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BENZODIAZEPINE USE AND THE RISK OF MOTOR VEHICLE CRASHES IN THE ELDERLY

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ABSTRACT

Benzodiazepines, one of the most frequently prescribed class of medications in the elderly population, are known to impair motor function and cognitive skills. The evidence based on laboratory and experimental driving studies reporting the performance impairing effects of benzodiazepines is very convincing. However epidemiologic studies of the association between benzodiazepine use and the risk of motor vehicle crashes are inconclusive. The primary objective of this thesis was to determine the risk of injurious motor vehicle crashes among elderly drivers following the initiation of treatment with long and short half-life benzodiazepines. We also sought to determine when, after initiating treatment, the risk of experiencing this adverse event became elevated, and whether there was a continued risk with prolonged use.

The study was a nested case-control design within a cohort of 224,734 drivers from the province of Quebec, age 67 to 84, and followed from 1990 to 1993. The study outcome was involvement of a cohort member as a driver in a motor vehicle crash in which at least one victim (not necessarily the driver) sustained bodily injury. All 5,579 drivers involved in an injurious motor vehicle crash (cases) were identified from this cohort. A random sample of 10 subjects per case was selected as controls from a sub-cohort of 13,265 subjects. Study subjects were linked to the Quebec health insurance databases and a complete history of drugs dispensed was obtained. The rate ratio of crash involvement was estimated from logistic regression models controlling for demographic characteristics, a measure of health status, exposure to other central nervous system drugs and previous injurious crashes.

For long half-life benzodiazepines, the adjusted rate ratio of crash involvement within the first week of treatment initiation was 1.45 (95% CI 1.04-2.03). The rate ratio for continuous use of longer duration up to one year was slightly lower, but remained significantly elevated (rate ratio 1.26; 95% CI 1.09-1.45). In contrast, there was no increased risk following the initiation of treatment with short half-life

benzodiazepines (rate ratio 1.04; 95% CI 0.81-1.34), or with their continued use (rate ratio 0.91; 95% CI 0.82-1.01).

In conclusion, brief or extended periods of exposure to long half-life benzodiazepines are associated with an increased risk of motor vehicle crash involvement in the elderly population. There appears to be no such raised risk for short half-life benzodiazepines.

RÉSUMÉ

Les benzodiazépines, une des classes de médicaments les plus prescrites auprès de la population âgée, ont des effets secondaires connus sur la fonction motrice et la fonction cognitive. Les resultats des études laboratoires et expérimentales de conduite routière soulignant l'effet négatif des benzodiazépines sont très convaincants. Néanmoins, les études épidémiologiques sur l'association de l'utilisation des benzodiazépines et le risque des accidents de la route sont contradictoires. Le but premier de cette thèse était de déterminer le risque d'accidents de la route entrainant des blessures suite à l'initiation du traitement avec des benzodiazépines à demi-vie longue et courte chez les conducteurs âgés. Nous avons aussi tenté de déterminer à quel moment après le début du traitement, le risque d'accident s'élève, et si ce risque se maintient suite à un usage prolongé.

L'étude utilise un devis cas-témoin imbriqué dans une cohorte de 224,734 conducteurs de la province du Québec âgés de 67 à 84 ans et suivis de 1990 à 1993. La variable dépendante principale était l'implication d'un membre de la cohorte comme conducteur dans un accident de la route au cours duquel au moins une victime (pas nécessairement le conducteur) a été blessé. Tous les 5,579 conducteurs impliqués dans des accidents (les cas) furent identifiés à partir de la cohorte. Un échantillon aléatoire de 10 contrôles a aussi été selectionnés d'une sous-cohorte de 13,265 sujets. Les données des sujets de l'étude ont été appariées avec les bases de données de la Régie de l'assurance maladie du Québec afin d'obtenir tous les médicaments prescrits à chaque sujet. Le risque relatif d'un accident de la route à été éstimé à partir de modèles de régression logistique contrôlant les caractéristiques démographiques, une mesure du statut de santé, l'exposition à d'autres médicaments ayant un effect sur le système nerveux central et l'implication antérieure dans des accidents de la route.

Pour les benzodiazépines de longue demi-vie, le risque relatif ajusté d'accident de la route pendant la première semaine de traitement était 1,45 (IC 95% 1,04-2,03). Le risque relatif d'une utilisation continue de plus longue durée (jusqu'à un an) était réduit, mais demeurait significatif (1,26; IC 95% 1,09-1,45). Par contre, il n'y avait

pas d'augmentation de risque suite à l'initiation du traitement avec les benzodiazépines de courte demi-vie (1,04; IC 95% 0,81-1,34), ni avec leur usage continu (0,91; IC 95% 0,82-1,01).

Pour conclure, l'exposition aux benzodiazépines de longue demi-vie durant des périodes courtes ou longues est associée à un risque élevé d'accidents de la route auprès de la population âgée. Il ne paraît pas y avoir une telle augmentation de risque pour les benzodiazépines de courte demi-vie.

STATEMENT OF ORIGINALITY

The work undertaken for this thesis represents original work. Although previous research has focused on the use of benzodiazepines and risk of adverse events such as hip fractures and motor vehicle crashes, this study represents one of the initial attempts to determine when, following the initiation of treatment, the risk of experiencing an adverse event is elevated, and whether there is a continued risk with prolonged use.

Previous research of benzodiazepine use and risk of motor vehicle crashes in the elderly have focussed on benzodiazepines as a class. This study characterized several features of benzodiazepine exposure, including their elimination half-life, dose and concurrent exposure to multiple benzodiazepines. Thus this study represents an original contribution to the medical literature. This study also represents the first time that data from three agencies in the province of Quebec, namely the Société de l'assurance automobile du Québec, the Régie de l'assurance maladie du Québec and the Ministère de la Santé et des Services sociaux, have been linked for research purposes.

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CHAPTER ONE
INTRODUCTION

1.1 Significance of the Problem

Injury resulting from motor vehicle crashes (MVCs) are a significant cause of morbidity and mortality in the elderly population. MVCs are the leading cause of fatal injuries in Canada (Riley & Paddon 1989, Millar & Adams 1991), and are second only to falls as the major cause for injury among the elderly in the United States (Rice et al 1989). A closer examination of crash rates reveals that older drivers' crash involvement is no greater than that of the overall population, and considerably lower than that of younger drivers. However, when the number of miles driven by subjects over 65 are taken into account studies generally show a U-shaped curve, with the crash rates per mile driven in this group twice as high as those for middle-aged drivers, and exceeded only by the under-25 age group (Hogue 1982, Graca 1986, Evans 1988a, Reuben et al 1988, Williams & Carsten 1989, Stutts & Martell 1992). This elevated crash rate occurs despite the fact that older drivers, as a group, are less likely to drive at night or in more demanding circumstances.

