models using alternative representations of cumulative dose and duration should be considered for

further analyses. This will allow the selection of the model that best fits the data and will provide insight into the mechanisms behind the risk associated with individual benzodiazepine exposure among users of these medications.

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7.0 PREFACE TO MANUSCRIPT 4

This is the final article in a series of four that addressed specific components of the overall thesis objective of assessing the risk of injuries from falls associated with patterns of benzodiazepine use in community-dwelling elderly people. This article presented the final analyses using methods developed according to the findings from the first three articles in the series. The patient characteristics that were included in the analysis to control for potential confounding, were identified from the research contained in the first manuscript. The research in this final paper attempted to gain more insight into the mechanisms underlying the adverse effects of benzodiazepines by investigating different aspects of patterns of use that were evaluated and characterized in the second manuscript. Using a prospective cohort design, the analyses were conducted using state-of-the-art statistical methodology developed in the third manuscript . In the third article, the best fitting models for estimating the impact of benzodiazepine exposure on risk of injuries varied between products but always included a measure of weighted cumulative duration or cumulative dose. Based on these findings and the conclusions that analyses that were restricted to incident users were able to focus on in-depth evaluation of the impact of different aspects of exposure, alternative representations of cumulative dose and duration were used to allow for the selection of the model that best fit the data.

The results from the research in this manuscript provided evidence of an increased risk of injuries with almost all benzodiazepine exposure with increasing duration of past use or cumulative exposure for elderly patients. Modeling of the more complex patterns of benzodiazepine exposure provided insight into the role that physiological dependence may play in increasing the risk of injury in this population.

Abstract

Background Due to concerns about the increased risks of falls benzodiazepines have come under intense scrutiny and criticism. Previous studies on the risks of injuries from falls associated with benzodiazepine use have methodological limitations that might affect the accuracy and precision of results and contribute to the inconsistency of the findings.

Objectives To evaluate the risk of injuries from falls associated with different aspects of patterns of use, such as duration of past use, current dose, and cumulative dose, for individual products in an elderly population.

Methods In a cohort of 78,367 elderly incident benzodiazepine users, time-dependent covariates, representing past duration of benzodiazepine use and past cumulative dose, while weighting past exposure by its recency, were calculated. Four alternative versions of Cox proportional hazards model with different time-dependent covariates were used to estimate the impact of individual benzodiazepine use on risk of injuries from falls. Beginning of follow-up was set to the date of the first prescription and all analyses were adjusted for baseline patient characteristics. Negative log likelihoods were compared to determine goodness-of-fit.

Results All benzodiazepines except clonazepam were significantly associated with an increased risk of injuries from falls ($p<0.05$). The best predictive model for triazolam, oxazepam, alprazolam, bromazepam, temazepam and clonazepam included cumulative duration and current dose. The best models for lorazepam, nitrazepam, chlordiazepoxide, diazepam and flurazepam included cumulative dose. The optimal weight function varied among benzodiazepines, indicating that relative importance of most recent versus earlier exposure may depend on their specific pharmacokinetic and pharmacodynamic profile.

Conclusions Benzodiazepines were associated with an increased risk of injuries from falls in elderly patients, however duration of exposure may have been more critical than current dose. Physiological dependence and withdrawal symptoms appeared to play an important role in increasing the risk for many benzodiazepines.

7.0 BENZODIAZEPINES AND RISK OF INJURIES IN THE ELDERLY (MANUSCRIPT 4)

7.1 INTRODUCTION

With extensive use in the elderly community, benzodiazepines have come under intense scrutiny and criticism.[1-4] Due to concerns about adverse events, particularly the increased risks of falls, as well as physiological dependence, restrictions have been placed on the use of benzodiazepines and many clinicians are discouraged from prescribing them for elderly patients.[2;5-11] However, benzodiazepines can be a valuable therapeutic tool for a wide range of clinical conditions, and restrictions in use often means either a switch to alternative treatments that also have a risk for dependence and are not necessarily safer or more effective[5;9;12] or no treatment at all for debilitating conditions such as chronic anxiety and insomnia.[1;5;9]

Evidence from our previous study (Chapter 5.0) and from other research indicates that the use of benzodiazepines is often non-optimal and that there is an increased risk for physiological dependence in the elderly.[4;13-16] Furthermore, many studies conclude that there is an increased risk of injury from falls associated with benzodiazepines but there is little agreement on which benzodiazepines have the highest risk.[17-22] However, previous studies on the impact of benzodiazepines on the risks of injuries from falls have some methodological limitations that might affect the accuracy and precision of their results and possibly contribute to the inconsistency of the findings. Even in the recent studies there is a great deal of discrepancy in the approaches used to assess and classify exposure to benzodiazepines with several researchers using patient self-reports[21-23] while others retrieve information from pharmacy billing records contained in provincial databases.[18-20] A few

studies attempt to control for timing of the exposure by categorizing users according to time since the prescription,[18-20;23] but only Tamblyn et al (1998) use survival analyses to model the time-dependence of benzodiazepine dose on the risk of falls.[20] While all of the reviewed studies adjusted for age and sex, there is a great deal of heterogeneity between the remaining variables that are included in the analyses in order to control for potential confounders.[18;19;21-23]

We have shown that in order to avoid bias in the evaluation of the risk of injuries from falls associated with benzodiazepine use, whether from symptoms associated with withdrawal or from the psycho-motor impairment effects of the medication, a study must adequately control for the presence of confounding factors, as elderly who become benzodiazepine users have different profiles of risk factors for injuries from falls (Chapter 4.0). Moreover, previous studies of the impact of benzodiazepine use on the risks of injuries from falls consider only very simple measures of exposure such as a yes/no binary variable,[19;21;22] or classification of exposure into a few groups based on the duration of elimination half life of the specific benzodiazepines used.[18;23]

In one of the few studies to include a measure of current dose, Tamblyn et al (1998) used Quebec pharmacy billing records to assess benzodiazepine use in the elderly.[20] Ten different benzodiazepines were assessed by individual products. The use of a benzodiazepine was treated as a time-dependent variable in a survival analysis for the risk of injury from falls. Two types of analyses were conducted. In the first, periods of benzodiazepine use are compared to periods of non-use in persons using the same drug and in the second, periods of use and non-use in new users were compared to a random sample of non-users. Current dose is also included as a covariate and standardized using the World Health Organization defined daily dose for benzodiazepines.[20;24] In order to facilitate the

administrative health databases of the elderly population in Quebec offered an ideal data source for such analyses. This assessment of risk allowed for a more balanced evaluation of the relative advantages and disadvantages of benzodiazepine use in the elderly.

7.2 METHODS

A cohort of elderly Quebec residents was studied from January 1, 1989 to December 31, 1994 using information from provincial administrative health databases. Details of the cohort and the available subject information are provided in Chapter 4.0, Sections 4.2.1 to 4.2.3. Since no information on benzodiazepine use was available before January 1, 1989, and in order to restrict the assessment to incident users only, subjects who did not fill a benzodiazepine prescription during this year were eligible to be included in the study. Furthermore, subjects for whom the first detected benzodiazepine prescription during the study period, January 1, 1990 to December 31, 1994, was a refill were excluded (n=209,732). The remaining subjects were included in the study if a record for at least one new benzodiazepine script was detected during the study period. Thus, all new incident users of benzodiazepine were assessed.

For the final cohort, data were retrieved on several baseline characteristics including age, sex, area of residence, disabilities, co-morbidity, hospitalization, health care use, use of other selected prescription medications and diagnoses for fractures and soft tissues injuries during the baseline year. Further details are provided in Chapter 4.0 with details of diagnostic codes listed in Appendices V and VI.

This study was conducted in accordance with the ethical standards of the McGill Faculty of Medicine Institutional Review Board for research involving human subjects (Appendix I).

7.2.1 Benzodiazepine Exposure

Information on benzodiazepine use included start and end dates for each uninterrupted period of exposure, exact drug type, and dosage for each prescription. Further details on the measurement of benzodiazepine exposure are provided in Chapter 5.0. Clorazepate and clobazam were not included in any of the analyses since these drugs were included in the provincial formulary for only part of the observation period.

Periods of benzodiazepine use were represented by a binary time-dependent covariate (later on referred to as "on/off" variable with on/off = 1 for the periods where the subject filled a benzodiazepine prescription, and 0 in the remaining time periods). A second time-dependent covariate was constructed to represent the standardized daily dose. The standardized daily dose was calculated for each prescription, to facilitate between drug comparisons, according to the following formula:

$$\left(\frac{\text{total number of pills}}{\text{duration of prescription in days}}\right) \times \left(\frac{\text{dosage per pill in mg}}{\text{WHO recommended adult daily dosage in mg}}\right)$$

where the first term represented the average number of pills per day and the second term converted a given dosage into the percent of the World Health Organization (WHO) recommended adult daily dose[24] for the respective drug (see Appendix III). If the prescribed dose was close to the recommended daily dose for this specific product then the standardized dose would be close to one. To avoid implausible values, the range of the standardized dose was truncated at 3.0, which exceeded the 99th percentile for the distributions of average dose among incident users (Chapter 5.0). Thus, all values higher than 3.0 were replaced by 3.0. For periods of benzodiazepine use where dose information was missing, the value was set to the dose for all subjects exposed to that particular benzodiazepine.

events were excluded. To take into account the imprecision of administrative dates, only injuries recorded in the first five days of hospitalization were considered as an outcome for our study. The observation for all of these subjects was stopped at the time of the event. If the event occurred within 5 days of hospitalization, this subject would not be recorded as hospitalized for these five days in order to avoid conflicts with temporary censoring that was applied to all periods of hospitalization (see below). A subject with an event that occurred more than five days after hospital admission but before hospital discharge was permanently censored at that time as lost to follow-up.

The date of the first injury in the study period was determined to be the end of the observation for that subject. Subjects who did not have any injury during the study period were censored at the end the five year follow-up (December 31, 1994)or at the date of loss to follow-up caused by placement in a nursing home or long term care facility or caused by death. Furthermore, since no prescription information was available during hospitalization temporary censoring was applied during each distinct hospital stay longer than five days. These periods of hospitalization were subtracted from the total observation time for all subjects.

7.2.3 Statistical Analyses

The impact of benzodiazepine use on risk of injuries from falls was analyzed using the Cox proportional hazards model with time-dependent covariates.[27] These analyses focused on individual benzodiazepines and were restricted to separate subsets of incident users of particular benzodiazepines. T_0 was set to the date of the first benzodiazepine prescription. Each benzodiazepine was modeled in a separate analysis and subjects were censored at the time of a switch or an addition of a different type of benzodiazepine

prescription. Due to the substantial computational resources necessary to represent the continuous-in-time, time-dependent covariates for each benzodiazepine, we could not carry out the analyses for the full cohort of lorazepam users (n=31,062, matrix of 56,719,212 records). Therefore, we divided the full cohort randomly into two disjoint sub-cohorts and conducted the analyses on only one of the sub-cohorts (n=15,529).

All the models included covariates measuring baseline patient characteristics. These covariates were selected based on results from Chapter 4.0 and included a quadratic term of age and an interaction between gender and age; the use of other prescription medication; impairments and disabilities, and health care utilization. Due to the reduction in power caused by the restricted sample size and the need to ensure the adequate ratio of the number of events to the number of model parameters for the less commonly used benzodiazepines, baseline variables with small frequencies of occurrence were not included in the model (the use of estrogen, miscellaneous psychotropics, and partial opiate agonists or the presence of osteoporosis, alcohol abuse, drug abuse, and miscellaneous impairments).

Four versions of the Cox model were considered for the incident users of the eleven different benzodiazepines to assess the impact of past cumulative dose and duration of use. In the first model, the binary time-dependent representation of current standardized dose was included. In the second model, the benzodiazepine effect was represented only by the time-dependent covariate indicating weighted duration while the third model included only the time-dependent covariate representing weighted cumulative dose. The fourth model included two benzodiazepine related time-dependent covariates, one representing the weighted cumulative duration, and a second representing the standardized current dose. All three models that include the cumulative exposure variables were estimated twice, using the two

different functions to weight past exposure. The four models are discussed in more detail in Chapter 6.0. The log likelihood of the corresponding models were compared to determine which model provided the best fit.[28]

Statistical analyses were conducted using SAS Systems 8.0 for Windows.[29]

7.3 RESULTS

Baseline characteristics of incident users are described in Chapter 4.0 (Table 4.1) while details of the patterns of benzodiazepine exposure appear in Chapter 5.0.

Table 7.1 describes the distribution of standardized dose among the different groups of benzodiazepine users. Users of nitrazepam, triazolam and temazepam had median and mean doses near or equal to the recommended daily maximum adult dose. Other benzodiazepine users had a median standard dose close to half of the recommend adult dose, whereas median doses for oxazepam and bromazepam were below one-third of the recommended maxima, and clonazepam doses were very low. However, for almost all products, except clonazepam, there was considerable between-subject variation in these individual doses, with occasionally very high doses and some subjects exceeding the daily adult recommended dose (Table 7.1).

Table 7.1 also shows that the proportion of injuries detected in each group of benzodiazepine users was similar for most products (8.6 to 6.7%), with clonazepam and chlordiazepoxide having the highest proportions (9.0% and 9.2%, respectively).

Table 7.2 reports, separately for each of the 11 benzodiazepines, the estimated hazard ratios with p-values and 95% confidence for benzodiazepine exposure in the different models with the best fitting model indicated (‡). Using the minimum values for the log likelihood as a measure of goodness-of-fit, for all benzodiazepines except nitrazepam, flurazepam,

Table 7.1 Descriptive statistics for standardized daily doses by type of benzodiazepine use.*

Type of Benzodiazepine	No. of Events (%)	No. of Incident Users	WHO Recommended Adult Daily Dose (mg)	Median Standardized Daily Dose	Mean Standardized Daily Dose (sd)	Range	Inter Quartile Range†
Triazolam	191 (8,6)	2,220	0,25	1,00	0,92 (0,40)	0,07 - 10,00	0,50 - 1,00
Temazepam	255 (6,7)	3,798	20,0	0,75	1,05 (0,49)	0,07 - 15,00	0,75 - 1,50
Nitrazepam	116 (8,4)	1,385	5,0	1,00	1,31 (0,61)	0,09 - 11,00	1,00 - 2,00
Alprazolam	273 (7,2)	3,783	1,0	0,50	0,58 (0,41)	0,025 - 10,00	0,25 - 0,75
Oxazepam	1,042 (7,2)	14,460	50,0	0,30	0,43 (0,28)	0,01 - 10,00	0,30 - 0,60
Bromazepam	278 (7,5)	3,723	10,0	0,30	0,47 (0,29)	0,01 - 6,30	0,30 - 0,60
Lorazepam	2,345 (7,5)	31,062	2,5	0,40	0,53 (0,35)	0,001 - 14,40	0,40 - 0,67
Clonazepam	153 (9,0)	1,701	8,0	0,10	0,12 (0,12)	0,007 - 2,00	0,06 - 0,12
Flurazepam	391 (7,6)	5,111	30,0	0,50	0,73 (0,32)	0,12 - 7,5	0,50 - 1,00
Chlordiazepoxide	79 (9,2)	850	30,0	0,67	0,82 (0,86)	0,02 - 12,50	0,33 - 1,00
Diazepam	392 (8,3)	4,736	10,0	0,50	0,71 (0,56)	0,02 - 16,7	0,50 - 1,00

* The standardized daily dose was calculated by dividing the prescribed daily dose (number of pills per day*dosage per pill/duration of prescription) by the World Health Organization recommended adult daily dose.

† In the analyses, the standardized dose range was truncated at 3,0, so that each dose >3,0 was replaced by 3,0, to avoid implausible values that would excessively influence the parameter estimates.

Table 7.2 Estimated hazard ratios (p-values) with 95% confidence intervals (CI) for different models of benzodiazepine exposure.*

Benzodiazepine (half-life, hrs)	Model†	Benzodiazepine Exposure	$W(\Delta t)$=0.5 (days)	Hazard Ratio (p-value)	95% CI	-2 Log Likelihood
Triazolam (1.5-5.5)	I	current dose	n.a.	1.74 (0.0009)	1.26-2.41	2523.26
	II	cumulative dose	4	1.14 (0.0001)	1.07-1.22	2520.56
			30	1.02 (0.001)	1.01-1.03	2523.45
	III	cumulative duration	4	1.19 (<.0001)	1.10-1.27	2513.46
			30	1.03 (<.0001)	1.02-1.04	2514.07
	IV	cumulative duration	4	1.30 (0.0006)	1.12-1.51	2511.54‡
		current dose		0.59 (0.18)	0.28-1.27	
		cumulative duration	30	1.03 (0.002)	1.01-1.05	2514.03
		current dose		0.94 (0.83)	0.55-1.62	
Oxazepam (5-20)	I	current dose	n.a.	0.69 (0.04)	0.49-0.98	18128.51
	II	cumulative dose	4	1.00 (0.98)	0.93-1.07	18133.16
			30	1.00 (0.70)	0.99-1.01	18133.01
	III	cumulative duration	4	1.00 (0.96)	0.97-1.03	18133.16
			30	1.00 (0.71)	0.99-1.01	18133.02
	IV	cumulative duration	4	1.11 (0.0006)	1.05-1.18	18116.65‡
		current dose		0.25 (0.0002)	0.12-0.52	
		cumulative duration	30	1.01 (0.004)	1.00-1.02	18120.35
		current dose		0.40 (0.0008)	0.23-0.68	
Alprazolam (6-20)	I	current dose	n.a.	1.24 (0.33)	0.81-1.89	3977.99
	II	cumulative dose	4	1.07 (0.12)	0.98-1.17	3976.65
			30	1.02 (0.01)	1.00-1.03	3973.67
	III	cumulative duration	4	1.10 (0.002)	1.03-1.16	3969.70
			30	1.02 (<.0001)	1.01-1.03	3962.60
	IV	cumulative duration	4	1.20 (0.0002)	1.09-1.33	3964.33
		current dose		0.39 (0.03)	0.16-0.93	
		cumulative duration	30	1.03 (<.0001)	1.02-1.05	3956.75‡
		current dose		0.45 (0.02)	0.22-0.90	
Bromazepam (8-19)	I	current dose	n.a.	1.35 (0.30)	0.76-2.39	4059.73
	II	cumulative dose	4	1.09 (0.18)	0.96-1.23	4059.06
			30	1.02 (0.02)	1.00-1.04	4055.92
	III	cumulative duration	4	1.05 (0.11)	0.99-1.12	4058.30
			30	1.01 (0.01)	1.00-1.02	4055.03
	IV	cumulative duration	4	1.07 (0.20)	0.96-1.20	4058.11
		current dose		0.79 (0.67)	0.27-2.30	
		cumulative duration	30	1.02 (0.02)	1.00-1.03	4054.45‡
		current dose		0.72 (0.45)	0.31-1.69	

* Adjusted for baseline characteristics: age, sex, region of residence, number of prescribing doctors and hospital stays longer than 7 days, other medication use (anti-depressants, anti-psychotics, sedatives, cardiac drugs, anti-hypertensives, thaizide diuretics, vasodilators, opiate agonists, diuretics) and disabilities or impairments (history of injury, depression, seizure and neurological disorders, stroke, arthritis, and visual impairments) and the Charlson Comorbidity Index.