Not only is the crash rate per mile driven higher, but the clinical implications of these injuries are far more serious among the elderly. Compared to younger individuals, the elderly are more vulnerable to injury and have a reduced capacity for recovery (Barancik et al 1986, McCoy et al, 1989). At age 70, the risk of fatality from physical trauma sustained in an automobile crash is about three times what it is at age 20 (Evans 1988b). A review of motor vehicle traffic accidents in Canada over a 10 year period (1978-87) revealed that the fatality to injury ratios were highest among men and women aged 65 years and older (Waters et al 1993). Similar results have been obtained in the United States where both hospital admission rates and fatality rates as a result of motor vehicle trauma were nearly twice as high for subjects aged 75 and over compared to any other age group (Barancik et al 1986). Mortality rates as a result of MVCs in Canada for 1987 were highest among males age 15 to 24 (50 per 100,000

population) followed by males 65 and over (28 per 100,000 population) (Millar & Adams 1991).

The extent of the problem regarding MVCs among elderly drivers is expected to increase. The elderly are the fastest growing segment of the population and comprise an increasing proportion of our licensed drivers (Stutts & Martell 1992, Barr 1991). In the province of Quebec alone, from 1987 to 1991, the number of licensed drivers 65 years of age and older increased by 31% (from 240,421 licensed drivers in 1987 to 314,768 in 1991) (Société de l'assurance automobile du Québec 1992a). It is projected that by the year 2000 more than 25% of all drivers will be over 55 years of age (Underwood 1992). It is imperative therefore that determinants of crash risk among this segment of the population be identified and modification of such factors be undertaken to prevent further morbidity and mortality.

1.2 Risk Factors for MVCs in the Elderly

A number of risk factors for MVCs have been identified, although these are primarily directed at the overall population, or younger subjects, and are not specific to the elderly. However an exploration of the characteristics of traffic violations and crashes provides evidence to suggest that factors unique to this segment of the population may increase their risk of a MVC.

Although motor vehicle crash rates are highest among the younger age groups, this is believed to be related both to their inexperience in operating motor vehicles as well as their risk taking behavior, which includes high speed and use of alcohol. The elderly, however, are less likely to employ such risk taking behavior. Elderly individuals drive shorter distances, drive less at night and avoid rush hours (Retchin & Anapolle 1993). Compared to younger drivers, crashes in which elderly drivers are involved are more likely to occur at intersections, at lower speeds, during the day and are five times more likely to involve two or more vehicles (Graca 1986). These crashes are also less likely to involve alcohol as a contributing factor compared to those of younger drivers (Wells-Parker et al 1983, Waller 1985, Health & Welfare Canada 1987).

With respect to traffic violations, older drivers tend to make errors of omission, such as failure to read traffic signs and obey traffic lights, and demonstrate difficulty in manoeuvres requiring a series of rapid judgements (Waller 1985, Underwood 1992). Older drivers are also more likely to be responsible for those crashes they are involved in. These crash and traffic violation characteristics suggest that some older drivers may have problems with traffic decisions requiring complicated perceptual and cognitive functioning, and that attention deficiencies may be contributing factors to driving abilities (Retchin & Anapolle 1993). Thus, factors unique to the elderly must be examined in an attempt to identify determinants of crash risk in this segment of the population.

Driving is a complex task that requires ability to assess multiple environmental stimuli at once, cognitive capacity to process this information, and motor capacity to undertake the actual driving tasks. The elderly may be particularly vulnerable to impairment in any of these tasks for a variety of reasons. First of all, the normal physiological changes associated with aging results in a decrease in sensory, cognitive, and motor function (Gaylord 1985, Reuben et al 1988, Stemlach & Nahom 1992, Troncale 1996). Secondly, medications that interfere with the functioning of the central nervous system, most notably the benzodiazepines and antidepressants, impair cognition, produce a sedative effect and limit motor skills and reaction time (Sepalla et al 1979, Cowart & Kandela 1985, Polen & Friedman 1988). This impairment is more pronounced in the elderly because of their increased sensitivity to the central nervous system effects of these drugs (Swift et al 1981, Cook et al 1984, Cook 1986, Swift 1990). The age-related pharmacokinetic and pharmacodynamic changes may result in a variety of adverse drug effects impairing driving ability (Greenblatt et al 1989, Underwood 1992). Finally, medication use increases with age, particularily the use of psychotropic drugs which are among the most frequently used medications in elderly populations (Quinn et al 1990, Kruse 1990, Ray 1992a). As a result, more elderly people are exposed to medications, as well as particular combinations of medications, which may further impair their basic psychomotor function.

The combination of these three factors, normal physiologic changes resulting in decreased sensory, cognitive and motor skills, increased use of medications, and increased sensitivity to the central nervous system effects of medications, may seriously impede the ability of the elderly driver to safely operate a motor vehicle. Because of their widespread use and resultant central nervous system depression, benzodiazepines have been identified as a class of drugs with the potential to impair driving capabilities among the elderly, a longstanding concern which has been raised on numerous occasions (Cowart & Kandela 1985, Polen & Friedman 1988, Linnoila 1992, Ray 1992a, Ray 1993). This concern is based upon both the pharmacologic properties of the benzodiazepines, as well as several laboratory and experimental driving studies reporting performance impairing effects. However, the epidemiologic studies which have addressed this topic have produced inconclusive results.

1.3 Characteristics of Benzodiazepines as a Risk Factor for MVCs

It is believed that the benzodiazepine's influence on specific areas of the brain, including the limbic areas and cerebral cortex (important for thought and decision-making, movement and sensation), as well as the cerebellum (balance and co-ordination) may result in an increased risk of falls, fall related injury and impairment of driving ability (Gudex 1991).

However, there is evidence from the literature to suggest that the risk of experiencing an adverse event may also vary according to specific characteristics of benzodiazepines themselves. These specific drug effects include the elimination half-life (short versus long), dose, duration of use and the development of tolerance to their psychomotor impairing effects with continued use. Unfortunately, most studies have not taken these characteristics into account.

The majority of the epidemiologic literature concerning psychotropic drugs as a risk factor for injury in the elderly have targeted falls and fall related injury as their outcome (Ray et al 1987, Taggart 1988, Tinetti et al 1988, Ray et al 1989b, Grisso et al 1991, Thapa et al 1995, Cummings et al 1995). For the most part these studies have focussed on specific drug classes, despite the fact that there is considerable variation in

drug effects within a class, particularly for benzodiazepines. Of the studies which have taken into account the elimination half-life of the benzodiazepines, most (Ray et al 1987, Ray et al 1989b, Cummings et al 1995), but not all (Taggart 1988, Grisso et al 1991), have demonstrated an increased risk of adverse events such as hip fractures associated with use of long, as opposed to short, half-life products.

In addition, none of the previous epidemiologic studies have attempted to determine the risk of an injurious event as a function of the duration of benzodiazepine use, and in particular following the initiation of use. Evidence from the literature suggests that some degree of tolerance or adaptation develops to the psychomotor impairing effects of benzodiazepines within the first few weeks of starting treatment (Roehrs et al 1986, American Psychiatric Association Task Force 1990, Woods et al 1992, Shader & Greenblatt 1993). It has been proposed that the risk of experiencing an adverse event as a consequence of these sedative effects is highest after initiating treatment, and is subsequently reduced, or even returned to baseline, with continued use. However this evidence is based on experimental studies in which the subjects are typically healthy volunteers, and exposure is limited to a few weeks in duration.

Therefore, the exploration of benzodiazepine use as a risk factor for MVCs must go beyond simply examining benzodiazepines as a class, and must also take into account important characteristics of these drugs, including their elimination half-life, as well as the potential development of tolerance to their sedative effects with continued use.

1.4 Relevance and Implications

In Canada, physicians have a legal responsibility to detect and discuss with their patients medical conditions and factors which may impede driving ability and, if necessary, report the patient's condition to the appropriate licensing body. Coopersmith et al (1989) reviews and cites case examples of the legal responsibilities physicians face in determining a patients' fitness to drive. The authors point out that physicians may face potential legal action from patients who are not warned of the

dangers of driving as a result of certain medications or disease conditions, as well as from victims who are injured by patients whom the physician has failed to report.

The Canadian Medical Association produces and regularly updates a physicians' guide to driver examination, the purpose of which is to provide guidance to physicians in determining the ability of their patients to drive a motor vehicle safely (Canadian Medical Association 1991). The majority of the Guide emphasizes specific disease conditions or physical impairments which may influence the ability of the individual to safely operate a motor vehicle, although a brief section is included on drugs and driving ability. The Guide provides examples of prescription drugs that may impair driving skills (including benzodiazepines), and states that physicians should warn patients that these medications may affect their ability to drive safely.

Although the Canadian Medical Association guidelines and provincial highway safety acts provide some guidance to physicians in this matter, there is a definite lack of scientific evidence with which to base these decisions, particularly in regards to benzodiazepine use and driving performance in the elderly (Drachman 1988, Reuben et al 1988, Ray 1992a, Underwood 1992, Johnston 1993).

1.5 Study Objectives

MVCs are a significant cause of morbidity and mortality in the elderly population. Given the increase in the number of elderly drivers and the high prevalence of benzodiazepine use, drugs with known performance impairing effects, this study was designed to determine the association between benzodiazepine use and risk of MVCs in elderly drivers. In particular, we sought to focus on particular characteristics of benzodiazepine exposure. The specific objectives of this study therefore were to:

1) determine whether there was an association between the initiation of treatment with short and long half-life benzodiazepines and the risk of injurious MVCs among elderly drivers.

2) determine when, following the initiation of treatment, the risk of experiencing an injurious MVC was the greatest, and whether there was a continued risk with prolonged use.

3) determine whether the risk of experiencing an injurious MVC following the initiation of benzodiazepine use was associated with specific characteristics of the drug including dose, individual products and use of multiple benzodiazepines.

4) determine whether there was an association between current use of long and short half-life benzodiazepines, irrespective of the duration of their use, and risk of injurious MVC.

5) determine whether the risk of experiencing an injurious MVC and current benzodiazepine use was associated with specific characteristics of the drug including dose, individual drugs and use of multiple benzodiazepines.

6) develop a procedure for linkage of computerized data between three agencies in the province of Quebec, namely the Société de l'assurance automobile du Québec, the Régie de l'assurance maladie du Québec and the Ministère de la Santé et des Services sociaux (MED-ECHO).

1.6 Epidemiologic Terminology

Use of the term "accident" in this area of research has been criticized as being inappropriate and misleading in that it implies simply an element of chance, without human participation in the occurrence of the event (Doege 1978, Council on Scientific Affairs 1983, Evans 1993). It has been emphasized in the injury literature that injuries are not distributed randomly, or "accidentally" among populations, just as cancer, cardiovascular disease and infections are not random occurrences. Injuries in general, including those related to motor vehicles, involve specific groups of persons capable of

being described by specific demographic characteristics, such as age, sex, and occupation, as well as specific risk factors. By replacing "accident" with terms such as "injury" (or when motor vehicles are involved "motor vehicle crash"), the concept of chance, or lack of human involvement are avoided. For these reasons, and to the extent that it is possible, motor vehicle crashes (MVCs) will be used to refer to the outcome event throughout this thesis, as opposed to another term commonly used, namely that of motor vehicle accidents.

CHAPTER TWO
REVIEW OF THE LITERATURE

This chapter will be divided into three primary sections. Initially, the literature specific to benzodiazepines will be reviewed, including topics such as mechanism of action, indications for use, as well as prevalence and duration of use. The concept of pharmacodynamic tolerance to benzodiazepines will conclude discussion of the exposure. The effects of benzodiazepines on psychomotor skills and driving performance, from both clinical trials and observational epidemiologic studies, will be reviewed in the second section. In an attempt to address the issues of confounding by indication, whereby the disease conditions leading to the use of benzodiazepines may themselves increase the risk of motor vehicle crashes (MVCs), the clinical trials will be further subdivided into those which focussed on subjects with insomnia and subjects with anxiety specifically (the most common indications for the use of benzodiazepines), as well as trials with healthy elderly subjects. The third and fourth sections will deal with topics of particular relevance to the methods of the present study, including issues related to exposure characterization as well as risk factors for MVCs which may serve as potential confounders.

2.1 Benzodiazepines

2.1.1 Pharmacodynamic Properties: Mechanism of Action

Although benzodiazepines were first marketed in 1961, it was not until 16 years later that a major advance in understanding their mechanism of action was made. In 1977 it was discovered that these drugs act on specific receptor sites within the central nervous system (Mohler & Okada 1977), sites that are closely associated with receptors for gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the central nervous system. GABA operates by increasing inward chloride flow, resulting in membrane hyperpolarization and neuronal inhibition. Benzodiazepines, when bound to their receptor sites, seem to potentiate GABA's effect and thus further inhibit neuronal activity. The potency of a benzodiazepine is correlated with its affinity

for its binding sites. Relatively high densities of benzodiazepine central receptors are found in the cerebral cortex, structures of the limbic system and the cerebellar cortex (American Medical Association 1994). The pharmacodynamic results of the benzodiazepine agonist activity includes drowsiness, sedation, sleep, anti-anxiety effects, anti-convulsant effects, ataxia and performance impairment, as well as memory impairment.

2.1.2 Pharmacokinetic Properties: Absorption, Distribution and Elimination

Variations in the pharmacokinetic properties of benzodiazepine absorption, distribution and elimination form the basis on which a particular compound is selected for use because of their influence on the onset of action, duration of effect, and elimination of these drugs. Each of these three factors, and the alterations which may result with the aging process, will be discussed.