† Model I includes a binary time-dependent representation of benzodiazepine dose; Model II includes weighted cumulative duration; Model III includes weighted cumulative dose; Model IV includes weighted cumulative duration and current dose. Time zero is date of first benzodiazepine script.

‡ Indicates the model with the best fit.

Table 7.2 Continued

Benzodiazepine (half-life)	Model†	Variable	$w(\Delta t)$=0.5 (days)	Hazard Ratio (p-value)	95% CI	-2 Log Likelihood
Lorazepam (10-20)	I	current dose	n.a.	1.23 (0.07)	0.98-1.53	20218.10
	II	cumulative dose	4	1.08 (0.001)	1.02-1.13	20211.70
			30	1.01 (0.0003)	1.01-1.02	20209.05‡
	III	cumulative duration	4	1.05 (0.001)	1.02-1.08	20211.10
			30	1.01 (0.009)	1.00-1.01	20214.57
	IV	cumulative duration	4	1.08 (0.003)	1.02-1.13	20209.23
		current dose		0.75 (0.18)	0.50-1.14	
		cumulative duration	30	1.01(0.06)	1.00-1.01	20214.57
		current dose		1.00 (0.98)	0.73-1.37	
Temazepam (8-24)	I	current dose	n.a.	1.10 (0.42)	0.87-1.40	3595.93
	II	cumulative dose	4	1.04 (0.15)	0.99-1.09	3594.56
			30	1.01 (0.05)	1.00-1.02	3593.01
	III	cumulative duration	4	1.07 (0.03)	1.01-1.13	3591.74
			30	1.01 (0.003)	1.00-1.02	3588.35
	IV	cumulative duration	4	1.23 (0.001)	1.08-1.40	3585.51
		current dose		0.49 (0.02)	0.27-0.89	
		cumulative duration	30	1.03 (0.0002)	1.01-1.04	3582.24‡
		current dose		0.59 (0.02)	0.38-0.91	
Nitrazepam (20-40)	I	current dose	n.a.	1.05 (0.77)	0.76-1.43	1414.63
	II	cumulative dose	4	1.03 (0.41)	0.96-1.10	1414.05
			30	1.01 (0.04)	1.00-1.02	1410.97‡
	III	cumulative duration	4	1.03 (0.53)	0.94-1.13	1414.33
			30	1.01 (0.17)	1.00-1.02	1412.90
	IV	cumulative duration	4	1.09 (0.42)	0.89-1.33	1413.99
		current dose		0.81 (0.56)	0.39-1.66	
		cumulative duration	30	1.02 (0.07)	1.00-1.05	1411.44
		current dose		0.73 (0.24)	0.43-1.23	
Chlordiaze-poxide (10-30)	I	current dose	n.a.	2.19 (0.002)	1.32-3.62	900.62
	II	cumulative dose	4	1.19 (0.002)	1.06-1.33	900.55
			30	1.04 (0.0009)	1.01-1.06	899.24‡
	III	cumulative duration	4	1.12 (0.07)	0.99-1.28	904.32
			30	1.02 (0.07)	1.00-1.04	904.30
	IV	cumulative duration	4	0.99 (0.97)	0.83-1.19	900.62
		current dose		2.21 (0.03)	1.09-4.48	
		cumulative duration	30	1.01 (0.64)	0.98-1.03	900.41
		current dose		2.03 (0.02)	1.11-3.74	

† Model I includes a binary time-dependent representation of benzodiazepine dose; Model II includes weighted cumulative duration; Model III includes weighted cumulative dose; Model IV includes weighted cumulative duration and current dose. Time zero is date of first benzodiazepine script.

‡ Indicates the model with the best fit.

Table 7.2 Continued

Benzodiazepine (half-life)	Model†	Variable	$w(\Delta t)$=0.5 (days)	Hazard Ratio (p-value)	95% CI	-2 Log Likelihood
Clonazepam (20-80)	I	current dose	n.a.	1.54 (0.66)	0.22-10.95	1879.76
	II	cumulative dose	4	1.19 (0.36)	0.82-1.72	1879.23
			30	1.03 (0.35)	0.97-1.09	1879.21
	III	cumulative duration	4	1.05 (0.18)	0.98-1.13	1878.19
			30	1.01 (0.10)	1.00-1.02	1877.29
	IV	cumulative duration	4	1.07 (0.18)	0.97-1.19	1877.87
		current dose		0.40 (0.60)	0.01-11.62	
		cumulative duration	30	1.01 (0.09)	0.99-1.03	1876.95‡
		current dose		0.43 (0.58)	0.02-8.52	
Diazepam (14-100)	I	current dose	n.a.	1.39 (0.04)	1.01-1.92	5986.34
	II	cumulative dose	4	1.08 (0.02)	1.01-1.16	5985.43‡
			30	1.01 (0.02)	1.00-1.02	5985.78
	III	cumulative duration	4	1.06 (0.07)	0.99-1.13	5986.89
			30	1.01 (0.09)	1.00-1.02	5987.13
	IV	cumulative duration	4	1.03 (0.59)	0.94-1.12	5986.06
		current dose		1.27 (0.34)	0.78-2.06	
		cumulative duration	30	1.00 (0.47)	0.99-1.02	5985.84
		current dose		1.28 (0.23)	0.85-1.92	
Flurazepam (40-100)	I	current dose	n.a.	2.16 (<.0001)	1.63-2.85	5814.87
	II	cumulative dose	4	1.21 (<.0001)	1.14-1.28	5806.02‡
			30	1.03 (<.0001)	1.02-1.04	5811.77
	III	cumulative duration	4	1.15 (<.0001)	1.09-1.21	5812.63
			30	1.02 (<.0001)	1.01-103	5818.34
	IV	cumulative duration	4	1.10 (0.08)	0.99-1.22	5811.77
		current dose		1.35 (0.35)	0.72-2.50	
		cumulative duration	30	1.01 (0.16)	1.00-1.02	5812.91
		current dose		1.71 (0.02)	1.10-2.65	

† Model I includes a binary time-dependent representation of benzodiazepine dose; Model II includes weighted cumulative duration; Model III includes weighted cumulative dose; Model IV includes weighted cumulative duration and current dose. Time zero is date of first benzodiazepine script.

‡ Indicates the model with the best fit.

It is interesting to note that when the more sophisticated modeling methods are used, all benzodiazepines except clonazepam have a statistically significant ($p<0.05$) increased risk of injury with increased duration and/or cumulative dose. Furthermore, clonazepam, the only benzodiazepine that did not have a statistically significant increase in association with the risk of injuries from falls, had an extremely restricted range of low standardized doses (Table 7.1). If the representation of exposure were limited to current dose alone (Model I in Table 7.2), then only triazolam, flurazepam and chlordiazepoxide would have shown a statistically significant increase in risk for injury.

7.4 DISCUSSION

The models proposed in this study to assess the impact of benzodiazepine exposure provided some new insights into the role that benzodiazepines may play in increasing the risk of injury. The fact that the model of benzodiazepine exposure that appeared to fit the data best was different for individual benzodiazepines, offered support for the theory that sensitivity to adverse events experienced by the elderly was related to the pharmacokinetic and pharmacodynamic properties of specific benzodiazepines.[16] Our study showed that the best model for most of the benzodiazepines included a measure of cumulative duration and current dose. If withdrawal symptoms occurred when a patient attempted to stop the medication, this would have been when the elderly patient was at greatest risk of injury from falls due to dizziness and impaired coordination.[16] Given that benzodiazepines are typically prescribed for at least a few weeks (Chapter 5.0), a patient who recently stopped treatment would have had a relatively high value of duration of recent use. For example, if the patient experienced an event soon after finishing a therapeutic course of temazepam, then at that point the cumulative duration of exposure and the cumulative dose would still have been

of benzodiazepines on the risk of injury.[17-19;21;22] First, the hazard ratio was adjusted for possible confounding due to other medications and baseline factors implicated in the risk of injuries from falls (details in Chapter 4.0). Second, time-to event analyses was used to allow for time-dependent changes in benzodiazepine exposure represented by standardized daily dose. Yet, this model almost always provided the worst fit to the data (Table 7.2). Furthermore, the conclusions that would have been drawn from the results of this model were quite different than those that were made based on the results from the more complicated modeling of benzodiazepine exposure. According to the current dose model, the only statistically significant increases in risk were associated with increasing current dose of flurazepam, chlordiazepoxide and triazolam. In contrast, in a better fitting, though more complex model, that also accounted for the duration of recent exposure, the current dose did not have a significant independent effect on risks of injuries, and if anything, showed a trend towards a protective effect. On examination of the findings by Tamblyn et al (1998) for an analysis of increased risk of injury that includes non-users and time-dependent covariates for current dose of 10 benzodiazepines, it is interesting to note that a significant effect is only found for benzodiazepines that showed relatively strong effects in our analyses. The only benzodiazepine that did not have a statistically significant increase in risk, clonazepam, also had an extremely restricted range of very low standardized doses (mean = 0.12) in a small group of subjects (n=1,700, Table 7.1). Since the best model included a measure of cumulative duration and current dose, it is likely that evaluation of exposure to this benzodiazepine in a larger group of subjects, would also identify a statistically significant increase in risk associated with injuries from falls.

The methods we developed to model complex aspects of benzodiazepine exposure that vary over time provided new insights into the potential role that physiological dependence and withdrawal symptoms may play in increasing the risks of injuries from falls. However, confirmation of this finding would require explicit modeling of the impact of withdrawal symptoms on increasing the risk of injuries from falls. This type of modeling would require better information on the exact timing of the benzodiazepine exposure than that provided by records from the administrative health databases. At the same time, the methods developed in this study (Chapter 6.0) should be explored further using computer simulations and different analytical forms and/or parametrization of the different functions describing how recent exposures are weighted relative to more distant past.

7.4.1 Conclusion

Falling is a significant risk for all elderly people with potentially serious sequella including injuries requiring hospitalization and that may even be responsible for fatalities.[31-35] Furthermore, injuries from falls are the cause of 40% of nursing home admissions.[31] Since we have used novel methods to assess the complex benzodiazepine exposure, our findings of increased risk of injury in the elderly for most benzodiazepines need to be investigated further, and replicated in an independent study of a similar population. However, if our conclusions are valid, then some of the risks associated with benzodiazepine use may be modifiable. Benzodiazepines can continue to be a useful therapeutic tool as long as elderly patients are cautioned against both prolonged exposure and abrupt termination and physicians ensure a proper regime of tapering to avoid severe withdrawal symptoms.[1;4;5;16;36]

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8.0 DISCUSSION

8.1 SUMMARY

We found an increased risk of injury associated with the majority of the benzodiazepines studied in the elderly Quebec population. However, unlike other researchers who examined the risk of individual benzodiazepines based on current exposure,(Leipzig et al., 1999; Ray et al., 1989; Neutel et al., 1996; Tamblyn et al., 1998b; Cumming et al., 1993; Ryynanen et al., 1993) we found that the risk of injury was specific to the certain time-dependent aspects of the benzodiazepine exposure (Chapter 7.0). For all the benzodiazepines, the best model of exposure included either a measure of cumulative dose or a measure of cumulative duration with current dose. The optimal weight function for recency of cumulative dose or duration, was different for different benzodiazepines. Furthermore, use of cumulative dose or duration allowed us to establish that after adjusting for several potential confounders, only clonazepam did not have a statistically significant increase in risk. By contrast, only three among 11 benzodiazepines considered had significant dose-response relationships in a conventional model, in which exposure measurement was restricted to current dose. Yet, many previous studies model benzodiazepine exposure using either current exposure or current dose (Leipzig et al., 1999; Ray et al., 1989; Neutel et al., 1996; Tamblyn et al., 1998b; Cumming et al., 1993; Ryynanen et al., 1993). Interestingly, our analyses suggested that the effect of current dose changes substantially after adjusting for cumulative duration, which significantly improved the model's fit to the data. This finding may provide some insight into mechanisms by which benzodiazepine exposure increases the risk of injuries from falls in elderly patients.

Specifically, our results appeared to corroborate that withdrawal from a benzodiazepine may adversely affect the risk.

This complex modeling of the exposure required a large sample size, an adequate observation period and a range of exposure among the subjects. The cohort of Quebec elderly met these requirements, and by using this database with novel methods developed specifically to evaluate benzodiazepine exposure over time (Chapter 6.0), we were able to enhance the accuracy and precision in evaluating the risk of injury.

The large number of subjects in our database allowed us to focus on individual benzodiazepine products. Like many other researchers, we found that this class of medications had a high prevalence of use in the elderly (see Chapter 4.0) (Egan et al., 2000b; Gleason et al., 1998; Rojas-Fernandez et al., 1999; Taylor et al., 1998; Olfson et al., 1994; Kirby et al., 1999; Jorm et al., 2000; van Hulten et al., 1998). We also found a high incidence rate but this was specific to individual drugs. Evaluation of predictors for new use of individual drugs revealed systematic differences not only among users of specific benzodiazepines but also between incident users and those subjects who never filled a prescription (Chapter 4.0). This emphasized the importance of adjusting for relevant subjects' characteristics when estimating the overall risk associated with benzodiazepine use and when comparing the impact of particular medications.

A further investigation into patterns of use after the initial prescription revealed that benzodiazepine use varied greatly over five years in terms of duration, dose, type of benzodiazepine, addition of a prescription for another drug and switching to a different benzodiazapine (Chapter 5.0). Although most elderly seemed to follow clinical guidelines for use of benzodiazepines, there was a significant proportion who did not, and a small but

important fraction who seem to abuse the medications (extremely high doses, multiple simultaneous prescriptions and continuous use). Most importantly, we found evidence for dependence and tolerance in escalating duration and/or dosage with subsequent periods of benzodiazepine use. The most significant risk factor for increasing duration and dosage was older age at the date of the first prescription. This factor was significant after controlling for other medication use and illnesses, emphasizing the fact that patients become more susceptible to the risk of dependence with increasing age, independent of increasing co-morbidity (Martinez-Cano et al., 1999; Holroyd et al., 1997; Kan et al., 1997; Nelson et al., 1999; Ashton, 1994).

This finding was particularly relevant since our analyses of the impact of benzodiazepines on the risk of injuries seemed to indicate that a recent withdrawal from many benzodiazepines provided a significant increase in risk. Indeed, for a number of benzodiazepines, the best fitting models showed a protective effect for current dose with an increased risk associated with cumulative duration. Since the analyses were restricted to users of a specific benzodiazepine, one possible interpretation was that subjects who were recently exposed to benzodiazepines, but were not currently using the medication, i.e. had a current dose of zero, had an increased risk of injury compared to subjects either not recently exposed or those who currently continue using benzodiazepines. This interpretation was only viable if the exposure to the benzodiazepine caused physiological dependence and the risk of injury was affected by symptoms of withdrawal (Nelson et al., 1999; Schweizer et al., 1998; Lader, 1999).

One of the most consistent findings throughout all of our studies, was that many factors, including characteristics associated with benzodiazepine use, patterns of use and

increased risks of injury with use, were all specific to individual products. Much of the previous research on benzodiazepines in the elderly has used a pharmacokinetic parameter, elimination half-life, to classify benzodiazepines (Jensen et al., 1991; MacDonald, 1985; Ray et al., 1987; Stevens et al., 1989; Taggart, 1988). We found that none of the aspects of benzodiazepine use were comparable among different benzodiazepines with similar elimination half-lives (see Chapters 4.0 - 7.0). Nor was there any similarity among benzodiazepines with overlapping clinical indications (i.e. benzodiazepines used mainly as hypnotics versus those used mainly as anxiolytic agents). Therefore, any analyses that combined different benzodiazepines by the half-life would be biased due to missclassification, and would likely result in a dilution of effects (Mohane et al., 1996). The fact that analyses of each benzodiazepine provided distinct information was not surprising since so many of the aspects associated with benzodiazepine use are unique, included pharamokinetic factors (i.e. pathway of metabolism), pharmacodynamic parameters (i.e. potency), and clinical indication (i.e. night-time hypnotics for insomnia versus daytime sedation for anxiety) (Nelson et al., 1999). The combination of these factors along with patient characteristics created a unique profile for each type of benzodiazepine and classification by a single parameter may have resulted in inaccurate conclusions that would mislead both researchers and clinicians.

8.2 LIMITATIONS

Our study could not avoid some limitations typical of all analyses relying on administrative health databases. One of the study limitations was the lack of prescription information during hospitalization. Evidence from previously published studies indicates that benzodiazepines are frequently prescribed for elderly patients during periods of

hospitalization (Zisselman et al., 1994; Woods et al., 1992; Kruse, 1990; Grad et al., 1999) and that in-hospital use may be associated with an increased risk of falling (Passaro et al., 2000; Mendelson, 1996). Since we did not have any prescription information during periods of hospitalization, we were not able to verify if subjects terminated or started benzodiazepine use at the time of hospitalization. If the risk of injury was associated with current or recent use and/or withdrawal symptoms for many benzodiazepines, this limitation would have biased our results in two ways. First, a subject who was exposed to a benzodiazepine only for the duration of hospitalization (e.g. for problems with sleeping) and then experienced a fall after returning home, would have been missclassified as a non-exposed, thereby underestimating the risk of injury when comparing benzodiazepine users with non-users. Second, if the abrupt termination of therapy due to hospitalization resulted in a within-hospital fall, our study would have missed this event and again underestimate the risk of injury associated with benzodiazepine use. We used two methods to minimize the possible bias from lack of prescription information during hospitalization. First, periods of hospitalization longer than five days were censored in the time-to-event analyses for both users and non-users. Second, the pre-hospitalization exposure status was assigned to the first five days of hospital admission and injuries that occurred within the first five days of hospitalization were included in the analyses.