Absorption: The rate of absorption of benzodiazepines from the gastro-intestinal tract following their oral administration affects the onset of action. Clorazepate, alprazolam, lorazepam, temazepam, triazolam, flurazepam and diazepam are absorbed rapidly (0.5 to 2 hours), while chlordiazepoxide, clonazepam and oxazepam are absorbed more slowly (2 to 4 hours) (American Medical Association 1994). In general, the onset of benzodiazepine drug effect is usually about 30 to 45 minutes after ingestion, and two to three hours are typically required for full absorption (Abernethy 1992). In the absence of severe diffuse gastrointestinal pathology, the rate of absorption of benzodiazepines from the gastrointestinal tract is not significantly altered in the elderly.

Distribution: Volume of distribution indicates how widely a particular drug is distributed throughout the body (Hardman et al 1996). Benzodiazepines are lipid soluble, therefore the volume of distribution of these agents is related to the amount of fat or lipid tissue in which the drugs will be sequestered. As people age, total body fat tends to increase, while the fraction of lean mass and body water decreases

correspondingly (Troncale 1996). Drugs which are lipid soluble, such as benzodiazepines, are therefore distributed more extensively in the peripheral body tissues of an elderly subject. Elimination of lipid soluble drugs from adipose tissue tends to be slow, therefore these drugs may remain in the body for extended periods of time. An increased volume of distribution, without a compensatory increase in clearance, will result in a prolongation of elimination half-life (Abernethy 1992). Thus, in the elderly, benzodiazepines may have a prolonged half-life because of a reduced clearance, an increased volume of distribution, or both.

Protein binding also affects drug distribution and serum half-life. Benzodiazepines are highly protein bound and bind to plasma protein upon entering the systemic circulation (Abernethy 1992). Only the free fraction of the drug, that component not bound, is active and exerts a pharmacologic effect or undergoes hepatic metabolism. Any impairment in the clearance of this free fraction will result in an increased plasma concentration, with a resultant increase in the sedative effects. With age there is a decrease in plasma albumin levels, and therefore a higher fraction of the benzodiazepines remain unbound and active with increased distribution to peripheral tissues.

Benzodiazepines in general consist of highly lipophilic molecules that rapidly cross the blood-brain barrier and enter brain tissue. Diazepam, a highly lipophilic drug, enters brain tissue rapidly, but is also rapidly redistributed to other regions of the body. The less lipophilic drugs such as lorazepam and oxazepam may persist longer in the brain because of their reduced peripheral distribution (Greenblatt et al 1983a), thereby increasing the time during which they exert their effects on the central nervous system.

Elimination: The classification of benzodiazepines into long and short-acting is made based on their elimination half-life (Teboul & Chouinard 1990). The relationship between the duration of action of many benzodiazepines and their elimination half-life is complicated by the metabolic processes involved in the elimination of the drug. Drugs in general are eliminated from the body either unchanged or as metabolites.

Lipid soluble drugs, such as the benzodiazepines, are not readily eliminated until they are metabolized in the liver. Chlordiazepoxide, clorazepate, diazepam, flurazepam and nitrazepam undergo oxidative metabolism in the liver and have relatively long-acting metabolites. Alprazolam, clonazepam, lorazepam, oxazepam, temazepam and triazolam require conjugative liver metabolism and do not produce active metabolites (Burch 1990). The benzodiazepines without active metabolites are recommended for use in the elderly because their effects are more predictable than those with active metabolites (Maletta et al 1991). Any process that slows oxidative metabolism, including normal aging and hepatic conditions, will prolong the elimination of long-acting metabolites, thus making their effects less predictable. As discussed above, the elimination half-life may be further prolonged in the elderly because of the increase in the proportion of fat to total body weight, which increases the volume of distribution.

2.1.3 Indications

Benzodiazepines are a class of drugs widely used for their anxiolytic and sedative-hypnotic properties. Chlordiazepoxide was the first benzodiazepine to be introduced into clinical medicine in 1961. Since that time more than 3000 benzodiazepines have been synthesized, over 120 have been tested for biological activity, and approximately 35 are available worldwide for clinical use (Hardman et al 1996).

The benzodiazepines that have been marketed have been chosen because of their high anxiolytic potential relative to their potency to depress central nervous system function. They have become extremely popular because of their ability to relieve symptoms of anxiety. However, the benzodiazepines all possess sedative-hypnotic properties to varying degrees, and it is these properties which have been exploited clinically, specifically to facilitate sleep. A sedative drug decreases activity, moderates excitement and calms the patient, while a hypnotic drug produces drowsiness and facilitates the onset and maintenance of a state that resembles natural sleep (Hardman et al 1996).

As noted previously, even benzodiazepines with very similar chemical structures can have very different pharmacokinetic properties. It is on the basis of these differences that a decision is made to use a particular derivative in a specific clinical situation.

Anxiety disorders: Anxiety is described as apprehension, tension or uneasiness related to anticipated danger. It may be a response to stress associated with environmental stimuli, or may have no apparent cause. The anxiety disorders typically include anxiety states, as well as phobic disorders.

The type of anxiety which warrants pharmacologic treatment is that which is considered to be pathologic in nature, and typically includes symptoms of apprehension, hyperresponsiveness, and motor tension lasting more than one month (Greenblatt et al 1983b). Although pharmacologic treatment of such conditions are generally short-term, for some patients with chronic anxiety long-term anxiolytic pharmacotherapy may be necessary (Greenblatt et al 1983b, Teboul & Chouinard 1991). Three short acting benzodiazepines, oxazepam, lorazepam and alprazolam, are the drugs of choice for the treatment of anxiety in the elderly (Salzman 1992).

Insomnia: The efficacy of benzodiazepines in the treatment of short- or intermediate-term insomnia has been well established for years (Greenblatt et al 1983b). Reports issued by experts in the field suggest that the main, and perhaps the only, indication for benzodiazepine hypnotics are two noncontinuous sleep disorders - insomnia in the elderly and transient insomnia in young and middle aged adults (Consensus Conference 1984). The prevalence of insomnia, defined as at least some trouble with insomnia in a 12 month period, among the elderly has been reported to be as high as 45%, with approximately one-third of elderly people taking prescription hypnotics for insomnia on a daily basis (Mellinger et al 1985).

As in the treatment of anxiety, short half-life products are recommended for the treatment of insomnia in the elderly. However, these drugs have been shown to be associated with the development of early morning insomnia after one to two weeks of

continuous treatment, as well as with rebound insomnia when they are withdrawn. For this reason, some experts in the field recommend that they should be used for one week or less (Gillin & Byerley 1990).

Although the primary indications for benzodiazepine use are anxiety and insomnia conditions, they may also be prescribed for the relief of tension states that may accompany skeletal muscle spasm, or as a preoperative medication. One benzodiazepine in particular, clonazepam, is marketed specifically as an anti-convulsant.

The indications for which benzodiazepines are prescribed in the elderly are often non-specific. Results of population surveys suggest that anxiety is the most common indication for which benzodiazepines are prescribed to subjects less than 65 years of age, while insomnia is the most common indication in subjects older than 65 (Nolan & Malley, 1988; Dunbar et al, 1989). Other surveys and reviews suggest that benzodiazepines are used primarily for their anxiolytic effect (Catalan et al 1988, Maletta et al 1991, Salzman 1992).

2.1.4 Prevalence of Benzodiazepine Use

Studies in a number of different countries have been undertaken to determine the prevalence of psychotropic drug use. Although these studies have primarily consisted of population surveys, they have differed with respect to the type of drugs covered (psychotropics in general vs specific drug classes), the definition of drug use (regular, occasional, any use, etc), and the exposure period of interest (yesterday, past 30 days, past 12 months, etc). However, despite their limitations, population surveys provide a general picture of the prevalence of psychotropic drug use as well as the socio-demographic characteristics of the users.

Only a limited number of these studies have focussed specifically on the non-institutionalized elderly, or included the prevalence of use stratified by age (Balter et al 1984, Morgan et al 1988, Dunbar et al 1989, Ried et al 1990, Swartz et al 1991). The results of these studies, summarized in table 2.1, indicate that although the prevalence of psychotropic drug use among elderly subjects varies from country to country, it is

consistently higher among females. Focussing on benzodiazepine use in particular results indicate that, in addition to higher use among females, levels of use increase with age (Nolan & Malley 1988, Dunbar et al 1989, Swartz et al 1991, North et al 1992).

Survey data available from Canada reveals similar patterns of sedative-hypnotic drug use, except for noted regional variation. Results from two of the most recent Canadian surveys are presented in table 2.2a and 2.2b. The National Alcohol and Other Drugs Survey 1989 (Health & Welfare Canada 1990) reported that among subjects 65 years of age and older, 11.1% used sleeping pills in the 30 days preceding the survey, compared to 3.6% of individuals age 15 and older (table 2.2a). Prevalence of tranquillizer use also increased with age. The 1990 Health Promotion Survey (Health & Welfare Canada 1993), which assessed use in the prior 12 months, also clearly shows the increased prevalence of use by age (table 2.2b). However, unlike the National Alcohol and Other Drugs Survey, a larger proportion of males than females reported using tranquillizers in the 12 months prior to the survey.

As alluded to previously, psychotropic drug use appears to vary within Canada. A detailed review and synthesis of four separate surveys undertaken by Rawson and D'Arcy (1991) revealed that Quebec was the only province where the percentage of residents using sleeping pills (4.5%) was greater than the national rate (3.6%). The highest rates of tranquillizer use were also reported from Quebec (the surveys reviewed included: International Collaborative Study of Medical Care Utilization, 1968-9; Canada Health Survey 1978-9; Health Promotion Survey 1985; and National Alcohol and Other Drugs Survey 1989). More detailed information on the extent of benzodiazepine use in the province of Quebec specifically was provided from a large population survey conducted in 1987 by Santé Quebéc. Results of the survey, based on respondents 15 years of age and older, showed that about 1 person in 20 (5.1%) reported using benzodiazepines in the two previous days, with prevalence of use higher among females (6.7%) than males (3.4%). Reported use also increased with age, 18% for females 60 years of age and older and 12% for males (Laurier et al, 1992).

While these surveys of sedative-hypnotic use suggest that prevalence is higher in the elderly, particularly in the province of Quebec, the accuracy of self reported use of psychotropic medications is often questioned because of the potential for the respondents to be influenced by social desirability or denial, or simply the inability to recall details of drug use. Computerized prescription drug information, which provides an accurate and detailed account of drugs dispensed, was another source of data documenting the prevalence of benzodiazepine use in 1990 among the elderly in Quebec (Tamblyn et al 1994). Among those who made at least one visit to the health care system in 1990 (approximately 90% of the elderly), and were not living in a health care institution for the entire year, 51% of women and 33% of men were prescribed a benzodiazepine at least once in a 12 month period. The true extent of these exceptionally high prevalence rates for Quebec are evident when comparisons are made with reports from the province of Saskatchewan, where computerized prescription information also formed the source of exposure data (Quinn et al 1990). Among subjects 65 years of age and older, 20% of females and 12% of males received at least one prescription for a benzodiazepine in 1989. This is less than half the prevalence of reported use among Quebec elderly.

A number of other factors in addition to age and gender have been considered as to their relationship to benzodiazepine use. Various measures of health status indicators have been shown to be associated with benzodiazepine use, including multiple medical problems and poor perceived health status (Mellinger et al 1984, Rodrigo et al 1988, Simpson et al 1990, Laurier et al 1992). The use of benzodiazepines also appears to be related to psychological distress (Swartz et al 1991, Laurier et al 1992). After controlling for age, gender, and health status, neither income nor level of education are associated with use of tranquillizers, sedatives or benzodiazepines specifically (Allugander 1989, Swartz et al 1991, Laurier et al 1992).

In summary, benzodiazepines are frequently prescribed to elderly people living in the community, and their use is much more prevalent in women. The effects of age and gender on the use of prescribed psychotropic drugs, and benzodiazepines in particular, remain even after controlling for differences in health status and other

demographic factors (Wells et al 1985, Laurier et al 1992). On a national level the highest prevalence of sedative-hypnotic use, as well as benzodiazepines specifically, are consistently reported from the province of Quebec.

2.1.5 Duration of Benzodiazepine Use

Concern regarding potential dependence and tolerance associated with long-term benzodiazepine use has resulted in a more detailed evaluation of duration of use (Woods et al 1988, Salzman 1991, King et al 1990). These studies have similar limitations to those reported above in the assessment of prevalence of use, namely variations in specific drugs studied, definitions of exposure, and definitions and classification of long-term use. However, the results obtained are useful in that a general assessment of the duration of sedative-hypnotic and benzodiazepine use can be made.

An earlier study conducted by Balter et al (1984) is of particular interest in that it enables multi-country comparisons to be made. In this cross national survey of anti-anxiety/sedative use among the general population of the United States and 10 Western European countries, the authors reported that, among users, the proportion of regular daily users for durations of 12 months or more was highest for Belgium and France (33.2% and 31.5% of users respectively). Regular daily use for durations of less than one month was reported for Sweden and the U.S.A (76.9% and 71.7% of users respectively). Unfortunately results for duration of use were not stratified by age.