The other main limitation with using a database for our study was that we were not able to verify actual benzodiazepine consumption and had to use the characteristics of the benzodiazepine prescriptions as a proxy measure for duration of exposure and actual dose. Therefore, we would systematically overestimate the intensity of exposure for (i) patients who did not consume their entire prescription, (ii) patients who reduced their dosage by

taking only half or a quarter of a tablet per day, and (iii) if the prescription was given with instructions to "take as needed"(PRN). In the first scenario, the patient would be considered exposed when they were actually not taking a benzodiazepine which would underestimate any non-zero risk due to exposure, regardless of what specific measure of exposure was assessed. However, this first scenario was unlikely because the patient had actually filled the prescription. In the second scenario there were two possibilities. First, the patient may have used the medications at a reduced dose, but only for the period covered by the prescription. Then the effect of an on/off variable indicating current use and the duration of use would not be affected but the impact of current dose and cumulative dose would be underestimated. Alternatively, it is quite possible that a patient will use the remaining stock of pills for a period extending beyond the "official" end of the prescription. In that case, the exposure would have been overestimated in the period corresponding to the actual recorded ("official") duration of the prescription and underestimated after the end of the prescription, when, in our analyses, the subject would have been considered to be unexposed. Therefore, both biases in exposure would have reduced the true difference between periods of exposure and non-exposure and would have resulted in attenuation of the effects of the on/off current exposure variable as well as the dose-related variables. Similar biases in the risk estimate would have occurred with PRN prescriptions although it would have been more sporadic and dependent on the patient's actual perception of when and how often they "needed" to take the medication. It is quite likely that we overestimated benzodiazepine exposure in intermittent users of benzodiazepines since prescriptions are often given on a PRN basis and approximately 10% of elderly report taking a benzodiazepine at a lower dose than prescribed (Gleason et al., 1998; McElnay et al., 1997). This bias would have been less likely to occur

with patients who regularly filled consecutive prescriptions, however a validation of drug exposure assessment would have been necessary to fully assess the level of bias in our results. This type of validation would have required sampling patients and verifying database records against self-reported use by patients for assessment of consumption, PRN prescribing, and patient self-dosing.

While we did attempt to control for as many potential confounders as possible, there were several factors that we were not able to include in our study. Since this was a database study, we were also not able to assess psychosocial variables that have been implicated in higher rates of benzodiazepine use (van Hulten et al., 2000) and may play an important role in modifying risk associated with falls (Buchner et al., 1987; Avorn, 1998). Preliminary evidence for an increased risk of falls with use of corticosteroids only began to emerge after we constructed our database to include this variable in our list of medications that possibly increased the risk of injuries from falls (NIH Consensus Development Panel on Osteoporosis Prevention, 2001). Furthermore, many of the patient characteristics such as presence of illnesses or impairments, use of non-benzodiazepine medications, and levels of co-morbidity undoubtably changed over time. We only assessed these variables during the baseline year, 1989. However, given the important differences between the characteristics of the users of individual types of benzodiazepines (Chapter 4.0), it would have been useful to measure the changes in these variables over time and include them as time-dependent covariates (Tamblyn et al., 1998b). This would have been particularly important for strong confounders such as anti-depressant medications (Chapter 4.0). Many elderly develop more impairments and disabilities with increasing age, therefore many of these factors that occurred after the baseline period would not have been detected, and their effect on risk of injury may have

8.3 AREAS OF FUTURE RESEARCH

Since our new methods to represent benzodiazepine exposure allowed us to investigate new aspects of their putative effects on the risks of injuries, it is essential that our findings be replicated in an independent study using similar methods. Furthermore, the conjecture that withdrawal symptoms related to physiological benzodiazepine dependence are associated with an increased risk of injury, and supported by our analyses of the independent effects of duration of use and current dose, needs to be investigated more carefully. At the same time, the methods developed in this study (Chapter 6.0) should be explored further using computer simulations and different analytical forms and/or parametrization of the different functions describing how recent exposures are weighted relative to more distant past.

Our study was based on data from the first half of the 1990s. The importance of our finding of an increased risk of injuries with benzodiazepine exposure depends on continued high levels of consumption among the elderly. While it is unlikely that elderly patients will stop using benzodiazepines, the rate of usage may decrease or increase over time due to temporal changes in perception of the relative safety and efficacy of different types of benzodiazepines, changes in clinical guidelines and recommendations, and changes in patient or physician perceptions or behaviours (Ashton, 1994; Moller, 1999; Nelson et al., 1999; Argyropoulos et al., 1999; Lader, 1999; Uhlenhuth et al., 1999; McNutt et al., 1994; Johnson et al., 1997). For example, after implementation of triplicate prescription program in the state of New York, the number of benzodiazepine prescriptions for elderly patients was reduced by 40-50% across all products (McNutt et al., 1994). In Quebec, a major change was administered for the prescription drug coverage in the mid-1990's, so that medication costs

for many elderly substantially increased (Legras, 1998). Whereas the policy resulted in an overall decrease of use of medications by the elderly, the implications specifically for the frequency and patterns of benzodiazepine use in the elderly have not been investigated since this policy was introduced (Tamblyn et al., 2001).

Any evaluation of the relative advantages and disadvantages of benzodiazepine use in the elderly should reflect not only the serious adverse effects that require medical attention but should also look at the patient's perception of adverse effects. In our study we focused on the adverse effects that might increase the risk of injuries from falls. However, we also found that a large proportion of the subjects that used benzodiazepines for more than one period of time switched from one type of medication to another. It may well be that patients experience effects that are unpleasant or uncomfortable enough to switch medications but not serious enough to require hospitalization. Such effects may include dizziness and the subjective feeling of a hangover that has been reported with many benzodiazepines (Ashton, 1994). Since the presence of such effects is a common reason for abruptly discontinuing treatment, further investigation of the frequency and reasons for stopping a treatment or switching to another product may provide more insight into which specific benzodiazepines demonstrate these effects (McElnay et al., 1997). This becomes especially relevant in view of our results that suggested that abrupt withdrawal of many benzodiazepines may be associated with an increased risk of serious events such as injuries due to falls. Furthermore, the impact of changing or adding a new medication should be carefully investigated using appropriately constructed time-dependent variables (Tamblyn et al., 1998a).

Another area for investigation would be the characteristics of the physicians involved in prescribing benzodiazepines for the elderly. There is a great deal of evidence that the

choice of and appropriateness of benzodiazepine prescribing is associated with physician characteristics (Tamblyn et al., 1996; Monette et al., 1994; Aparasu et al., 1999; Egan et al., 2000a; Morabia et al., 1992; Olfson et al., 1993). Researchers have examined the types of benzodiazepines prescribed in terms of physician characteristics,(Aparasu et al., 1999; Egan et al., 2000a; Morabia et al., 1992; Monette et al., 1994) but the overall patterns of benzodiazepine use in terms of physician characteristics and perception of the risks involved with individual benzodiazepines needs to be evaluated. Despite existing evidence of the apparent risks associated with benzodiazepines, many clinicians continue to favour benzodiazepines as a pharmacotherapy (Uhlenhuth et al., 1999; Uhlenhuth et al., 1998). The perceptions of the physician may actually play the biggest role in the decision to initiate the benzodiazepine treatment and may explain in part why lorazepam dominated the use of benzodiazepines in our study.

8.4 FINAL CONCLUSION

Any evaluation of risks associated with drug use, especially in context of non-experimental epidemiological studies in high risk populations such as elderly patients faces important methodological challenges. We have demonstrated the considerable variation in the patterns of benzodiazepine use among the elderly. To address the complexity of such research, the choice of statistical methodology and assessment of exposure to the medication require careful consideration (Linden et al., 1993). Although complex modeling is not always possible in view of limitations in data and in existing statistical software, conclusions based on simpler analyses must be interpreted in that light. Evidence from our study has shown that inadequate control for confounding factors can lead to overestimation of risk, and that limiting the exposure measurement to current use or current dose only can also bias the

estimation of risk and result in failure to detect statistically significant effects of many benzodiazepines. In either situation, the risk profile may be misleading. The evidence from previous studies of the risk of falls has mainly concluded that there is an increase in risk, especially for benzodiazepines with longer elimination half-lives (Leipzig et al., 1999; Ray et al., 1989; Neutel et al., 1996; Tamblyn et al., 1998b; Cumming et al., 1993; Ryynanen et al., 1993). These findings have lead to restrictions in the use of some benzodiazepines resulting in switches to alternative treatments that may have an even worse safety profile or to no treatment at all (Moller, 1999; Johnson et al., 1997; Straand et al., 1997; Smith et al., 1998; McNutt et al., 1994; Lader, 1999; Woods et al., 1992; Kruse, 1990). Our findings that the increased risk for injuries from falls may be associated with specific aspects of benzodiazepine exposure, such as duration of recent exposure and the recency of treatment termination, need to be validated in further studies. However, if these findings are valid then the increased risk would be subject to modification through patient education and use of tapering regimes to avoid more severe withdrawal symptoms. More careful management of patients, based on solid research findings, would decrease the risk of adverse events and improve the utility of this treatment in elderly (Argyropoulos et al., 1999).

Methods developed in our study provided new insight into the role benzodiazepines play in the risk of injuries from falls among the elderly. These findings may have important implications for clinicians, researchers and elderly patients. Many other medications, such as oral contraceptives or hypotensives, are commonly used in a variety of patients and have a complicated exposure history (Monane et al., 1997; Suissa et al., 2000; Fourrier et al., 2000). The method we propose for assessing the past and present exposure to

benzodiazepines and the associated risk of adverse events can be utilized in investigations of the effects of these medications.

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Appendix I

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

Appendix II

DATABASES FROM RAMQ AND OTHER SOURCES

The following is a list of the raw variables from RAMQ and other sources used to generate variables for the current study.

PATIENT DEMOGRAPHIC DATABASE (*demopt*)

Variable name	Definition
PID	Patient identification - encrypted health insurance number. When the patient was assigned a temporary number, the region number was labeled "0".
sex	Patient gender: M=Male, F =Female
dtnais89 –dtnais94	Age of the patient for each study year.
reg89 to reg94	Region of residency from 89-94: 01 = Bas-Saint-Laurent 02 = Saguenay-Lac-St-Jean 03 = Québec 04 = Mauricie-Bois-Francs 05 = Estrie 06 = Montréal 07 = Outaouais 08 = Abitibi-Témiscamingue 09 = Côte-Nord 10 = Nord-du-Québec 11 = Gaspésie 12 = Chaudières-Appalaches 13 = Laval 14 = Lanaudière 15 = Laurentides 16 = Montérégie 17 = Kativik 18 = Terres-cries-de la B.-J.
dsc89 to dsc94	DSC - code of 1 digit dividing the region into several administrative units.
clsc89 to clsc94	CLSC – code of 2 digits dividing the DSC into several points of service.
codep89 to codep94	Forward sortation area (i.e. first 3digits of the postal code).
dtdeces	Date of death (in Julian format of 5 digits). 2 categories of death (2 unsafe sources = 1 safe source): 1) death from safe source, 2) death from unsafe source 2 categories of date of death: precise (dd/mm/yy), imprecise (31/mm/yy) or (28, 29 or 30) depending on the month. Sources of information for the RAMQ — Type • MD claims for certificate of death (***codeacte***= 0013 or 0014) — unsafe • Bureau de la statistique du Québec(name, date of birth, sex) — safe • Régie des rentes du Québec (name, date of birth, sex, SIN) — unsafe • Société de l'Assurance-auto. du Québec (name, date of birth, sex) — unsafe • Curatelle publique (10K-12K people) (name, date of birth, gender, SIN, health insurance number) — safe • Health Canada (for people ≥65 of age who received the maximum for old age pension – about 60K-80K people in Québec) (name, date of birth, gender, SIN) — unsafe • Patient's family (health insurance number & RAMQ data form) — safe • Undertaker (health insurance number & RAMQ data form) — safe

PHARMACEUTICAL SERVICES DATABASE (*rx*)

Variable name	Definition
PID	Patient id - unique identifier
clprof	Class of professional (see Physician Demographics Database).
noprof	Prescribing physician id - unique identifier
nopharm	Pharmacy id - unique identifier. Encrypted pharmacy number.
codespc1-codespc5	Special consideration code: A = there is another document attached to claim or additional relevant information entered under "complementary information" B = rebilling after payment was refused or cancelled C = service for patient less than a year old D = emergency service T = reduced length of treatment or lesser quantity of drugs supplied than prescribed
codemed	Code of the prescription drug supplied, as shown in RAMQ "Liste des médicaments".
cdenom	Common name code of the prescription drug (*e.g.* diazepam, lorazepam). This unique code for generic drug is provided by RAMQ.
codeahf	American Hospital Formulary code of drug class: 08:00 Anti-infective Agents 10:00 Antineoplastic Agents 12:00 Autonomic Drugs 16:00 Blood Derivatives 20:00 Blood Formation and Coagulation 24:00 Cardiovascular Drugs 28:00 Central Nervous System Agents 36:00 Diagnostic Agents 40:00 Electrolytic, Caloric, and Water Balance 48:00 Antitussives, Expectorants, and Mucolytic Agents 52:00 Eye, Ear, Nose, and Throat (EENT) Preparations 52:32 Vasoconstrictors 56:00 Gastrointestinal Drugs 60:00 Gold Compounds 64:00 Heavy Metal Antagonists 68:00 Hormones and Synthetic Substitutes 76:00 Oxytocics 84:00 Skin and Mucous Membrane Agents 84:80 Sunscreen Agents 86:00 Smooth Muscle Relaxants 88:00 Vitamins 92:00 Unclassified Therapeutic Agents 99:00.00 Diet Supplements 99:00.03 Special Medications 99:00.05 Supplies 99:00.10 Special Topical Mixtures 99:00.20 Additives
qntymed	Quantity of drug supplied
duretr	Duration of the treatment in number of days. When the format of the drug is spray or cream, this variable is meaningless.

MED-ECHO HOSPITALIZATION DATABASE cont.

Variable name	Definition
diasec1-diasec8	Secondary diagnoses. Other diagnoses for treatment during hospitalization.
cmd1-cmd4	Physician's code: Anonymous code identifying the treating physician within a specific institution, in relation to medical specialty as specified by the Professional Association. The first part of the code is composed of one digit identifying the professional class of the treating physician: 1=physician living in Québec 2=dentist living in Québec 3=physician living in Québec, caring for a long term patient occupying a short term bed. 6=physician living outside of Québec 7=dentist living outside of Québec
dtacc1	Accident date If the admission is attributed to an accident, the date of the latter will be indicated as year-month-day.
cacc1	Accident code. Code identifying the cause of the trauma for which the patient was admitted. The codes used are taken from the 9th Edition of the International classification of diseases (ICD-9).
cdest	Destination code. Destination where the patient was sent on discharge (8 digit codes assigned by "Le ministère des Consommateurs, Coopératives et Institutions financières"). This number is used in licensing by the "Ministère de la Santé et des Services Sociaux". First digit =1 principal establishment =5 pavilion =0 out of province establishment
ctra1-ctra9	Treatment code. General term identifying diagnostic, therapeutic or surgical procedures during hospitalization in Canada.
typede	Destination type. Where the patient discharged (Med-Echo nomenclature): ° 01= public hospital, short term care ° 02=public hospital, long term convalescent care (abolished 1985) ° 03=public hospital, long term care ° 04=private hospital, short term care ° 05=private hospital, long term convalescent care (abolished 1985) ° 06= private hospital, long term care ° 07= federal hospital, short term care ° 08= federal hospital, long term care ° 09= out of province hospital, short term care ° 10= out of province hospital, long term care ° 12= transition center ° 13= rehabilitation center ° 14= public long term care living facilities ° 15= private long term care living facilities ° 16= Social Service Center (CSS) ° 17= Local Community Service Center (CLSC) ° 18= outpatient services ° 20= registered foster homes and group homes ° 21= home without in-home care ° 22= home with in-home care ° 23= day care center ° 24= private clinic/consultant ° 25= protected workgroup ° 30= death ° 31= discharge against medical advice ° 32= missing

Appendix III

ALGORITHMS FOR THE GENERATION OF THE STUDY DATABASE

Appendix III Instructions for Generation of Database
BENZODIAZEPINE I - Eligibility & Fixed Variable Definitions