Isacson et al (1992), using computerized prescription drug data from a Swedish community, followed a cohort of benzodiazepine users for eight years to determine duration and patterns of use among various age groups. More than 75% of benzodiazepine users in the oldest age groups, 65-74 and 75-84 years, continued to use the drug after the first year of follow-up. After eight years of follow-up, 40 and 45% respectively in these two age groups remained as benzodiazepine users. It is important to consider the broad definition of use applied in this study, at least one prescription for a benzodiazepine per year, when interpreting the results.

Computerized data from Saskatchewan was also used to assess long-term benzodiazepine use (Quinn et al, 1990). Duration of use in this instance was estimated

based solely on the number of prescriptions dispensed. Using the average number of prescriptions dispensed to a patient per year, as well as the standard therapeutic dose ranges, an estimate of the number of days that patients took each of these drugs in 1989 was obtained. Patients were prescribed enough triazolam (the most frequently prescribed benzodiazepine) in 1989 to take it every day for 5 months at 0.25 mg per day, or 10 months at 0.125 mg per day. This assessment was based on the entire population, and would therefore be even higher if limited to the elderly. A much stricter definition of use was applied by Tamblyn et al (1994), in which the number of consecutive days of uninterrupted use was assessed using computerized data for elderly Quebec residents. The results indicated that as many as 70% of elderly psychotropic drug users were exposed to benzodiazepines specifically for durations greater than 30 days.

Attention has also been focussed on describing typical characteristics of the long-term user. A British study, in which the subjects were identified from general practitioner records, concluded that long-term users of benzodiazepine hypnotics are usually elderly females with a history of physical illness. It was also noted that they are less likely to be psychologically distressed or to take other psychotropic drugs (Simpson et al, 1990). In contrast, although long-term users of tranquillizers also tend to be older females, they report higher levels of emotional stress and chronic health problems than non users (Mellinger et al, 1984).

In summary, these studies have consistently found that age and gender are related not only to the use of benzodiazepines and other psychotropic drugs in general, but to prolonged use in particular, with long-term use of benzodiazepines most common among elderly females. Unfortunately these studies have not attempted to identify the characteristics of subjects prescribed long, as opposed to short, elimination half-life benzodiazepines. Closely associated with this topic of long-term use of benzodiazepines is the issue of pharmacodynamic tolerance.

2.1.6 Pharmacodynamic Tolerance

When multiple doses of a benzodiazepine are administered, such as that associated with regular benzodiazepine use, accumulation of the drug may result depending on both the distribution and the rate of elimination (Carskadon et al 1982, Roehrs et al 1986, Teboul & Chouinard 1990). From a purely pharmacokinetic model one could reasonably assume that the degree of psychomotor impairment would increase as the drug accumulates. However, a process known as pharmacodynamic tolerance or adaptation is believed to influence the degree of central nervous system depression accompanying the long term use of these drugs. Tolerance is said to have developed when, after repeated administration, a given dose of a drug produces a decreased effect, or when larger doses of the drug must be taken to obtain the effects observed with the original dose (Hardman et al 1996). Tolerance can develop to both the therapeutic effects as well as the adverse reactions of a drug.

With respect to benzodiazepines, following a single dose the brain mechanisms responsible for the clinical effects "adapt" to the presence of the drug (Teboul & Chouinard 1990). More specifically, the tolerance is attributable to a decrease in receptor sensitivity, rather than a reduction in plasma drug concentrations (Shader & Greenblatt 1993). This has been termed pharmacodynamic tolerance, and is an acquired adaptive change which occurs within affected systems, such that the response is reduced despite a stable, or even increased, concentration of the drug (Hardman et al 1996). Therefore, with repeated doses, the degree of psychomotor impairment is not as great as one would expect based on the increased plasma concentration due to drug accumulation (Greenblatt 1992). This is the primary explanation for the relative safety of benzodiazepines, even when they are consumed at extremely high doses taken with the intention of self-poisoning (Kruse 1990). Multiple doses of benzodiazepines with a short half-life are not believed to accumulate to the same degree as do the long half-life derivatives. The extent of this partial adaptation or tolerance with the different benzodiazepine derivatives is not clearly understood at present, and the evidence which is available remains inconclusive.

While some degree of tolerance or adaptation to the unwanted effects of benzodiazepines (drowsiness, psychomotor impairment, or excessive sedation) is believed to develop over time following continuous administration (Greenblatt & Shader 1986, Roehrs et al 1986, Woods et al 1992, Shader & Greenblatt 1993), the duration of treatment in studies reporting these effects is often relatively short. A double-blind cross over trial in eight healthy subjects assessed the effect of one week of treatment with lorazepam and diazepam on psychomotor performance (Aranko et al 1983). The results suggest that coordination and attention were most impaired on the first day following treatment and diminished thereafter, although improvements in performance did not develop similarly to the various psychomotor functions. It is not possible to determine the extent to which "tolerance" is in fact related to the learning effect of the various psychomotor tests, particularly among this group of young subjects. Despite the limitations and lack of generalizability of the study, the authors concluded that tolerance developing to benzodiazepine actions is to some extent task related, which can result from effects on different receptors (Aranko et al 1983), and is more likely to develop to some effects than to others (Golombok et al 1988). Roehrs et al (1986), in a double-blind cross over trial with 12 healthy adults, also reported an impairment on performance tests following the initial administration of flurazepam, which was no longer significant after more than one week of nightly use. van Laar et al (1992) also reported impairment of driving performance during three weeks, with no impairment during the fourth week, of treatment with diazepam 15 mg.

In contrast, Linnoila et al (1983) in a study of the psychomotor effects of diazepam in anxious patients and healthy volunteers found that the diazepam induced impairment remained stable throughout a three week treatment period - there was no evidence that tolerance developed to the adverse effects in either anxious or healthy subjects. Moskowitz et al (1982) also reported continued impairment of driving related skills beyond nine days of treatment with diazepam.

Assessment of tolerance associated with long-term benzodiazepine use has been limited. In one study of long term hypnotic treatment, Petursson et al (1983) compared 22 patients who had received benzodiazepines for at least one year with a control group

of healthy drug free individuals. The results suggest that most cognitive skills, attention, vigilance and pure motor speed are not adversely affected by prolonged benzodiazepine treatment. However, the patients demonstrated impaired performance on tasks requiring the combined use of sensory and finer motor skills. These results should be interpreted with caution due to the limitations of the study, most notably a small sample size and an inadequate control group.