Eligible Elderly	**Definition**	The patient demographic database contains complete information on subjects 65 years during the period of Jan. 1, 1989 to Dec. 31, 1994 and residents of Quebec during a portion of this period. The year 1989 (from January 1 to December 31) is called the **washout period.** Individuals collected in the washout period are tested for eligibility, then observed for a period of five years (from January 1, 1990 to December 31, 1994), called the **study period.** Throughout this document, we refer to the washout and study periods as those periods specified above. Eligible subjects will be >65 years of age in 1989 and be residents of Quebec for the entire washout period and the first year of the study period.
	Database	patient demographic (demopt); prescription (rx); RAMQ billing; MED-ECHO
	Variable	PID, ageat94, dtdeces, regclsxx and codepxx in demopt; dateserv in rx; dtsort, typede in med-echo; dacte, noetable in billing
New Identification Number	*npid*	new numeric subject identification based on key to entire RAMQ population database (id=1 to 727,294); motivation - numeric keys are easier to handle than long alpha-numeric keys
Record Deletions	**Definition**	**Subjects removed due to premature death, unknown place of residence, institutionalization in washout, moving during washout and the first year of the study period, and permanent hospitalization. We begin with the number of subjects in demopt database which contain unique patient identifiers (PID) and proceed to count the number of subjects at each rule:**
		1. Record the number of unique identifiers (PID) in demopt. NUMBER: 727,295 2. Records with all 6 variables regclsxx=0 indicates that a temporary PID was issued, which might not be unique. Delete records with regcls89=0.and.regcls90=0.and.regcls91=0.and.regcls92=0.and. regcls93=0.and.regcls94=0. Record the number of subjects in this step. NUMBER: 4,186 3. Delete subjects with age in 1989 (ageat94-5) less than 66 years (<66) or ageat94 missing. Record the number of subjects in this step. NUMBER: 205,547 4. Delete subjects with 0< dtdeces < 90001. Record the number of subjects in this step. NUMBER: 18,258 5. An eligible subject is a Québec resident during the **washout** and first year of the **study** period. A Québec resident is recognized with a permanent PID (regclsxx>0) and a valid postal code (1st letter of 1st 3 digits of codepxx=G, H or J), for years xx=1989 and 1990. Delete subject if not[(regclsxx>0) and ({1st letter of 1st 3 digits}codepxx=G, H or J)], xx=1989 and 1990 Record the number of subjects in this step. NUMBER: 9,509
		6. A subject institutionalized during the washout period is not eligible for the study. Restrict query to dates <90002. Match the first date occurrences *(dtsort, dacte)* to the associated Destination code *(typede)* or Establishment code *(noetabl)*. Delete records if min*(dtsort, dacte)*<90002. Subject Institutionalization (MED-ECHO, Billing): - MED-ECHO: *dtsort* – Discharge date *typede* – Discharge destination codes: 03,06,08,10,12,14,15 - Billing: *dacte* – Medical procedure date *noetabl* – Establishment code 0xxx4: Unité de longue durée (soins prolongés) 0xxx5: Unité de longue durée (hébergement) 1xxx5: Hébergement public 2xxx5: Hébergement privé Record the number of subjects in this step. NUMBER: 23,247

		7. Permanent hospitalization During **washout** period: Delete subject if a single associated MED-ECHO record *(dtadm, dtsort)* shows *dtadm* ≤ January 1, 1989 and *dtsort* ≥ December 31, 1989. During **study** period: Delete subject if a single associated MED-ECHO record *(dtadm,dtsort)* shows *dtadm* ≤ January 1, 1990 and *dtsort* ≥ December 31, 1994. Record the number of subjects in this step. NUMBER: 3,307 8. Isolated Region Delete subject if regcls89=10 or 17 or 18; NUMBER= 697
Cohort for Study		The remaining subjects are used for extraction of the eligibility status of subjects using data from the prescription database (rx).
Eligibility and Exposure for Benzodiazepine use	**Definition**	**Eligibility status of subjects by benzo use: A benzo rx is identified by a date of prescription (dateserv) for AHF codes (codeahf)=282408 or 281208, *excluding* DIN (codemed) 0908606, 1925989, 1925970 and 1911821 (subclass chlor. d'ondansétron - zofran). Eldelig=1 will identify the set of individuals at risk of benzodiazepine exposure. Subjects with eldelig>1 will be known as the prevalent users. Create an exposure variable to characterize, among the eligible subjects (at risk), those who were dispensed a new benzo rx during the study period, thus identifying a group of subjects exposed to benzodiazepine.**
Eldelig		1. Set eldelig=1 as the default value of an eligible subject; 2. Set eldelig=2 if a 1st benzo rx is dispensed during **washout** period; 3. Set eldelig=3 if the 1st benzo rx issued during the **study** period is a refill (codereno=2); 4. Set eldelig=4 if a 1st benzo rx issued during the **study** period is unknown (codereno=0).
Expos		1. Set expos=2 if eldelig>1 (prevalent subjects); 2. Set expos=1 if eldelig=1 and 1st benzo rx during the **study** period and codereno=1 (new prescription); 3. Set expos=0 if eldelig=1 and **no** benzo rx during the **study** period .
Storage	**Definition**	**Store PID, npid, eldelig, expos in file BENTOT.**
Characteristics for New Users	**Definition**	**Collect information about individuals stored in BENTOT who have *expos=1*. Look for specific diagnosis in the year before the date of the first benzo script. This will only be for a subset of the individuals stored in BENTOT.**
	Database	BENTOT; billing; med-echo; rx
	Variable	PID, expos in BENTOT; dateserv, codeahf in rx; cdiag, dacte in billing; diaprin, dtsort in med-echo
Indication for Benzo	**Definition**	Indicate whether a diagnosis of one of the main labeled indications for prescribing benzodiazepines was made **at least once** in the year previous to the date of the first benzodiazepine script dispensed for individuals with *expos=1*(1=yes, 0=no). Listed below, for each indication, are the diagnostic codes by *cdiag* (billing) and *diaprin*[1] (med-echo). The first benzodiazepines dispensed is identified by date of prescription (*dateserv*) for AHF codes (*codeahf*)=282408 or 281208, *excluding* DIN (codemed) 0908606, 1925989, 1925970 and 1911821 (subclass chlor. d'ondansétron - **zofran**).
anxind ***insomind*** ***seizind*** ***spasind*** ***alcoind***		Diagnosis of anxiety disorders - *cdiag* and/or *diaprin*: 300.0, 300.2, 309.0 308.0, 309.2 Diagnosis of insomnia - *cdiag* and/or *diaprin*: 307.4, 780.5 Diagnosis of seizure disorders - *cdiag* and/or *diaprin*: 345, 780.3 Diagnosis of muscle spasticity - *cdiag* and/or *diaprin*: 728.8, 781.0 Diagnosis of alcohol abuse/dependence - *cdiag* and/or *diaprin*: 303, 305.0, 291, 265.2, 425.5, 535.3, 571.0 - 571.3
Storage	**Definition**	**Store in file BENTOT.**

[1] REMINDER: After review of ICD-9 codes for principal diagnosis (*diaprin*) in MED-ECHO, it was found that records may have been missed because some codes contain alphanumeric characters beyond the 4-digit definition. The rule now is to take the first 4 digits and ignore the rest of the field.

Characteristics of prevalent users and non-users	**Definition**	**Collect information about individuals stored in BENTOT. Of immediate interest is the examination of the following fixed characteristics during the washout period: a) age and sex; b) drug use; c) disability; d) illness score; e) health care use and; f) injuries. For d) and e), variables will also be created for each year of the study period.**
	Database	BENTOT: demopt, rx, billing, med-echo
	Variable	PID in BENTOT, sex, ageat94 in demopt; codemed (DIN), cdenom, codeahf and dateserv in rx; cdiag,dacte and cacte in billing; diaprin, diasec1-diasec8, dtadm and dtsort in med-echo.
sex	**Definition**	Sex of subject.
age	**Definition**	Age of subject in 1989.
Drug Use	**Definition**	*Appendix 3.1.1* describes the drugs that influence the risk of injury. Thiazides and Estrogens are said to be "protective" while Psychotropics and Drug-Altering Motor Stability are said to increase the risk of injury. *Appendix 3.1.1* lists, where needed, the *codeah, cdenom and DIN*'s of each drug class. The tasks involved are to count, during washout: 1. The total number of prescriptions dispensed (# rx): The counts are computed according to DIN, *cdenom* or *codeahf*, where indicated below; 2. The total number of unique pharmacological substances (unique *cdenom* – # sb): This step is not required for Hydrochlorohiazide.
thiarx		Hydrochlorohiazide Diuretics: #rx according to *cdenom*.
estrorx,estrosb		Estrogens: # rx according to distinct cdenom , to distinct *DIN* for chlorotrianisène, #sb according to distinct *cdenom* (note: count chlorotrianisène *DIN* as one cdenom).
psydeprx,psydepsb ***psytrarx,psytrasb*** ***psysedrx,psysedsb*** ***psymisrx, psymissb***		Psychotropics: #rx according to *codeahf*; #sb according to distinct *cdenom*.
motcarrx,motcarsb ***mothyprx,mothypsb*** ***motdilrx,motdilsb*** ***motopirx,motopisb*** ***motporx,motpopsb*** ***motdiurx,motdiusb***		Drugs Altering Motor Stability: #rx according to *codeahf*; #sb according to distinct *cdenom* (except *cdenom*: 04537 for Drug Class Diuretics).
Disability	**Definition:**	Disability or impairment due to illness during washout. *Appendix 3.1.2* lists, for each disability, the diagnostic codes by *cdiag* (billing), *diaprin, diasec1-diasec8* (med-echo) and, in one case, by *cacte* (billing). Drugs dispensed are identified by *codeah* (rx) and by *cdenom* (rx). The task consists of counting the number of diagnoses or number of drugs prescribed.
visbil, vismed ***visrx***		Diagnosis of visual impairment: *cdiag, diaprin, diasec1-8*. Drug Rx for visual impairment: *codeahf*.
strokbil, strokmed		Diagnosis of stroke: *cdiag, diaprin, diasec1-8*.
neubil, neumed, ***neurx***		Diagnosis of neurological disorders: *cdiag, diaprin*. Drug Rx for dementia and/or Parkinson disease: *cdenom*.
arthbil1, arthmed ***arthbil2***		Diagnosis of arthritis or lower extremity instability: *cdiag, diaprin, diasec1-8*. Diagnosis of arthritis and lower extremity instability: *cacte*
seizbil, seizmed ***seizrx***		Diagnosis of Seizure Disorders including Epilepsy: *cdiag, diaprin*. Drug Rx for Seizure Disorders: *codeahf*.
osteobil, osteomed		Diagnosis of Osteoporosis: *cdiag, diaprin*.
depbil, depmed		Diagnosis of Depression: *cdiag, diaprin*.
alcobil, alcomed		Diagnosis of Alcohol Abuse and/or Dependence: *cdiag, diaprin*.
drugbil, drugmed		Diagnosis of Drug Abuse and/or Dependence: *cdiag, diaprin*.

Illness Score	**Definition**	Compute a Charlson Co-Morbidity Index (modified by RA Deyo) based on diagnostic codes (*cdiag, diaprin, diasec1-diasec8*). Jimmy Fragos has algorithms to produce these scores. The tasks involved are to compute for records collected during washout.
morbbxx		1. Charlson Co-Morbidity Index based on medical services (*cdiag*);
morbhxx		2. Charlson Co-Morbidity Index based on diagnostic codes (*diaprin, diasec1-diasec8*);
morbbhxx		3. Charlson Co-Morbidity Index based on **either** *cdiag* or *diaprin, diasec1-diasec8*.
	Database	BENTOT; billing, med-echo
	Variable	PID in BENTOT; noprof, clrprof, cacte and dacte in billing; dtsort and typeta in med-echo; noprof and codemed in rx.
Health care use	**Definition**	During **washout**, count the number of billed visits. Valid "classes of professional" are *clrprof*=1 and 6 (billing). Count the number of admissions from hospital discharges (*dtsort*).
physpxx		1. Number of physicians prescribing medication (unique *noprof* associated with each *codemed* in rx database).
physvxx		2. Number of physicians visited in the calendar year (unique *noprof* in each day).
visitaxx		3. Number of billed visits (*cacte*) made on different days (*dacte*). Each day with one or more billed visits counts as one.
visitbxx		4. Number of billed visits made on same or different days: Same day billings count as one when *noprof* is the same. If *noprof* is different for a same day billing, the number of visits is equal to the number of unique *noprof* values for that day.
cadmxx ***typshrtxx***		5. a) Count the number of discharges from hospital (*dtsort*); b) Where ***cadm***>0, count the occurrences of *typeta*=1 or 4 (Short stay in public or private hospital).
	Database	BENTOT; billing, med-echo
	Variable	PID in BENTOT; cdiag, cacte and dacte in billing; dtadm, and diaprin in med-echo.
History of Injuries	**Definition**	Count the number of injuries a patient has suffered during the **washout**. Names, Procedure Codes, ICD codes and E codes are listed in *Appendix 3.1.3*, sections *a* to *c*. The types of injuries examined are: a) Fractures; b) Soft-Tissue Injuries; c) Falls and Other Accidents.
SPECIFIC TO:		Search for all injuries matching those listed in *Appendix 3.1.3 a)* and *b)*. Record only the first injury, unless the next same injury occurs at least 30 days later. Continue searching until the end of the **washout** period. Repeat the procedure for *varb* (*cdiag, dacte*), *varm* (*diaprin, dtadm*) and *varc* (*cacte, dacte*).
• **Fractures:** ***fhipb,fhibm,fhipc*** ***fmspb,fmspm,fmspc*** ***fmnfb,fmnfm,fmnfc*** ***fanyb,fanym,fanyc*** • **Any Injury:** ***injanyb ,injanym, injanyc***		See *Appendix 3.1.3.a)* for the list of codes: Use ICD9 codes for *cdiag* and *diaprin* (excluding *diasec1-diasec8*) and Procedure code for *cacte*. See *Appendix 3.1.3.b)* for the list of codes: Use ICD9 codes for *cdiag* and *diaprin* (excluding *diasec1-diasec8*) and Procedure code for *cacte*.
Storage		Save all newly created variables in BENTOT.

Appendix 3.1.1: Drugs That Influence Risk of Injury

Variable Name	Drug Class	AHF Class	Drug Name	Code dénom.	DIN
			Thiazides		
thiarx	*Thiazide Diuretics*	402800	Hydrochlorothiazide	04537	
	Potassium Sparing Diuretics	402810	Amiloride/Hydro	41772	
			Spironolactone/Hydro	38158	
			Triamterene/Hydro	38197	
			Estrogens		
estrorx, estrosb	*Oral Contraceptive*	681200	Ethinyl Estradiol	45447	
	Estrogens	681600	Chlorotrianisene	NA	017965, 017973
			Estradiol (17-beta)	34232	
			Esterified Estrogens	43072	
			Estradiol Valerate	45022	
			Conjugated Estrogens (natural)	45582	
			Conjugated Estrogens (synthetic)	45583	
			Estrone (piperazino-sulfate)	47031	
			Psychotropics		
psydeprx,psydepsb	*Antidepressants*	281604	amitriptyline, amoxapine, clomipramine, desipramine, doxepine, fluoxetine, fluvoxamine, imipramine, maprotiline, moclobemide, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine		
psytrarx,psytrasb	*Anti-psychotics*	281608	chlorpromazine, flupenthixol, fluphenazine, fluspirilene, haloperidol, loxapine, mesoridazine, pericyazine, perphenazine, pimozide, pipotiazine, prochlorperazine, promazine, thioproperazine, thioridazine, thiothixene, trifluoperazine		
psysedrx,psysedsb	*Misc. Anxiolytics Sedatives & Hypnotics*	282492	Buspirone, chloral, hydroxyzine, methotrimeprazine, promethazine		
psymisrx, psymissb	*Misc. Psychotropics*	282800	lithium, l-tryptophan		
			Drugs Altering Motor Stability		
motcarrx,motcarsb	*Cardiac Drugs*	240400	acebutolol, amiodarone, atenolol, digitoxine, digoxine, diltiazem, disopyramide, flecainide, metoprolol, mexiletine, nadolol, nicardipine, nifedipine, pindolol, procainamide, propafenone, propanolol, quinidine, sotalol, timolol, tocainide, verapamil		
mothyprx,mothypsb	*Anti-hypertensive Agents*	240800	amlodipine, benazepril, captopril, cilazapril, clonidine, diazoxide, doxazosine, enalapril, felodipine, fosinopril, guanethidine, hydralazine, indapamide, labetalol, lisinopril, methyldopa, minoxidil, oxprenolol, pindolol, prazosin, quinaprel, reserpine, terazosine		
motdilrx,motdilsb	*Vasodilating Agents*	241200	isosorbide dinitrate, nitroglycerin		
motopirx,motopisb	*Opiate Agonists*	280808	anileridine, codeine, hydromorphone, levorphanol, meperidine, morphine, opium, oxycodone, oxymorphine		
motpoprx,motpopsb	*Opiate Partial Agonists*	280812	pentazoine		
motdiurx,motdiusb	*Diuretics (excluding Hydrochlorothiazide)*	402800	bendroflumethiazide, ethacrynate sodium, enthacrynic acid, furosemide, indapamide, methyclothiazide, metolazone	**not** 04537	

Appendix 3.1.2: Disabilities or Impairment due to Illness

	Diagnostic Codes			Drug Rx	
	cdiag (billing)	diaprin (med-echo)	cacte (billing)	ahf class (rx)	cdenom (rx)
Visual Impairment ***visbil, vismed*** ***visrx***	360 to 379			522000	
Stroke ***strokbil, strokmed***	430[2], 431[2], 434[2], 436[2] 432, 433, 435, 437, 438				
Neurological Disorders ***neubil, neumed*** ***neurx***	290[2], 294, 331 to 337, 340-342, 344				18426,34323,34466, 03744,06747,06734, 08138,45544,09828, 37651,05226,41824, 33829
Arthritis or lower extremity instability ***arthbil1, arthmed***	710 to 725, 726.1 726.5, 726.6, 726.7,727, 274, 728, 729, 730,733.1-733.9				
arthbil2 • *hip arthroscopy and arthroplasty* • *knee arthroscopy and arthroplasty*			2419,2753,2759,2760 2297,2333,2335,2338,2342, 2415,2416,2417,2480,2613, 2614,2615,2617,2644 2146,2147,2148,2149, 2150,2151,2577,2724,2814, 2815,2832,2837,2838,2881, 9538, 2400, 2401,2402, 2403,2442,2465,2491,2492, 2493,2497,2498,2499		
Osteoporosis ***ostebil, osteomed***	733.0, 731.0				
Other Conditions *othbil, othmed*	737.1-737.3, 737.9, 738.3, 738.4, 739.1-739.3, 739.5, 739.8, 805.2, 805.4, 805.8, 840.4, 840.6, 840.9, 842.0, 842.1, 844.0, 844.1, 844.2, 844.9, 845 0, 845.1, 846.0, 846.1, 847.0, 847.2, 847.9, 848.3, 848.9, 879.8 908.9 919.0, 919.6, 921.0, 923.1, 924.1, 924.4, 924.8, 924.9, 927.3, 928.3, 929.9, 948.0, 949.0, 959.0, 959.9, 991.9, 995.2, 995.8				
Depression ***depbil, depmed***	311, 298.0, 296.2, 296.3, 309.1, 300.0-300.4				
Alcohol Abuse/Dep ***alcobil, alcomed***	303, 291, 305.0, 535.3, 571.0-571.3, 265.2,425.5				
Drug Abuse/Dep. ***drugbil, drugmed***	304, 305.1-305.9, 292				
Seizure Disorders ***seizbil, seizmed*** ***seizrx***	345, 780.3			281204 281292 281212 281220	

[2] Included in Charlson Comorbidity Index.