One of the more rigorous studies conducted to address the issue of cognitive impairment specifically among long-term users of benzodiazepines was that undertaken by Golombok et al (1988). In this study subjects currently taking benzodiazepines for at least one year (n=50) were matched for age, education, and scores on an intelligence test to a group of subjects who had never taken these drugs, or who had done so in the past for less than one year (n=61). Subjects completed a variety of tests assessing cognitive functioning, as well as a scale to measure anxiety. A multivariate analysis, controlling for anxiety, suggested that long-term use of benzodiazepines was associated with impairment in two areas of cognitive functioning: visual-spatial ability and sustained attention. It is not possible to determine the practical implications of these results from the information presented in the paper, although the authors conclude that long-term use of benzodiazepines affects functioning in everyday life, including the ability to safely operate a motor vehicle. These results also suggest that tolerance is more likely to develop to some effects than to others, and that tolerance does not develop to the cognitive effects of benzodiazepines, or that tolerance to these effects is minimal. The impaired performance observed in the study by Golombok et al (1988) was present even after the effects of anxiety had been accounted for, evidence that the impairment is a side effect of the drug, as opposed to being a consequence of the disease condition for which the drugs were prescribed.

There is a limited amount of information on unwanted effects specifically in elderly long term users of benzodiazepines, and the resultant impact on psychomotor performance. A survey of 248 elderly non-institutionalized patients prescribed a benzodiazepine hypnotic, of whom 80% were taking these medications on a nightly basis, suggested some evidence of psychomotor impairing effects (Swift et al 1984). Of

patients receiving nitrazepam, 7.5% reported occasional morning drowsiness, and 40.1% occasional dizziness, lightheadedness or unsteadiness. The figures for patients on flurazepam were 6% and 36% respectively. However, the extent to which this may be attributed to drug exposure is unknown due to the lack of a comparable group of unexposed subjects. Support for a continued effect of psychomotor impairment among elderly long-term users of benzodiazepines was provided in a study by Ray et al (1989b), where the increased risk of hip fractures associated with use of long half-life benzodiazepines persisted even after the first 30 days of therapy.

The suggestion that chronic users of benzodiazepines are not aware of their reduced cognitive abilities or psychomotor impairment (Golombok et al 1988) may help to explain the conflicting results from studies based on subjective measures of impairment (Swift et al 1984). Greenblatt et al (1991), in a study of the sensitivity of the elderly to triazolam, concluded that the elderly may either remain unaware of, or fail to report, sedative effects of these drugs. This was apparent by a discrepancy between their perception of the sedative effects and results of tests of psychomotor function and memory. This is consistent with clinical evidence that patients who withdraw from their medication often report improved concentration and increased sensory appreciation (Curran & Golombok 1985), suggesting that the tolerance may also involve a subjective component, in addition to that of pharmacodynamic adaptation.

Clearly the extent of psychomotor impairment associated with the long term use of benzodiazepines is not fully understood. Woods et al (1992), in an extensive review of the literature, concluded that studies of the repeated administration of benzodiazepines show that psychomotor impairing effects diminish over time. It was also noted, however, that these studies are typically limited to a few weeks in duration, and that the effects on performance of benzodiazepines administered over longer periods have not been adequately studied. It appears that some degree of tolerance to the unwanted sedation and drowsiness side-effects may develop within the first few weeks of treatment, however the degree of tolerance which develops among the elderly

who are long-term users of benzodiazepines, and the impact this has on their ability to safety operate a motor vehicle, remains to be explained.

2.2 Effects of Benzodiazepines on Psychomotor Skills, Driving Performance and Risk of MVC

The initial administration of benzodiazepines to young healthy volunteers produces sedation and impairment of the central nervous system and ultimately on a variety of psychomotor tasks that measure motor speed, visual-motor coordination, and cognitive function (Wittenborn 1979, Pomara et al 1984). Similar effects have been reported among the elderly (Boston Collaborative Drug Surveillance Program 1973, Salzman et al 1983, Cook et al 1983, Swift et al 1985) as well as with anxious patients (de Ger. et al 1981, Linnoila et al 1983) and those experiencing insomnia (Carskadon et al 1982, Chen et al 1990). Details regarding these, and other related studies, will be presented in the following section. Initially, a summary of the clinical trials, divided according to the various outcome measures of interest, will be provided. To further assess if the effect of benzodiazepines varies according to the subject's health status, the clinical trials will be divided into those that focus on subjects with insomnia and anxiety (the primary indications for which benzodiazepines are prescribed), as well as the healthy elderly. A review of observational studies exploring the relationship between benzodiazepines and various injury-related outcomes will conclude this section.

2.2.1 Experimental Studies

A number of randomized trials have been conducted in an attempt to characterize the central nervous system side effects related to benzodiazepine therapy. The performance outcome measures evaluated in these trials consist of specific tests designed to objectively measure different aspects of performance including psychomotor related skills, cognitive impairment, daytime sleepiness and assessment of driving performance. Each of these performance outcome measures will be briefly outlined so that their relevance to the issue at hand, namely the ability to safely operate a motor vehicle, may be assessed.

Psychomotor skills are routinely assessed by the divided attention task, whereby subjects are required to monitor two stimuli concurrently, the critical flicker fusion test, which tests the subjects ability to discriminate the fusion of flickering light, and reactive and co-ordinative skills, which are measures of the subjects response to various visual, light, and/or sound stimuli. *Cognitive impairment* is most often assessed by word recall tasks, such as the William Word Memory Task. The multiple sleep latency test (MSLT), which measures sleep-wake tendency at periods of rest during the day using electroencephalograms and electromyograms, is a very objective method of assessing *daytime sleepiness*. There are a variety of different *driving performance* measures assessed. Except for the weaving and gap estimation, other driving performance tasks used to assess vehicle handling are usually performed on roadways to replicate normal driving situations. A common measure of driving performance, the lateral position control measured by an electronic transducer mounted on the vehicle, tests the ability of the subject to control the lateral position of the vehicle during high-speed travel on straight roads.

Although a variety of performance outcome measures are assessed, there is a lack of consensus in the literature as to whic

effects of either triazolam or temazepam in elderly insomniacs. These results however are in response to a single dose of each drug.

The presence and extent of cognitive impairment produced by benzodiazepines (table 2.4) also appears to vary by drug. In general, however, it would seem that lorazepam and triazolam produce some cognitive impairment, while clorazepate has no effect, even among the elderly. Daytime sleepiness also differs according to exposure (table 2.5), with flurazepam being the only drug which consistently showed an effect, except for performance measures following nine days of treatment (Roehrs et al 1986). Results are more consistent for the trials of driving performance (table 2.6), with the long half-life products, and short half-life products at higher doses, typically showing a mild to marked effect.