Appendix 3.1.3: Injuries due to Fractures and Soft-Tissue Injuries

Variable name	Category of Injury	RAMQ Procedure Code (cacte)	ICD9 CODE[3] (cdiag, diaprin)
A. fhipb,fhibm,fhipc	Fracture - hip	2675, 2695, 2715, 2716, 2714, 2739, 2740, 2742,	820
A. fmspb,fmspm,fmspc	Fracture -upper extremities	2559, 2532, 2537, 2531, 2534, 2536, 2590, 2605, 2630, 2591, 2606, 2631, 2655, 2592, 2607, 2632, 2593, 2608, 2633, 2594, 2609, 2640, 2634, 2641, 2610, 2635, 2595, 2612, 2636, 2624, 2649, 2569, 2570, 2571, 2585, 2586, 2587, 2588, 2589, 2599, 2645, 2651, 2652, 2653, 2654, 2735, 2736, 2768, 2769, 2770, 2604, 2618, 2642, 2611, 2620, 2643, 2600, 2621, 2616, 2601, 2622, 2627, 2646, 2602, 2623, 2647, 2603, 2626, 2648, 2896, 2820, 2823	810, 811, 812, 813, 814, 815, 816, 817, 818, 819
A. fmnfb,fmnfm,fmnfc	Fracture - lower extremities	2660, 2667, 2673, 9589, 9590,9549, 2683, 2705, 2725, 2681, 2694, 2696, 9591, 9592, 2721, 2743, 2693, 2708, 2727, 9542, 2886, 2887, 2684, 2686, 2687, 2710, 2730, 2734, 2744, 2685, 2709, 2729, 2688, 2689, 2711, 2731, 2732, 2690, 2712, 2733, 2848	821, 822, 823, 824, 825, 826, 827, 828
A. fanyb,fanym,fanyc	Fracture (any)	any of the above fracture RAMQ codes plus 2863, 2800, 2512, 7500, 7501, 7502, 7503, 7504, 7505, 7506, 7507, 2505, 2509, 2520, 2521, 2517, 2523, 2524, 2502, 2508, 2515, 2516, 2518, 2506, 2511, 2507, 2513, 2514, 2522, 7379, 2539, 2533, 2535, 2540, 2578, 2581, 2584, 2579, 2583, 2771, 2772, 2773	800, 801, 802, 803, 804, 807, 808, 809, 829
B. injanyb,injanym, injanyc	any injury	any of the above RAMQ fracture codes plus 2745, 2757, 2545, 2548, 2546, 2549, 2544, 2547, 2824, 2662, 2668, 2657, 2666, 2671, 2664, 2670, 2663, 2669, 2677, 2678, 2679, 2737, 2738, 2749, 2761, 2751, 2888, 2752, 2765, 2764, 2754, 2766, 2756, 2767, 2676, 2567, 2572, 1320, 1323, 1322, 1325, 1326, 1327, 5327, 5328, 7386, 7387, 7403	835, 831, 832, 834, 833, 836, 837, 838, 839, 871.0, 871.1, 871.2, 871.3, 871.4, 871.9, 872, 873, 874, 875, 876, 877, 880, 881, 882, 883, 884, 890, 891, 892, 893, 894, 870.0, 870.1, 870.2, 870.3, 870.8, 870.9

[3] REMINDER: After review of ICD-9 codes for principal diagnosis (*diaprin*) in MED-ECHO, it was found that records may have been missed because some codes contain alphanumeric characters beyond the 4-digit definition. The rule now is to take the first 4 digits and ignore the rest of the field.

BENZODIAZEPINE II - Time-Dependent Exposure

Eligible Subjects	**Definition**	Eligible subjects have PID stored in BENTOT (created from document BZCOHORT.DOC).
	Databases	BENTOT, RX, DEMOPT, MED-ECHO, Billing , DEMOMD
	Variables	Extract from the following databases, the variables required for the project. BENTOT: *pid* - original alpha-numeric subject ID *npid* – revised numeric subject ID number RX: • Drug identification as per *Appendix 3.2.1*: *codeahf* – AHF drug class code *cdenom* – Common name code of AHF drug class • Definition of covariate change of state, recommended dosage rates as per *Appendix 3.2.3*, and physician identification: *dateserv* – Date of prescription *qntymed* – Quantity of drug supplied[4] *duretr* – Duration of treatment in days *dosemed* – Dosage code associated to drug weight (or strength), usually expressed as mg/unit (*e.g.* code *xxx* = 15 mg/tablet)[5] *noprof* – Prescribing physician identification *codespc1-codespc5* – Special consideration code, in particular level ="B" Loss to follow-up *(lfu)* characterization: Residence Status (DEMOPT): *regclsxx*, *xx*=91 to 94 - Code of Region 01*yyy* to 18*yyy* *codepxx*, *xx*=91 to 94 - First 3 digits of postal code Death (DEMOPT): *dod* – Death date Placement to Nursing Home (MED-ECHO, Billing): - MED-ECHO: *dtsort* – Discharge date *typede* – Discharge destination codes 03,06,08,10,12,14,15 - Billing: *dacte* – Medical procedure date *noetabl* – Establishment code 0xxx4, 0xxx5,1xxx5, 2xxx5
Time-Dependent Exposure	**Definition**	The characterization of an eligible subject's use of benzodiazepines during the study period including start and end dates, dosages, number of physicians, their ID and hospitalization. All eligible subjects are enumerated with the variable *npid*. The end of the study period is set at 1826 days beginning from January 1, 1990 (Day 1) to December 31, 1994 (Day 1826). Day 0 begins on December 31, 1989 to generate the very first subject starting date. The study period is interrupted at a date earlier than 1826 if the subject is lost to follow-up during the study period for one of following reasons: 1. Death 2. Placement in a nursing home or long-term care facility 3. Migration (set to mid-year 1991 to 1994) Migration has only year information, so that migration date is set to mid-year. Examination of the demographic database by RDB shows some ambiguities between death of subject and year of departure. Subjects alive (about 4500 out of 489,226) and having left pose no problem. There is a small number of subjects who died but are coded as having left the province later (about 150). *Assuming that date of death is a more precise measurement of loss to follow-up than residence, combine both measures under the rule that if death occurs before departure, then loss is due to death, otherwise loss is due to departure* Throughout this document, arithmetic operations made on dates assume a **Julian format** *xxyyy*, where *xx* is the year 19*xx* and *yyy* is the day of the year. If the last three digits of the *xxyyy* represent a value less than 1 or greater than 366, then date is invalid.

[4] Scanning the RX database shows that *qntymed* from 1989 to 1991 have 2 decimal points and *qntymed* from 1992 to 1994 have 3 decimal points.

[5] In January 1997, Jimmy Fragos translated *dosemed* codes associated to all the existing Benzodiazepine prescriptions between 1989 and 1994. It was done manually by comparing the dosage strength code *(dosemed)* with the associated DIN dosage found in the RAMQ *Liste des médicaments* (any volume).

Time-Dependent Exposure		LIST OF APPENDICES *Appendix 3.2.1* lists the 13 types of Benzodiazepine drugs, clustered by their half-life activity (short, intermediate or long), main indication and identified by their *codeahf* and *cdenom*. Dosage rates are calculated based on recommended daily dosages given for adults (according to WHO). There is an intimate relationship between *Appendices 3.2.1* and *3.2.3*. *Appendix 3.2.2* illustrates a simplified counting process representation. *Appendix 3.2.3* describes the calculation of a daily dosage rate during the state of benzodiazepine use. See also *Appendix 3.2.1*. *Appendix 3.2.4* sets the rules to handle holes and overlaps of benzodiazepine drug prescriptions (also called Application of 3-day Rule). *Appendix 3.25* defines loss to follow-up (*lfu*) indicators and dates (*lfudt*) to be used against multiple records generated for time-dependent variables. *Appendix 3.2.6* Characterizes hospitalization indicator (for temporary censoring during the analyses). This compilation is to be done only after the generation of records for exposure, end of observation due to lfu (*lfudt*) and index of the record (*pindex*).
	PINDEX	Index of generated records (master record index).
Permanent Variables to Output -	NPID	New Patient Identification number (replaces old alphanumeric index)
	SDATE	Start date - Day of status change for which observation begins at day 0 (December 31, 1989). Values range from 0 to 1825 days, depending on the state of Benzodiazepine use. Each change of status generates a new record with new start and stop dates. See *Appendix 3.2.2* for Counting Process Representation and *Appendix 3.2.4* for application of 3-day rule.
	ENDDT	Stop date – Day of status change. Values range from 1 to 1826 days, the latter being the last day of observation because of end of study (December 31, 1994). A last stop date earlier than 1826 describes a subject lost to follow-up (LFU).
	LFU LFUDT	Loss to follow-up (0=at risk, 1=dead, 2=placement, 3=migration) and date of loss as per *Appendix 3.2.5*.
	HOSP	Hospitalization indicator (0=no, 1=yes) observed between time zero and *lfudt* - see *Appendix 3.2.6*.
	BZ1-BZ13	The state of Benzodiazepine drug use as per *Appendices 3.2.1* and *3.2.2* (0=no Rx, ≥1 Rx). Values greater than zero describes multiple prescriptions during a time interval ($sdate_i$, $enddt_i$)
	PBZ1-PBZ13	Dosage rates associated to status of BZx, x=1 to 13 – See *Appendix 3.2.3* for dosage rate calculations [if bzx=0 then pbzx=0, else pbzx>0].
NOTE:	Care is required on assigning values to SDATE and ENDDT. SDATE above is now defined as day 0= December 31, 1989 on the first record, so that first day of observation begins on January 1, 1990. See *Appendix 3.2.2* for further details.	
Initialization		Initialization of variables: *enddt=1826* *sdate=bz1=..=bz13=pbz1=..=0*
Record Generation	**Definition**	From this step onwards, examine drug use on all subjects. Each subject who never fills a prescription will consist of one record and each subject who fills a script will consist of at least two records. A record is generated at each valid drug prescription service date. Besides the proper identification of the drug of interest, dosage, duration, etc, another condition of validity is that the record have no "B" value in any of variables codespc1-5. According to database documentation, "B" means rebilling after payment was refused or cancelled. Begin observation at first subject record SDATE=0 and end observation at ENDDT ($t_0 <$ dateserv $\leq t_e$). *Appendix 3.2.2* illustrates the creation of multiple records.
Benzodiazepine Usage	**Definition**	Select dates of prescriptions and duration of treatment for the drugs listed in *Appendix 3.2.1*. Sort records in increasing order of service date, $t_0 <$ *dateserv* $< t_e$. Calculations are made for start and end dates, number of Rx by type (identified by one of the drug state vectors bzx), the relevant dosages, the number of different identified prescribing physicians. For a drug user, there is one necessary change of status: at a prescription date. Each change of status generates a new record, for any of the following reasons: 1. A non-renewal on same date as *dateserv+duretr*; 2. A renewal after or before *dateserv+duretr*; 3. A drug type change from bzx to bzy.

Change of Status	**Definition**	Generate a record based on Benzodiazepine activity between t_0 and t_n. It is difficult to state coherently and in a few lines the application of a counting process rule. Instead, a diagram is proposed in *Appendix 3.2.2.*
bz1-bz13		Indicate the state of drug use (0=use, ≥1 number of prescriptions) according to the diagram rules in *Appendix 3.2.2.*
Dosage	**Definition**	Daily dosage rates during Benzodiazepine activity
pbz1-pbz13		Calculate the Benzodiazepine dosage rate according to rules in *Appendix 3.2.3.*
Record Deletion	**Definition**	• Apply the three-day rule to delete records with short-term overlaps and absence of activity according to specifications stated in *Appendix 3.2.4.* • Assuming data is sorted by subject *sdate* and loss to follow-up indicator *lfu*>0, delete the *i+1* records until *lfudt* is between start dates record *i* and *i+1* ($sdate_i < lfudt <= sdate_{i+1}$) and assign *lfudt to enddt*$_i$. The variables *lfu* and *lfudt* are defined in *Appendix 3.2.5.*
Record Index	**Definition**	Index each record of the eligible subjects.
pindex		Sort in ascending order the variables *npid, enddt.* Assign to each record an index number *pindex.* The ordered index vector should range from 1 to the total number of records.
Record Addition	**Definition**	After record deletion (3-day rule and lfu) and creation of record index, generate new records to incorporate an indicator for hospitalization during the study period.
hosp		Hospitalization during time interval. See *Appendix 3.2.6* for instructions.
Storage	**Definition**	Output permanent variables listed in "Permanent Variables to Output". Because of the large number of variables, please output to the following files: 1. 3 variables (single subject records) associated with lfu (TDLFU): *npid, lfu, lfudt;* 2. 19 variables associated to exposure status (TDEXP): *pindex, npid, sdate, enddt, lfu, hosp, bz1-bz13;* 3. 14 variables associated to exposure dosage (TDDOSE) : *pindex, pbz1-pbz13;*

Appendix 3.2.1: List of Benzodiazepine Drugs

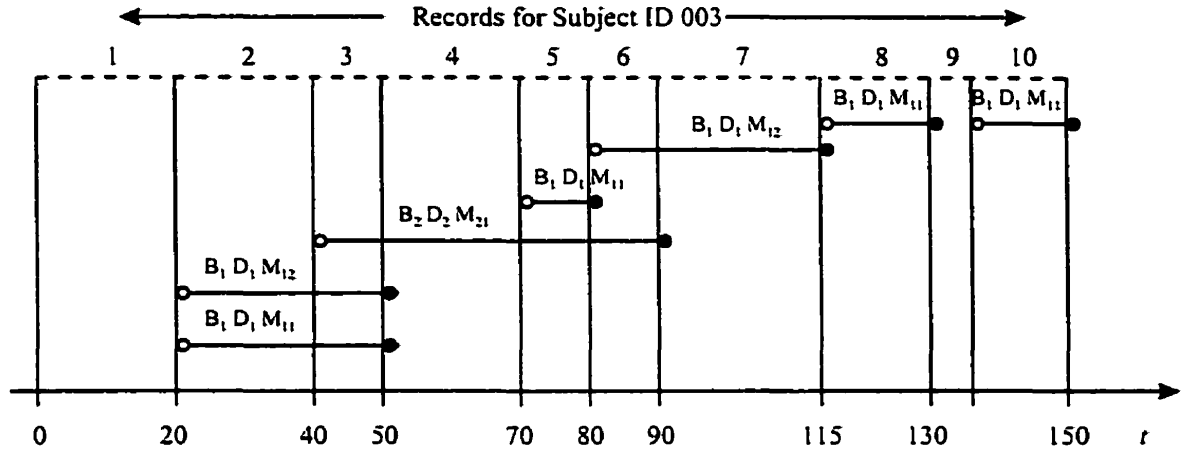
Benzodiazepine Drug					**Recommended Daily Dose (mg)**
Name	AHF Class *(codeahf)*	Common name *(cdenom)*	Half-life (hrs)	Therapeutic Category	Adult - WHO *(max1who)*
01 Triazolam	282408	39029	1.5-5.5	Hypnotic	0.25
02 Temazepam	282408	41590	8-24	Hypnotic	20.0
03 Nitrazepam	282408	42045	20-40	Hypnotic	5.0
04 Alprazolam	282408	43501	6-20	Sedative	1.0
05 Oxazepam	282408	06786	5-20	Sedative	50.0
06 Bromazepam	282408	43488	8-19	Sedative	10.0
07 Lorazepam	282408	37950	10-20	Sedative	2.5
08 Clonazepam	241208	37872	20-80	Anti-Conv.	8.0
09 Clobazam	281208	45591	10-46	Anti-Conv.	20.0
10 Flurazepam	282408	04095	40-100	Hypnotic	30.0
11 Chlordiazepoxide	282408	01807	10-30	Sedative	30.0
12 Diazepam	282408	02717	20-80	Sedative	10.0
13 Clorazepate[6]	282408	14768	30-100	Sedative	20.0

[6] Records with Clorazepate have detected use only in 1990.

Appendix 3.2.2: Illustration of a Simple Counting Process Representation

Initial start dates begin at zero. Each subject is represented by a set of observations: start time (t_0), an end time (t_1) represented by a risk interval $(t_0, t_1]$, open on the left and closed on the right with $(t_1-t_0)>0$.

A simplified illustration is the diagram below which describes a subject (ID 003) being observed from day 0 to 150, date at which subject dies (LFU=1). The diagram illustrates the counting process representation with two types of drugs (B_1 and B_2). To each drug type there is a drug dosage and a prescribing physician.



B_1: One of two drug types - D_1: Dosage rate of B_1 - M_{1j}: jth prescribing physician of B_1

The data set created from the diagram will look somewhat as follows:

Obs	Subject ID	Start *(sdate)*	Stop *(enddt)*	LFU	Drug Type Rx		Drug Dosage Rate	
					B_1	B_2	B_1	B_2
01	003	0	20	0	0	0	0	0
02	003	20	40	0	2	0	$2D_1$	0
03	003	40	50	0	2	1	$2D_1$	D_2
04	003	50	70	0	0	1	0	D_2
05	003	70	80	0	1	1	D_1	D_2
06	003	80	90	0	1	1	D_1	D_2
07	003	90	115	0	1	0	D_1	0
08	003	115	130	0	1	0	D_1	0
09	003	130	135	0	0	0	0	0
10	003	135	150	1	1	0	D_1	0

A new record is generated whenever there is a change in drug use activity. At each Rx date, record the number of drug prescriptions for the same type of drug, sum their dosage rates (*Appendix 3.2.3*). Handling of short-time renewals and non-renewals is explained in *Appendix 3.2.4*.

Appendix 3.2.3: Benzodiazepine Recommended Daily Dosage Rate

Consider the list of variables in *Appendix 3.2.1*:

codeahf - AHF class of drug;
cdenom - Drug subclass;
maxlwho - Recommended Daily Dosage from WHO (in mg);

Consider the variables in the pharmaceutical Rx Database:

qntymed – number of pills (drug quantity supplied[1]) ;
duretr - duration of treatment in days[2] ;
dosemed - dosage code to drug weight (or strength), usually expressed as mg/unit (*e.g.* code *xox* = 15 mg/tablet)[3] ;
codespc1-codespc5 – Special consideration code 1 to 5;

ASSUMPTION: Ignore drug prescriptions with any codespcx="B", x= 1 to 5.

When the relevant drug is selected from the list in *Appendix 3.2.1*, compute the daily recommended dosage rate (*pbzx*) for the subject. Let

$$nunits = qntymed / duretr$$

be the number of pills prescribed per day and let

$$proprec = dosemed / maxlwho$$

be the ratio of drug *x* dosage to recommended daily dosage (WHO). Dosages vary within *cdenom* and recommended dosages are fixed. Finally, the daily dosage rate associated to a drug type *x* is computed as follows:

$$pbzx = nunits * proprec$$

where *x* is one of the 13 benzodiazepine drugs under study. Only the variable *pbzx* is output to file.

For example, say a patient receives a prescription of 90 pills and the duration of treatment is 30 days. Suppose the recommended daily dosage is 1.0 mg per day (*e.g.* Alprazolam) and the drug dosage is 5 mg per tablet (decoded *dosemed*). The daily dosage rate is

$$pbz4 = (90 / 30) * (5 / 1.0) = 15.0$$

The above is an extreme example of how a drug prescription can far exceed the recommended daily dosage rate, which if appropriate, should have a value close to 1.

---

[1] The variable *qntymed* in the Rx database has 2 decimal points between 1989 and 1991, and 3 decimal points between 1992 and 1994.

[2] The Rx database is sometimes found to contain duration of treatment *duretr* > 181 and in very few cases *duretr* is missing. The following rule requires the additional use of the (corrected) variable *qntymed* when *duretr* > 181 days:

```
if duretr > 181 days then
        if duretr > qntymed
                duretr = qntymed
        endif
else if duretr = missing then
        duretr = qntymed
endif
```

[3] Jimmy Fragos translated *dosemed* codes associated to all the existing Benzodiazepine prescriptions between 1989 and 1994. It was done manually by comparing the dosage strength code *(dosemed)* with the associated DIN dosage found in the RAMQ *Liste des médicaments* (any volume).

Appendix 3.2.4: Application of Three Day Rule

The motivation for this rule is to remove records in which subjects fill their benzodiazepine prescriptions slightly early or slightly late. The first case produces an artificial overlap and the second an artificial period of non-usage. The application of a three-day rule will result in an appreciable reduction of records and will make data and statistical analyses more manageable. In this section, we assume a valid duration of treatment (i.e. manipulation of records with *duretr* > 181 - See *Appendix 3.2.3*).

The following three conditions must be respected before considering the removal of a record:

1. Start > 0
2. End < 1826
3. and LFU=0
4. Interval time = (End time - Start date) ≤ 3 days and previous record has detected Benzodiazepine activity.

A candidate record for removal must also satisfy the following two conditions:

1. No change from drug x to y from record i to record $i+1$: $bzx_i <> bzy_{i+1}$
2. No change in prescribing physician from one record to the next

Remove the records satisfying all of the above conditions and adjust the start and end times accordingly, such that the interval time has a unique covariate pattern. The following example attempts to illustrate the application of the three-day rule.
Suppose we have the following prescription renewal pattern for one subject (ID=45), with loss to follow-up (LFU=0), prior to the application of three-day rule. For simplicity, we assume that the drug type is the same in all 11 observations.

			Day		Interval	Rx frequency	
Observation	ID	LFU	Start	End	Time	Drug	MD
1	45	0	0	187	187	0	0
2	45	0	187	193	6	1	1
3	45	0	193	195	2	3	2
4	45	0	195	200	5	1	1
5	45	0	200	201	1	2	1
6	45	0	201	207	6	1	1
7	45	0	207	208	1	2	1
8	45	0	208	214	6	1	1
9	45	0	214	215	1	0	0
10	45	0	215	221	6	1	1
11	45	0	221	1826	1605	0	0

Application of the three-day rule requires that observations 5, 7 and 9 be removed from the data set. The covariate patterns for Drug and MD Rx frequencies (0,0),(1,1),(3,2),(1,1),(1,1),(1,1),(1,1),(0,0) are not unique.

			Day		Interval	Rx frequency	
Observation	ID	LFU	Start	End	Time	Drug	MD
1	45	0	0	187	187	0	0
2	45	0	187	193	6	1	1
3	45	0	193	195	2	3	2
4	45	0	195	200	5	1	1
5	45	0	200	207	7	1	1
6	45	0	207	214	7	1	1
7	45	0	214	221	7	1	1
8	45	0	221	1826	1605	0	0

Adjust the interval times such that covariate patterns between two adjacent observations are unique.

			Day		Interval	Rx frequency	
Observation	ID	LFU	Start	End	Time	Drug	MD
1	45	0	0	187	187	0	0
2	45	0	187	193	6	1	1
3	45	0	193	195	2	3	2
4	45	0	195	221	26	1	1
5	45	0	221	1826	1605	0	0

The number of observations is reduced from 11 to 5.

NOTE: This algorithm may not adequately handle all types of situations. In such case, the algorithm will be elaborated further.

Appendix 3.2.5: Definition of Censoring Indicator: Lost to Follow-Up

Initialize the following variables:
lfu=0, lfudt=1826, t_0=89365, t_n=94365, yrleft=0, yrevt=0

Define loss to follow-up *lfu* as
0= at risk,
1=death,
2=placement in a nursing home or long term care facility, and
3=migration (mid-year dates from 1991 to 1994).

Assume all dates are in Julian format. Match all subjects with death (*dod*), placement (*typede*) and/or migration dates (*regclsxx, codepxx*). Migration is given in year format only. If migration occurs on the same year as death or placement, then ignore migration. There are a small number of subjects who died but are coded as having left the province later (about 150). *Assuming that date of death is a more precise measurement of loss to follow-up than residence, combine both measures under the rule that if death occurs before departure, then loss is due to death, otherwise loss is due to departure.* If *lfu*=1 or 2, set *lfudt* to the number of days between event date and t_0. **If *lfu*=3, set *lfudt* to the number of days between the middle of the departure year and t_0.**

Use the following information to determine placement:

Match the first date occurrences *(dtsort, dacte)* to the associated Destination code *(typede)* or Establishment code *(noetabl)*.

Subject Institutionalization (MED-ECHO, Billing):

- MED-ECHO:
dtsort – Discharge date
typede – Discharge destination codes: 03,06,08,10,12,14,15

- Billing:
dacte – Medical procedure date
noetabl – Establishment code
0xxx4: Unité de longue durée (soins prolongés)
0xxx5: Unité de longue durée (hébergement)
1xxx5: Hébergement public
2xxx5: Hébergement privé

NOTE: There will certainly be discrepancies between placement dates found in MED-ECHO and RAMQ. In these cases, choose the earliest date.

Apply the following algorithm:

if placement then
lfu = 2; t_n = min(*dtsort,dacte*); *lfudt* = t_n-t_0; *yrevt* = int(t_n/1000);
else if death then
lfu = 1; t_n = *dod*; *lfudt* = t_n-t_0; *yrevt* = int(t_n/1000);
endif
for years xx=91 to 94;
if not(first letter of 3 digit postal code codepxx=G, H or J
and regclsxx>0) and *yrleft*=0 then *yrleft*=xx;
end for;
if (0 < *yrleft* < *yrevt*) or (*yrevt* = 0 and *yrleft* > 0) then
lfu = 3; t_n = *yrleft**1000+182; *lfudt* = t_n-t_0;
endif;

Keep the variables *lfu* and *lfudt* to stop observation of eligible subjects. Where *lfu* > 0, *lfudt* is assigned to *enddt* at the appropriate record.

Appendix 3.2.6: Illustration of Hospitalization Indicator to Insert into Exposure Records

Each record is represented by a time interval $(t_0, t_1]$ with $t_0 < t_1$. MED-ECHO dates are in YYMMDD format. For convenience, 0 <*lfudt*<=1826 is sometimes expressed as 89-12-31 < *lfudt* <= 94-12-31, where from starting date (t_0=0 is equivalent to calendar date 89-12-31 and t_n=1826 is equivalent to calendar date 94-12-31).

1. a) Use MED-ECHO variables *dtadm, dtsort* associated to eligible subjects. Sort hospital records by subject *dtadm*.

Original Hospital Dates			
Obs #	***npid***	***dtadm***	***dtsort***
1	003	89-12-27	90-01-02
2	003	90-04-01	90-04-01
3	003	90-04-02	90-04-11
4	003	90-04-11	90-04-16
5	003	90-04-30	90-05-02
6	003	90-05-05	90-05-11
7	003	90-05-28	90-05-29

b) Restrict observation to study period from t_0=0 (89-12-31) to t_n=*lfudt*=1826 (94-12-31) if *lfu*=0 else *lfudt*<1826 if *lfu*>0:

i) if *dtadm=dtsort* then *dtsort=dtsort*+1;
ii) if *dtadm* <89-12-31 and 89-12-31<*dtsort* <*lfudt*<=94-12-31 then *dtadm*=89-12-31 (t_0=0);
iii) if *dtsort>lfudt* and 90-01-01<*dtadm*<*lfudt*<=94-12-31 then *dtsort=lfudt*.

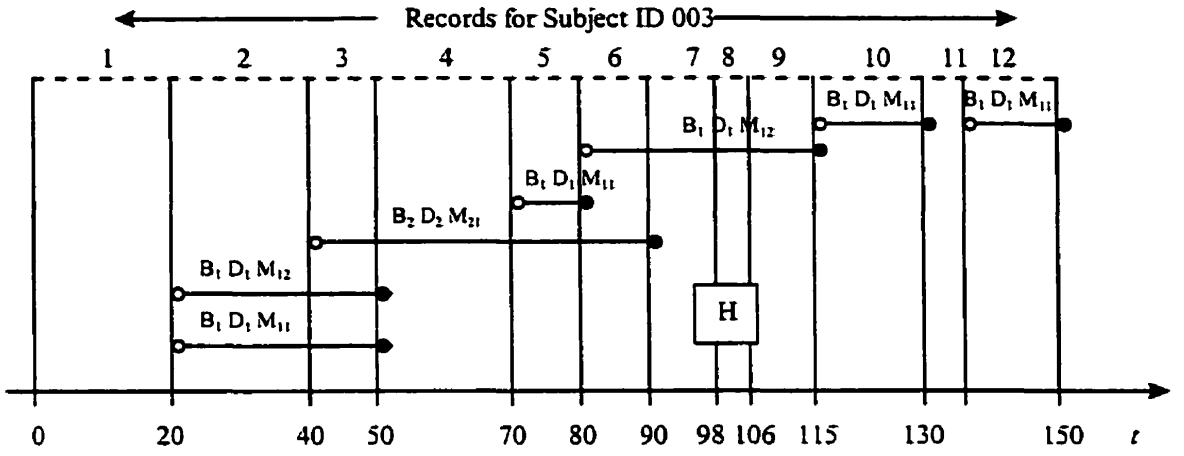
c) Create distinct non-overlapping and non-contiguous MED-ECHO time intervals:

Application of Rule 1b & c - Hospital dates						
Obs #	***npid***	***dtadm***	***dtsort***	**Start (t_0)**	**Stop (t_1)**	**t_1-t_0**
1	003	89-12-31	90-01-02	0	2	2
2	003	90-04-01	90-04-16	91	106	15
3	003	90-04-30	90-05-02	120	122	2
4	003	90-05-05	90-05-11	125	131	6
5	003	90-05-28	90-05-29	148	149	1

2. Add 7-day "grace" period to admission date: *dtadm7=dtadm*+7; if *dtadm7* >= *dtsort* then delete MED-ECHO record.

Application of Rule 2 - Hospital dates						
Obs #	***npid***	***dtadm***	***dtsort***	**Start (t_0)**	**Stop (t_1)**	**t_1-t_0**
1	003	90-04-08	90-04-16	98	106	8

3. Insert time intervals $[t_0,t_1]$ with hospital indicator (0=no, 1=yes) into multiple subject records shown below taken from illustration in Appendix 3.2.



Final results from application of Rule 3:

Record ID (*pindex*)	Subj. ID (*npid*)	Start (*sdate*)	Stop (*enddt*)	LFU	Drug Type Rx		Drug Dosage Rate		Hosp
					B_1	B_2	B_1	B_2	
01	003	0	20	0	0	0	0	0	0
02	003	20	40	0	1	0	$2D_1$	0	0
03	003	40	50	0	1	1	$2D_1$	D_2	0
04	003	50	70	0	0	1	0	D_2	0
05	003	70	80	0	1	1	D_1	D_2	0
06	003	80	90	0	1	1	D_1	D_2	0
07	003	90	98	0	1	0	D_1	0	0
07	003	98	106	0	1	0	D_1	0	1
07	003	106	115	0	1	0	D_1	0	0
08	003	115	130	0	1	0	D_1	0	0
09	003	130	135	0	0	0	0	0	0
10	003	135	150	1	1	0	D_1	0	0

An additional record is generated because of hospitalization, characterized by an indicator 1 under *hosp*. Record index (*pindex*) does not change value.

BENZODIAZEPINE III - Events

Eligible Subjects	**Definition**	Eligible subjects have PID stored in BENTOT.
	Database	BENTOT, Billing, MED-ECHO
	Variables	BENTOT: *pid* - original alpha-numeric subject ID *npid* – revised numeric subject ID number TDLFU: End of observation due to loss to follow up (*lfu, lfudt* - see TD covariates or exposure) Billing: *cdiag* - 4-digit ICD-9 diagnosis code *cacte* - RAMQ procedure code *dacte* - Date of cacte MED-ECHO: *dtadm* - Date of hospital admission *diaprin* - ICD-9 principal diagnosis code
Multiple Events	**Definition**	The events searched during the study period are the following: a) Fractures b) Any Fractures and/or Soft-Tissue Injuries *Appendix 3.3.1*, sections *a)* and *b)*, list the variable names, RAMQ procedure, and ICD-9 codes applicable to the injury interest. Output the dates associated to the injuries a patient has suffered during the study period, *according to the rules specified in this document.* **In each of the events described below, a 30-day window rule is applied from the first day an injury or an accident is detected during the study period.** The 30-day window rule applies to all variables, including *any. The study period begins Jan. 1, 1990 and ends on *lufdt*. If *lfu*=0 then *lfudt*=1826, else *lfudt*<1826.
30 DAY RULE		Match the first injury date *(dacte, dtadm)* of the study period to the earliest ICD-9 *(cdiag, diaprin)* or RAMQ procedure codes *(cacte)* listed in *Appendix 3.3.1*, sections *a)* and *b)*. Apply the following rule: 1. If the first event is ICD-9 and date < 90182, then search up to 6 months before for the associated procedure code *(Appendix 3.3.1)*. If found then ignore the selected event and select the next earliest ICD-9 or procedure injury code during the study period; Motivation: There appears to be a cluster of injuries at the beginning of the study period (during the first 30 days), causing a "dip" in the rates of first event occurrences (high early rates followed by a drop). It is possible that some of the detected injuries are in fact follow-ups which date back to the washout period. A further restriction is imposed but which will affect only the first injury detected in the first 6 months of the study period (see Rule 1).
• ***Fractures:*** ***Frahip1...n1*** ***Frasup1...n2 frainf1...n3*** ***fraany1...n4*** • ***Any Injury:*** ***Injany1... n5***		See *Appendix 3.3.1.a)* for the list of codes: ICD-9 *(cdiag, diaprin)* and RAMQ *(cacte)*. See *Appendix 3.3.1.b)* for the list of codes: ICD-9 *(cdiag, diaprin)* and RAMQ *(cacte)*.

Appendix 3.3.1: Injuries Due to Fractures and Soft-Tissue Injuries

Appendix 3.3.1.a: Fractures

Variable name	Category of Injury	RAMQ Procedure Code (cacte)	ICD-9 CODE* (cdiag, diaprin)
frahip1...n1	Fracture – hip	2675, 2695, 2715, 2716, 2714, 2739, 2740, 2742,	820
frasup1...n2	Fracture -upper extremities	2559, 2532, 2537, 2531, 2534, 2536, 2590, 2605, 2630, 2591, 2606, 2631, 2655, 2592, 2607, 2632, 2593, 2608, 2633, 2594, 2609, 2640, 2634, 2641, 2610, 2635, 2595, 2612, 2636, 2624, 2649, 2569, 2570, 2571, 2585, 2586, 2587, 2588, 2589, 2599, 2645, 2651, 2652, 2653, 2654, 2735, 2736, 2768, 2769, 2770, 2604, 2618, 2642, 2611, 2620, 2643, 2600, 2621, 2616, 2601, 2622, 2627, 2646, 2602, 2623, 2647, 2603, 2626, 2648, 2896, 2820, 2823	810, 811, 812, 813, 814, 815, 816, 817, 818, 819
frainf1...n3	Fracture - lower extremities	2660, 2667, 2673, 9589, 9590,9549, 2683, 2705, 2725, 2681, 2694, 2696, 9591, 9592, 2721, 2743, 2693, 2708, 2727, 9542, 2886, 2887, 2684, 2686, 2687, 2710, 2730, 2734, 2744, 2685, 2709, 2729, 2688, 2689, 2711, 2731, 2732, 2690, 2712, 2733, 2848	821, 822, 823, 824, 825, 826, 827, 828
fraany1...n4	Fracture (any)	Any of the above fractures RAMQ codes plus 2863, 2800[7], 2512, 7500, 7501, 7502, 7503, 7504, 7505, 7506, 7507, 2505, 2509, 2520, 2521, 2517, 2523, 2524, 2502, 2508, 2515, 2516, 2518, 2506, 2511, 2507, 2513, 2514, 2522, 7379, 2539, 2533, 2535, 2540, 2578, 2581, 2584, 2579, 2583, 2771, 2772, 2773	800–4, 807, 808, 809, 829

Appendix 3.3.1.b: Soft-Tissue Injuries

Variable name	Category of Injury	RAMQ Procedure Code (cacte)	ICD-9 CODE (cdiag, diaprin)
injany1...n5	any injury	any of the above RAMQ fracture codes plus 2745, 2757, 2545, 2548, 2546, 2549, 2544, 2547, 2824, 2662, 2668, 2657, 2666, 2671, 2664, 2670, 2663, 2669, 2677, 2678, 2679, 2737, 2738, 2749, 2761, 2751, 2888, 2752, 2765, 2764, 2754, 2766, 2756, 2767, 2676, 2567, 2572, 1320, 1323, 1322, 1325, 1326, 1327, 5327, 5328, 7386, 7387, 7403	835, 831, 832, 834, 833, 836, 837, 838, 839, 871.0, 871.1, 871.2, 871.3, 871.4, 871.9, 872, 873, 874, 875, 876, 877, 880, 881, 882, 883, 884, 890, 891, 892, 893, 894, 870.0, 870.1, 870.2, 870.3, 870.8, 870.9

* First three digits of 4-digit ICD9-code.

[7] Both procedure codes 2863 and 2800 define some form of immobilization.

Appendix IV

BENZODIAZEPINE EXPOSURE RECORDS FOR A SINGLE SUBJECT

Example of records for a single subject who had no periods of hospitalization >7 days and was followed until the end of the study on December 31, 1994 (Day 1826). The beginning of a record is indicated by "sdate" and the end of a record by "enddt" for days 0 - 1826. The different benzodiazepines are numbered from 1 - 13 (bz1-bz13) with the standardized dose for each prescription (pbz1-pbz13). The subject's fixed covariates were stored in separate files.

0bs	npid	pindex	sdate	enddt	hosp	oflu	pbz1	pbz2	pbz3	pbz4	pbz5	pbz6	pbz7	pbz8	pbz9	pbz10	pbz11	pbz12	pbz13
1	15	97	0	99	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
2	15	98	99	155	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
3	15	100	155	256	0	0	0	0	0	0	0.6	0	0	0	0	0	0.0	0	0	0	0	0	0
4	15	101	256	370	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
5	15	102	370	491	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
6	15	105	491	550	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
7	15	106	550	611	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
8	15	107	611	652	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
9	15	108	652	713	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
10	15	109	713	773	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
11	15	110	773	834	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
12	15	111	834	859	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
13	15	112	859	890	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
14	15	113	890	926	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
15	15	114	926	1014	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
16	15	119	1014	1030	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
17	15	120	1030	1061	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
18	15	122	1061	1133	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
19	15	125	1133	1158	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
20	15	126	1158	1189	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
21	15	127	1189	1211	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
22	15	128	1211	1270	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
23	15	132	1270	1306	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
24	15	134	1306	1350	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
25	15	135	1350	1374	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
26	15	136	1374	1405	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0
27	15	137	1405	1421	0	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0	0	0	0	0
28	15	138	1421	1826	0	0	0	0	0	0	0.0	0	0	0	0	1	0.5	0	0	0	0	0	0

Appendix V

ICD-9CODES FOR ILLNESSES, DISABILITIES OR IMPAIRMENTS DUE TO ILLNESS

Main Therapeutic Categories (Labeled Indications) for Benzodiazepine Use

Anxiety:

300.0 Anxiety States including anxiety state, unspecified; panic disorder; generalized anxiety disorder; other

300.2 Phobic Disorders including phobia unspecified; agoraphobia with and without panic attacks; social phobia; other isolated or simple phobias

308.0 Predominant disturbance of emotions as acute reaction to exceptional stress - including anxiety, emotional crisis, panic state

309.0 Brief depressive reaction

309.2 Adjustment Reaction with predominant disturbance of other emotions including separation anxiety disorder; adjustment reaction with anxious mood; adjustment reaction with mixed emotional features; other

Insomnia:

307.4 Specific disorders of sleep of nonorganic origin including transient and persistent disorder of initiating or maintaining sleep; transient or persistent disorder of initiating or maintaining wakefulness; phase-shift disruption of 24hour sleep-wake cycle; somnambulism or night terrors; repetitive intrusions of sleep; other

780.5 Sleep disturbances including unspecified; insomnia with sleep apnea; other insomnia; hypersomnia with sleep apnea; other hyprsomnia; disruptions of 24hour sleep-wake cycle; dysfunctions associated with sleep stages or arousal from sleep; other and unspecified sleep apnea; other

Seizure Disorders:

345 Epilepsy includes generalized nonconvulsive and convulsive epilepsy; petit mal status; grand mal status; partial epilepsy, with or without impairment of consciousness; epilepsia partialis continua; other forms of epilepsy; epilepsy, unspecified

780.3 Convulsions

Muscle Spasticity:

728.8 Other disorders of muscle, ligament, and fascia including interstitial myositis; foreign body granuloma of muscle; rupture of muscle, nontraumatic; diastasis of muscle; spasm of muscle

781.0 Abnormal involuntary movements including abnormal head movements; fasciculation; spasms NOS; tremor NOS

Alcohol Abuse/Dependence:

303 Alcohol Dependence Syndrome

305.0 Nondependent Abuse of Alcohol

291 Alcoholic Psychoses including alcohol withdrawal delirium; alcohol amnestic syndrome; other alcoholic dementia; alcohol withdrawal hallucinosis; idiosyncratic alcohol intoxication; alcoholic jealousy; other specified and unspecified alcoholic psychosis

265.2 Thiamine and niacin deficiency states - Pellagra (alcoholic)

425.5 Alcoholic cardiomyopathy

535.3 Alcoholic gastritis

571.0 Alcoholic fatty liver

571.1 Acute alcoholic hepatitis

571.2 Alcoholic cirrhosis of liver

571.3 Alcoholic liver damage, unspecified

Disabilities or Impairments due to Illness that may be Risk Factors for Falls

Alcohol Abuse/Dependence: see above

Depression:

311 Depressive disorder, not elsewhere classified
296.2 Major depressive disorder, single episode
296.3 Major depressive disorder, recurrent episode
298.0 Depressive type psychosis
309.1 Prolong depressive reaction
300.0 Anxiety States including anxiety state, unspecified; panic disorder; generalized anxiety disorder; other
300.2 Phobic Disorders including phobia unspecified; agoraphobia with and without panic attacks; social phobia; other isolated or simple phobias
300.3 Obsessive-compulsive disorders
300.4 Neurotic Depression including anxiety depression; depression with anxiety; depressive reaction; neurotic depressive state; reactive depression

Visual Impairment:

360 - 379 Disorders of the Eye and Adnexa

Stroke:

430 Subarachnoid hemorrhage
431 Intracerebral hemmorrhage
432 Other & unspecified intracranial hemorrhage including nontraumatic extradural hemorrhage; subdural hemorrhage; unspecified intracranial hemorrhage
433 Occlusion & stenosis of precerebral arteries including occlusion & stenosis of basilar artery; occlusion & stenosis of carotid artery; occlusion & stenosis of vertebral artery; occlusion & stenosis of multiple & bilateral precerebral arteries; occlusion & stenosis of other specified precerebral artery; occlusion & stenosis of unspecified precerebral artery
434 Occlusion of cerebral arteries including cerebral thrombosis; cerebral embolism; cerebral artery occlusion, unspecified
435 Transient cerebral ischemia, including basilar artery syndrome; vertebral artery syndrome; subclavian steal syndrome; other specified transient cerebral ischemias; unspecified transient cerebral ischemia
436 Acute, but ill-defined, cerebrovascular disease including apoplexy; cerebral seizure; cerebrovascular accident; stroke
437 Other & ill-defined cerebrovascular disease including cerebral atherosclerosis; other generalized ischemic cerebrovascular disease; hypertensive encephalopathy; cerebral aneurysm nonruptured; cerebral arteritis; moyamoya disease; nonpyogenic thrombosis of intracranial venous sinus; other ill-defined cerebrovascular disease; unspecified cerebrovascular disease
438 Late effects of cerebrovascular disease

Neurological Disorders:

290 Senile and presenile organic psychotic conditions including senile dementia, uncomplicated; presenile dementia; senile dementia with delusional or depressive features; senile dementia with delirium; arteriosclerotic dementia; other specified and unspecified senile psychotic condition
294 Other organic psychotic conditions (chronic) including amnestic syndrome; dementia in conditions classified elsewhere; other specified and unspecified organic brain syndromes (chronic)
331 Other cerebral degenerations including Alzheimer's disease; Pick's disease; senile degeneration of brain; communicating hydrocephalus; obstructive hydrocephalus; cerebral degeneration in diseases classified elsewhere; other cerebral degeneration; cerebral degeneration, unspecified
332 Parkinson's disease including paralysis agitans and secondary parkinsonism
333 Other extrapyramidal disease and abnormal movement disorders including other degenerative diseases of the basal ganglia; essential and other specified forms of tremor; myoclonus; tics of organic origin; Huntington's chorea; other choreas; idiopathic and symptomatic torsion dystonia; fragments of torsion

dystonia; organic writers' cramp; other and unspecified extrapyramidal diseases and abnormal movement disorders

334 Spinocerebellar disease including Friedreich's ataxia; hereditary spastic paraplegia; primary cerebellar degeneration; other cerebellar ataxia; cerebellar ataxia in diseases specified elsewhere; other and unspecified spinocerebellar diseases

335 Anterior horn cell disease including Werdnig-Hoffman disease; spinal muscular atrophy; motor nueron disease; other and unspecified anterior horn disease

336 Other diseases of spinal cord; syringomyelia & syringobulbia; vascular myelopathies; subacute combined degeneration of spinal cord in diseases classified elsewhere; myelopathy in other diseases classified elsewhere; other myelopathy; unspecified disease of spinal cord

337 Disorders of the autonomic nervous system; idiopathic peripheral autonomic neuropathy; peripheral autonomic neuropathy in disorders classified elsewhere; unspecified disorder of autonomic nervous system

340 Multiple sclerosis

341 Other demyelinating diseases of central nervous system; neuromyelitis optica; schilder's disease; other demyelinating diseases of central nervous system; demyelinating disease of central nervous system, unspecified

342 Hemiplegia; flaccid hemiplegia; spastic hemiplegia; hemiplegia, unspecified

344 Other paralytic syndromes; quadriplegia; paraplegia; diplegia of upper limbs; monoplegia of lower limb; monoplegia of upper limb; unspecified monoplegia; cauda equina syndrome; other specified paralytic syndromes; paralysis, unspecified

Arthritis And Other Rhumatological Disorders:

274 Gout including gouty arthropathy; gouty nephropathy; gout with other specified manifestations; gout unspecified

710-9 Arthropathies and related disorders including diffuse diseases of connective tissue; arthropathy associated with infections; crystal arthropathies; arthropathy associated with other disorders classified elsewhere; rheumatoid arthritis and other inflammatory polyarthropathies; osteoarthrosis and allied disorders; other and unspecified arthropathies; internal derangement of knee; other derangement of joint; other and unspecified disorders of joint

720 Ankylosing spondylitis & other inflammatory spondylopathies; ankylosing spondylitis; spinal enthesopathy; sacroiliitis, not elsewhere classified; other inflammatory spondylopathies; unspecified inflammatory spondylopathy

721 Spondylosis & allied disorders; cervical spondylosis without myelopathy; cervical spondylosis with myelopathy; thoracic spondylosis without myelopathy; lumbosacral spondylosis without myelopathy; thoracic or lumbar spondylosis with myelopathy; kissing spine; ankylosing vertebral hyperostosis; traumatic spondylopathy; other allied disorders of spine; spondylosis of unspecified site

722 Intervertebral disc disorders; displacement of cervical intervertebral disc without myelopathy; displacement of thoracic or lumbar intervertebral disc without myelopathy; displacement of intervertebral disc, site unspecified, without myelopathy; schmorl's nodes; degeneration of cervical intervertebral disc; degeneration of thoracic or lumbar intervertebral disc; degeneration of intervertebral disc, site unspecified; intervertebral disc disorder with myelopathy; postlaminectomy syndrome; other & unspecified disc disorder

723 Other disorders of cervical region; spinal stenosis in cervical region; cervicalgia; cervicocranial syndrome; cervicobrachial syndrome (diffuse); brachial neuritis or radiculitis nos; torticollis, unspecified; panniculitis specified as affecting neck; ossification of posterior longitudinal ligament in cervical region; other syndromes affecting cervical region; unspecified musculoskeletal disorders & symptoms referable to neck

724 Other and unspecified disorders of back

725 Polymyalgia rheumatica,

726.1 Rotator cuff syndrome of shoulder and allied disorders

726.5 Enthesopathy of hip region

726.6 Enthesopathy of the knee

726.7 Enthesopathy of ankle and tarsus

727 Other disorders of synovium, tendon, & bursa; synovitis & tenosynovitis; bunion; specific bursitides often of occupational origin; other bursitis disorders; ganglion & cyst of synovium, tendon, & bursa; rupture of synovium; rupture of tendon nontraumatic; other disorders of synovium, tendon, & bursa; unspecified disorder of synovium, tendon, & bursa

728 Disorders of muscle, ligament, & fascia; infective myositis; muscular calcification & ossification; muscular wasting & disuse atrophy, not elsewhere classified; other specific muscle disorders; laxity of ligament; hypermobility syndrome; contracture of palmar fascia; other fibromatoses of muscle, ligament, & fascia; other disorders of muscle, ligament, & fascia; unspecified disorder of muscle, ligament, & fascia

729 Other disorders of soft tissues; rheumatism, unspecified & fibrositis; myalgia & myositis, unspecified; neuralgia, neuritis, & radiculitis, unspecified; panniculitis, unspecified
fasciitis, unspecified; pain in limb; residual foreign body in soft tissue; other musculoskeletal symptoms referable to limbs; other & unspecified disorders of soft tissue

730 Osteomyelitis, periostitis, & other infections involving bone; acute osteomyelitis; chronic osteomyelitis; unspecified osteomyelitis; periostitis without mention of osteomyelitis; osteopathy resulting from poliomyelitis; other infections involving bone in diseases classified elsewhere; unspecified infection of bone

733 Other disorders of bone & cartilage; pathological fracture; cyst of bone; hyperostosis of skull; aseptic necrosis of bone; osteitis condensans; tietze's disease;
algoneurodystrophy; malunion & nonunion of fracture; other & unspecified disorders of bone & cartilage

Osteoporosis:

731.0 Osteitis deformans without mention of bone tumour

733.0 Osteoporosis

Drug Abuse/Dependence:

292 Drug psychoses including drug withdrawal syndrome; paranoid and/or hallucinatory states induced by drugs; pathological drug intoxication; other specified and unspecified drug induced mental disorders

304 Drug Dependence including opioid type dependence; barbiturate and similarly acting sedative or hypnotic dependence; cocaine dependence; cannabis dependence; amphetamine and other psychostimulant dependence; hallucinogen dependence; other specified and unspecified drug dependence; combination of drugs with or without opioid type

305.1-.9 Nondependent abuse of drugs including tobacco use disorder; cannabis abuse; hallucinogen abuse; amphetamine or related acting sympatheomimetic abuse; antidepressant type abuse; other; mixed or unspecified drug abuse

Other Conditions (not included in definitions of Injuries):

737.1 Kyphosis (acquired)

737.2 Lordosis (acquired)

737.3 Scoliosis

737.9 Kyphosis/scoliosis; unspecified

738.3 Acquired deformity; chest/rib

738.4 Degenerative spondylolisthesis

739.1 Somatic dysfunction; cervical region

739.2 Somatic dysfunction; thoracic region

739.3 Somatic dysfunction; lumbar region

739.5 Somatic dysfunction; pelvic region

739.8 Somatic dysfunction; rib cage

805.2 Fracture: dorsal; thoracic; closed

805.4 Fracture: Lumbar; closed

805.8 Fracture: vertebral; closed; unspecified

840.4 Sprain/strain: shoulder; rotator cuff

840.6 Sprain/strain: supraspinatus
840.9 Sprain/strain: shoulder and upper arm; unspecified
842.0 Sprain/strain: wrist; unspecified
842.0 Sprain/strain: wrist; carpal
842.1 Sprain/strain: hand; unspecified
844.0 Sprain/strain: knee; lateral collat.ligament
844.1 Sprain/strain: knee; medial collat.ligament
844.2 Sprain/strain: knee; cruciate ligament
844.9 Sprain/strain: knee/leg; unspecified
845.0 Sprain/strain: ankle; unspecified
845.0 Sprain/strain: ankle; deltoid ligament
845.1 Sprain/strain: foot; unspecified
846.0 Sprain/strain: lumbosacral ligament
846.1 Sprain/strain: sacroiliac ligament
847.0 Sprain/strain: neck
847.2 Sprain: lumbar
847.9 Sprain/strain: vertebral; unspecified
848.3 Sprain/strain: ribs
848.9 Sprain/strain: other site; unspecified
87 9.8 Open wound; head/neck/trunk; unspecified; w/o complication
908.9 Late effects of injury; unspecified
919.0 Abrasion; unspecified
919.6 Foreign body; skin; superficial; unspecified
921.0 Contusion; black eye
923.1 Contusion; upper limb; elbow
924.1 Contusion; knee
924.4 Contusion; multiple sites; lower limb
924.8 Contusion; multiple sites; no classified
924.9 Contusion; unspecified
927.3 Crushing injury; fingers
928.3 Crushing injury; toe
929.9 Crushing injury; unspecified
948.0 Burns; <10% body surface
949.0 Burn; degree unspecified
959.0 Head injury; NOS
959.9 Other trauma; unspecified
991.9 Cold injury; unspecified
995.2 Medication; adverse effects; unspecified
995.8 Adult physical abuse

Appendix VI

ICD-9 CODES FOR CHARLSON COMORBIDITY INDEX

Diagnostic Category	ICD-9 Codes	Description
Myocardial infarction	410-410.9	Acute myocardial infarction
	412	Old myocardial infarction
Congestive heart failure	428-428.9	Heart failure
Peripheral vascular disease	443.9	Peripheral vascular disease
	441.4-441.9	Aortic aneurysm
	785.4	Gangrene
	V43.4	Blood vessel replaced by prosthesis
	38.48	Resection and replacement of lower limb arteries
Cerebrovascular disease	430-438	Cerebrovascular disease
Dementia	290-290.9	Senile and presenile dementia
Chronic pulmonary disease	490-496	Chronic obstructive pulmonary disease
	500-505	Pneumoconioses
	506.4	Chronic respiratory conditions due to fumes and vapors
Rheumatologic disease	710.0	Systemic lupus erythematosus
	710.1	Systemic sclerosis
	710.4	Polymyositis
	714.0-714.2	Adult rheumatoid arthritis
	714.81	Rheumatoid lung
	725	Polymyalgia rheumatica
Peptic ulcer disease	531-534.9	Gastric, duodenal and gastrojejunal ulcers
	531.4-531.7	Chronic forms of peptic ulcer disease
	532.4-532.7	
	533.4-533.7	
	534.4-534.7	
Mild liver disease	571.2	Alcoholic cirrhosis
	571.5	Cirrhosis without mention of alcohol
	571.6	Biliary cirrhosis
	571.4-571.49	Chronic hepatitis
Diabetes	250-250.3	Diabetes with or without acute metabolic disturbances
	250.7	Diabetes with peripheral circulatory disorders
Diabetes with chronic complications	250.4-250.6	Diabetes with renal, ophthalmic, or neurological manifestations
Hemiplegia or paraplegia	344.1	Paraplegia
	342-342.9	Hemiplegia
Renal disease	582-582.9	Chronic glomerulonephritis
	583-583.7	Nephritis and nephropathy
	585	Chronic renal failure
	586	Renal failure, unspecified
	588-588.9	Disorders resulting from impaired renal function
Any malignancy, including leukemia and lymphoma	140-172.9	Malignant neoplasms
	174-195.8	Malignant neoplasms
	200-208.9	Leukemia and lymphoma
Moderate or severe liver disease	572.2-572.8	Hepatic coma, portal hypertension, other sequella of chronic liver disease
	456.0-456.21	Esophageal varices
Metastatic solid tumor	196-199.1	Secondary malignant neoplasm of lymph nodes and other organs
AIDS	042-044.9	HIV infection with related specified conditions

Injury Type	Billing Claims Procedure Codes	ICD-9 Diagnostic Codes
Fracture - hip	2675=hip fracture (neck or intertrochanteric) without reduction, with immobilization. 2695=hip fracture (neck or intertrochanteric) closed reduction 2715=hip fracture (neck or intertrochanteric), open reduction, nail only 2716=hip fracture (neck or intertrochanteric), nail and plate 2714=hip fracture (neck or intertrochanteric), Judet's pedicle graft, etc. 2739=hip fracture (neck or intertrochanteric), neck or per trochanter, open reduction and osteotomy 2740=hip fracture (neck or intertrochanteric), prosthetic replacement of head 2742=hip fracture (neck or intertrochanteric), subtrochanteric, open reduction	820=fracture of the neck of femur
Fracture - upper extremity	Fracture of any of the following: the scapula/clavicle, humerus, ulna/radius, carpal, hand	818: ill defined fractures of upper limb. 819: multiple fractures involving both upper limbs
scapula/clavicle	2532=clavicle fracture, simple immobilization, patient over 16 years of age 2537=clavicle fracture, open reduction 2531=clavicle fracture, scapula, without reduction, with immobilization 2534=clavicle fracture, scapula, closed reduction 2536=clavicle fracture, scapula, open reduction, neck 2559=clavicle fracture, simple immobilization	810=fracture of clavicle 811=fracture of scapula
humerus	2590=surgical neck without dislocation of head, without reduction, with immobilization, shoulder 2605=surgical neck without dislocation of head, closed reduction, shoulder 2630=surgical neck without dislocation of head, open reduction, shoulder 2591=surgical neck with dislocation of head, without reduction, with immobilization, shoulder 2606=surgical neck with dislocation of head, closed reduction, shoulder 2631=surgical neck with dislocation of head, open reduction, shoulder 2655=surgical neck with dislocation of head, open reduction with prosthetic replacement of humeral head, shoulder 2592=lesser tuberosity of humerus – greater tuberosity of humerus, without reduction, with immobilization 2607=lesser tuberosity of humerus – greater tuberosity of humerus, closed reduction 2632=lesser tuberosity of humerus – greater tuberosity of humerus, open reduction 2593=diaphysis, without reduction, with immobilization, humerus 2608=diaphysis, closed reduction, humerus 2633=diaphysis, open reduction, humerus 2594=above or through condyle, without reduction, with immobilization 2609=above or through condyle, closed reduction 2640=above or through condyle, closed reduction and percutaneous fixation 2634=above or through condyle, open reduction 2641=condyle, trochlea, epicondyle, epitrochlea, without reduction, with immobilization 2610=condyle, trochlea, epicondyle, epitrochlea, closed reduction 2635=condyle, trochlea, epicondyle, epitrochlea, open reduction	812=fracture of humerus
carpal/hand	2604=carpus (one or more bones, except scaphoid, semilunar), without reduction, with imm. 2618=carpus (one or more bones, excepting scaphoid and semilunar), closed reduction 2642=carpus (one or more bones, excepting scaphoid and semilunar), open reduction 2611=scaphoid, semilunar, without reduction, with immobilization 2620=scaphoid, semilunar, closed reduction 2643=scaphoid, semilunar, open reduction 2600=metacarpal, without reduction one or more, with immobilization 2621=metacarpal, closed reduction, one or more 2616=metacarpal, open reduction, or closed reduction with pin fixation 2601=Bennett's fracture, without reduction, with immobilization 2622=Bennett's fracture, closed reduction 2627=Bennett's fracture, closed reduction with pin fixation 2646=Bennett's fracture, open reduction 2602=proximal and/or middle phalanx (P1-P2), without reduction, with immobilization 2623=proximal and/or middle phalanx (P1-P2), closed reduction, each additional, same hand 2647=proximal and/or middle phalanx (P1-P2), open reduction 2603=distal phalanx (P3), without reduction, with immobilization 2626=distal phalanx (P3), closed reduction 2648=distal phalanx (P3), open reduction 2896=repair of distal interphalangeal articulation, reinsertion of tendon and/or percutaneous pinning 2820=immobilization with plaster cast, splints or taping, extremities, finger 2823=immobilization with plaster cast, splints or taping, extremities, hand	814=fracture of carpal bone(s) 815=fracture of metacarpal bone(s) 816=fracture of one or more phalanges of hand 817=multiple fractures of hand bones

ulna/radius	2595=olecranon, without reduction, with immobilization 2612=olecranon, closed reduction 2636=olecranon, open reduction 2624=Monteggia's fracture, closed reduction 2649=Monteggia's fracture, open reduction 2569=diaphysis, coronoid apophysis, without reduction, with immobilization, humerus 2570=diaphysis, coronoid apophysis, closed reduction, humerus 2571=diaphysis, coronoid apophysis, open reduction, humerus 2585=fracture-ulna only, without reduction, with immobilization 2586=fracture –ulna only, closed reduction 2587=fracture-ulna only, open reduction 2588=fracture-radius only, without reduction, with immobilization 2589=fracture-radius only, closed reduction 2599=fracture-radius only, open reduction 2645=fracture-radius and ulna, without reduction, with immobilization 2651=fracture-radius and ulna, closed reduction 2652=fracture-radius and ulna, open reduction 2653=distal epiphyseal fracture-radius and ulna, without reduction, with immobilization 2654=distal epiphyseal fracture-radius and ulna, intra- or extra-articular closed reduction 2735=distal epiphyseal fracture-radius and ulna, closed reduction and fixation with pin 2736=distal epiphyseal fracture-radius and ulna, open reduction 2768=head or neck of radius, without reduction, with immobilization 2769=head or neck of radius, closed reduction 2770=head or neck or radius, open reduction	813=fracture of radius and ulna
Fracture - lower extremity	Fracture of any of the following: femur, patella, tibia/fibula, ankle, foot	827: other, multiple and ill-defined fractures of lower limb
femoral shaft	2660=femur fracture, without reduction, with immobilization 2667=femur fracture (transcondyloid or subcondyloid diaphysis) patient over 16 years of age 2673=femur fracture (transcondyloid or subcondyloid diaphysis) open reduction, internal or external fixation 9589=femur fracture, closed focus osteosynthesis, including proximal locking 9590=femur fracture, distal locking, supplement	821=fracture of other and unspecified parts of femur
patella	9549=knee fracture, patella, open reduction or exeresis with repair of tendon wing, fascia 2683=knee fracture, patella, without reduction with immobilization	822= fracture of patella
ankle	2708=one, two, three malleoli, closed reduction 2727=open reduction, one malleolus 9542=open reduction, two malleoli 2886=open reduction, three malleoli 2887=open reduction, malleolus with torn ligament 2684=without reduction, with immobilization	824=fracture of ankle
tibia/fibula	2705=fibula only, closed reduction 2725=fibula only, open reduction 2681=fibula only, without reduction, with immobilization 2694=tibia (with or without fibula), closed reduction 2696=tibia (with or without fibula), open reduction, diaphysis, internal or external fixation with or without graft 9591=closed focus osteosynthesis, including proximal, locking 9592=closed focus osteosynthesis, including proximal, distal locking supplement 2721=closed focus osteosynthesis, including proximal epiphysis – plateau (1 or 2) 2743=closed focus osteosynthesis, including proximal, distal extremity of tibia 2693=without reduction, with immobilization	823=fracture of tibia and fibula
foot	2686=calcaneus or astragalus, without reduction, without plaster cast, with immobilization by means other than plaster cast 2687=calcaneus or astragalus, without reduction, with plaster cast 2710=calcaneus or astragalus, closed reduction 2730=calcaneus or astragalus, open reduction 2734=calcaneus or astragalus, open reduction (primary arthrodesis) 2744=calcaneus or astragalus, calcanean reduction by percutaneous pinning (Essex Lopresti) 2685=tarsus (excluding astragalus and calcaneus), one or more, without reduction 2709=tarsus (excluding astragalus and calcaneus), one or more, closed reduction 2729=tarsus (excluding astragalus and calcaneus), one or more, open reduction 2688=metatarsus, without reduction, one or more, with immobilization by means other than plaster cast 2689=metatarsus, without reduction, one or more, with plaster cast 2711=metatarsus, closed reduction, one or more 2731=metatarsus, open reduction, one 2732=metatarsus, open reduction, two or more 2690=phalanx, without reduction, with plaster cast each additional, same foot 2712=phalanx, closed reduction, each additional, same foot 2733=phalanx, open reduction 2848=immobilization with plaster cast, splints or taping, foot	825=fracture of one or more tarsal and metatarsal bones 826=fracture of one or more phalanges of foot

Fracture (any)	Any of the above fracture RAMQ codes plus skull & face, thorax, pelvis and 2863=temporary immobilization of a fracture with or without temporary reduction 2800=cast and splint, upper extremity (arm, elbow, forearm) or lower extremity (thigh, knee, leg)	Any of the above fractures plus 828=multiple fractures involving both lower limbs, lower with upper limb, and lower limb(s) with rib(s) and sternum 829=fracture of unspecified bones
thorax	2539=thorax fracture, ribs, with complication 2533=thorax fracture, sternum, closed reduction 2535=thorax fracture, sternum, open reduction 2540=thorax fracture, sternum, open stabilization of thoracic wall	807=fracture of rib(s), sternum, larynx and trachea 809=ill-defined fractures of trunk
pelvis	2578=pelvis fracture (acetabulum), without reduction 2581=pelvis fracture (acetabulum), closed reduction, central dislocation 2584=pelvis fracture (acetabulum), open reduction 2579=pelvis fracture, closed reduction, including bed rest and supervision 2583=pelvis fracture, open reduction: pubis 2771=pelvis fracture, Letournel's open reduction by ilioinguinal and enlarged iliocrural approach, with osteosynthesis by screw or plate and screw 2772=pelvis fracture, open reduction by posterior approach, with osteosynthesis by screw or plate and screw 2773=pelvis fracture (fracture of one or two columns together with fracture of posterior wall), open reduction by posterior approach with osteosynthesis by screw or plate and screw	808=Fracture of pelvis
skull & face	2512=skull fracture (zygomatic arch), open reduction 7500=skull fracture (surgical treatment), dura mater intact 7501=skull fracture (surgical treatment), with laceration of dura mater 7502=skull fracture (surgical treatment), with serious brain damage 7503=skull fracture (surgical treatment), involving the sinuses 7504=skull fracture (surgical treatment), dura mater plasty with graft for C.S.F. leak 7505=skull fracture (surgical treatment), open fracture with depression, dura mater intact 7506=skull fracture (surgical treatment), with laceration of dura mater 7507=skull fracture (surgical treatment), with serious brain damage (foreign body, haematoma, etc.) 2505=mandible fracture (surgical treatment), immobilization with Barton's bandage or other 2509=mandible fracture (surgical treatment), closed reduction, intermandibular-maxillary wiring 2520=mandible fracture (surgical treatment), open reduction, simple or multiple fracture unilateral 2521=mandible fracture (surgical treatment), open reduction, simple or multiple fracture bilateral 2517=mandible fracture (surgical treatment), condylectomy (for fracture of condyle) 2523=mandible fracture (surgical treatment), meniscectomy 2524=mandible fracture (surgical treatment), removal of coronoid process 2502=maxilla fracture (surgical treatment), intermaxillary fixation 2508=maxilla fracture (surgical treatment), closed reduction with intermandibular-maxillary 2515=maxilla fracture (surgical treatment), open reduction 2516=maxilla fracture (surgical treatment), fracture middle 1/3 of face 2518=maxilla fracture (surgical treatment), cranofacial separation 2506=nose fracture (surgical treatment), reduction of simple fracture 2511=nose fracture (surgical treatment), reduction of comminuted fracture 2507=malar bone fracture (surgical treatment), closed reduction 2513=malar bone fracture (surgical treatment), open reduction, simple 2514=malar bone fracture (surgical treatment), open reduction, complicated 2522=malar bone fracture (surgical treatment), open reduction, through sinus 7379=reduction of fractures of the orbit	800=fracture of vault of skull 801=fracture of base of skull 802=fracture of face bones 803=other and unqualified skull fractures 804=multiple fractures involving skull or face with other bones
Injury - any	Any of the above fracture codes plus subluxation of the hip, upper and lower extremity, and any laceration	
Subluxation - hip	2745=hip luxation (anterior or posterior), closed reduction with or without anaesthesia 2757=hip luxation (anterior or posterior), open reduction	835=dislocation of hip
Subluxation - lower extremity	2737=knee luxation, closed reduction 2738=knee luxation, open reduction 2749=knee luxation (patella), closed reduction 2761=knee luxation (patella), open reduction 2751=ankle luxation, closed reduction 2888=ankle luxation, open reduction, including ligament repair 2752=tarsus, tarsal or tarsometatarsal dislocation, closed reduction 2765=tarsus, tarsal or tarsometatarsal dislocation, closed reduction and percutaneous fixation 2764=tarsus, tarsal or tarsometatarsal dislocation, open reduction 2754=metatarsophalangeal dislocation, closed reduction 2766=metatarsophalangeal dislocation, open reduction 2756=interphalangeal dislocation, closed reduction 2767=interphalangeal dislocation, open reduction	836=dislocation of knee 837=dislocation of ankle 838=dislocation of foot

Subluxation - upper extremity	2545=shoulder luxation (acromioclavicular), closed reduction 2548=shoulder luxation (acromioclavicular), open reduction 2546=shoulder luxation (glenohumeral), closed reduction 2549=shoulder luxation (glenohumeral), open reduction 2544=shoulder luxation (sternoclavicular), closed reduction 2547=shoulder luxation (sternoclavicular), open reduction 2824=tendon, tendon sheaths, aponeuroses and ligaments plaster casts and splints, shoulder spica 2662=elbow luxation, closed reduction 2668=elbow luxation, open reduction 2657=elbow luxation, treatment of pulled elbow 2666=luxation (interphalangeal), closed reduction, one 2671=luxation (interphalangeal), open reduction 2664=luxation (metacarpophalangeal), closed reduction 2670=luxation (metacarpophalangeal), open reduction 2663=luxation (wrist), closed reduction 2669=luxation (wrist), open reduction 2677=luxation (carpometacarpal), closed reduction 2678=luxation (carpometacarpal), open reduction 2679=luxation ((carpometacarpal), closed reduction with percutaneous pinning	831=dislocation of shoulder 832=dislocation of elbow 833=dislocation of wrist 834=dislocation of finger
Subluxation - other	2676=sacroiliac luxation, closed reduction only 2567=sacroiliac luxation, closed reduction, traction, spica, etc... 2572=sacroiliac luxation, open reduction	839=other, multiple and ill-defined dislocations
Laceration (any)	1320=simple laceration (face and neck) 1323=simple laceration (other areas) 1322=complicated laceration (face and neck) 1325=complicated laceration (extensive, multiple or complicated wounds) 1326=complicated laceration, wound, exploration of wound under anesthesia, without repair of complicated wound requiring referral to another physician 1327=complicated laceration (debridement of wound only) 5327=tongue, repair, glossoplasty 5328=tongue, repair, minor laceration 7386=laceration of eyelid, involving free border 7387=laceration of eyelid, involving free border, full thickness 7403=laceration of eyelid, tarsorrhaphy	870=open wound of ocular adnexa 871=open wound to eyeball 872=open wound of ear 873=other open wound of head 874=open wound of neck 875=open wound of chest (wall) 876=open wound of back 877=open wound of buttock 880=open wound of shoulder and upper arm 881=open wound of elbow, forearm and wrist 882=open wound of hand except finger(s) alone 883=open wound of finger(s) 884=multiple and unspecified open wound of upper limb 890=open wound of hip and thigh 891=open wound of knee, leg (except thigh) and ankle 892=open wound of foot except toe(s) alone 893=open wound of toe(s) 894=multiple and unspecified open wound of lower limb