Subjects with insomnia: As is evident from the description of the population in tables 2.3 to 2.6, randomized trials have been conducted among patients with insomnia specifically. One of the most recent of these, a double-blind multicenter study of 107 patients with chronic insomnia, was undertaken to evaluate the effects of sedative hypnotics on sleep and performance (Chen et al 1990). Eligible patients were chronic insomniacs who were current users of benzodiazepines. Following a washout period, subjects were randomly assigned to a 14 day treatment with either flurazepam 30 mg, flurazepam 15 mg, midazolam 15 mg, or placebo. The major findings were that flurazepam 30 mg, but not 15 mg, significantly impaired psychomotor performance, and that the patients were unaware of this impairment. No changes in performance from baseline were recorded for the placebo group, except for a slight improvement attributed to a learning effect. The results of this study, based on a group of insomniacs randomized to treatment, provide evidence for performance impairment related to side effects of drug treatment, as opposed to the disease condition. In fact, the placebo group were the only patients where improvement of sleep was not experienced, and yet their performance was not affected, suggesting also that performance impairment does not appear to be related to a sleep deficit (Johnson et al 1990a). As in the majority of the randomized trials, the study subjects were relatively

young, with a mean age of 37.9 years. The extent to which these results can be generalized to the elderly population may be limited.

Driving performance was the outcome measure of interest in a double-blind cross-over design which compared flurazepam 30 mg, and larmetazepam 1 mg and 2 mg with that of placebo among a middle-aged group of insomniacs (n=16: age range 26-41) (Brookhuis et al 1990). Each treatment was administered for seven consecutive nights, with all groups receiving placebo for three nights between treatments. The results suggest that flurazepam 30 mg significantly impaired the ability to control the lateral position of the vehicle compared to baseline, with lormetazepam 1 mg having no effect. Volkerts et al (1986) also reported driving performance impairment among young female insomniacs following two nights of treatment with flurazepam 15 and 30 mg and loprazolam 1 and 2 mg.

The randomized trials which focussed on elderly insomniacs specifically often contained a relatively small sample size. In one such trial (n=13; age range 64-79), flurazepam 15 mg was shown to result in daytime sleepiness and decreased vigilance (Carskadon et al 1982). Younger insomniacs (n=23; mean age 36.8) also experienced daytime sleepiness when administered flurazepam 30 mg (Bliwise et al 1983), while triazolam had no effect on daytime sleepiness in either age group.

Subjects with anxiety: The effects of benzodiazepines on patients with anxiety have been tested by a limited number of more dated clinical trials (Saario et al 1976, de Grier et al 1981, Linnoila et al 1983, van Laar et al 1992). Linnoila et al (1983) was able to compare the psychomotor effects of diazepam in both anxious and healthy subjects by subjecting both groups to the randomization, treatment, and testing procedures. The authors reported that diazepam 15 mg per day had no effect on psychomotor skills in either the anxious or healthy group, however, after a single dose of diazepam 30 mg, the impairment in anxious patients and healthy volunteers was roughly of the same magnitude. de Grier et al (1981) reported that a maintenance dose of diazepam 5 mg three times a day impaired the driving performance of anxious outpatients. van Laar et al (1992) reported a similar effect in the first three weeks of

treatment, with no effect during the fourth week of treatment. The results of these studies suggest that the benzodiazepine-induced impairment of psychomotor skills observed in healthy subjects is comparable to that which occurs among anxious patients, and provide further evidence that impairment is related to the drug rather than the disease condition.

Healthy elderly subjects: Randomized trials with healthy elderly subjects have also been undertaken, and, in general, report impairment in all four performance outcome measures. Pomara et al (1984) found significant impairment of psychomotor performance among healthy elderly even at low doses of diazepam 2.5 mg, with the highest diazepam dose (10 mg) producing the greatest impairment. This study, however, was limited to only 12 subjects. Scharf et al (1985) is one of the few studies which reported no effect of clorazepate on recall ability of 43 elderly subjects. It is important to note however, that this study was based on response to a single dose of clorazepate.

There are a number of limitations to these trials, the most obvious being the small sample sizes, in which the study subjects were often young healthy volunteers. Not only does this limit the power of the studies, but the generalizability as well. Although a number of different drugs were included in the trials, the emphasis was often on the long, as opposed to short half-life benzodiazepines, therefore the pertinence to current prescribing practices, in which short half-life benzodiazepines are recommended for use in the elderly, is questionable. The length of the treatment period in which the effects were observed, usually a few weeks, or sometimes even following a single dose, is also less applicable to current patterns of use, particularly among the elderly. And finally, one may question the relevance of the outcome measures tested in the trials to that of the real driving situation. The validity of such measures, including driving under controlled conditions, as predictors of future injuries has not been assessed (Ray 1992b). Despite these limitations, the clinical trials do suggest that benzodiazepine use has a detrimental impact on driving skills.

2.2.2 Non-experimental Studies

Benzodiazepines and their relationship to falls, fall-related injuries and MVCs have been studied in a limited number of non-experimental studies. An increased risk of falls associated with benzodiazepine use (Sorock & Shimkin 1988, Tinetti et al 1988) and hip fractures associated with long half-life benzodiazepines (Ray et al 1987, Ray et al 1989b, Cummings et al 1995), have been reported in epidemiologic studies of elderly persons living in the community.

The association between injury requiring medical attention and use of benzodiazepines was the focus of a study conducted by Oster et al (1987). Over 7000 members of an "HMO-like" health insurance plan who had at least one claim for a benzodiazepine tranquillizer over a four-month time period, and an age- and sex-matched sample of over 65,000 subjects with a drug claim other than benzodiazepines, were identified (subjects 65 years of age and older were excluded as Medicare claims were not available). Health care claims relating to any type of accident were tabulated for the six month period following the drug claim. Results of the study indicated that benzodiazepine users were significantly more likely to experience an episode of accident related health care than nonusers (RR 1.13, $p < 0.01$). The results also showed that benzodiazepine users had a higher number of non-accident related health care services than the nonusers, implying that perhaps the association observed may be confounded by health care utilization patterns. In an attempt to further explore this assumption a second study was undertaken among "new-users" of benzodiazepines (no use in three months prior to "new" use), and a comparison group matched for age, sex, and calendar month during which drug therapy was initiated (Oster et al, 1990). Both accident- and non-accident-related medical care utilization during the three months prior to drug therapy were controlled for in the analysis. Benzodiazepine users were significantly more likely than nonusers to receive accident related emergency outpatient care (RR 2.09, 95% CI 1.27-3.42), as well as any medical encounter (RR 1.15, 95% CI 1.05-1.26), but there was no significant association observed for an accident-related hospital admission. Similar results were obtained when the sample was restricted to

persons who had no accident-related care in the three month period prior to starting drug therapy, providing evidence that the observed association was not related to individual differences in health care utilization.

Although psychotropic drugs have been reported in a limited number of epidemiologic studies to be a possible risk factor for MVCs (Skegg et al 1979, Honkanen et al 1980, Ray et al 1992c, Neutel 1993, Leveille et al 1994), this finding is still controversial (Jick et al 1981, Benzodiazepine/Driving Collaborative Group 1993). Except for studies by Ray et al (1992c) and Leveille et al (1994), none of the previous research separately identified drivers 65 years of age or older. In fact the majority of drivers were less than 30 years of age.

One of the first observational studies exploring the relationship between drug use and risk of motor vehicle crashes was conducted by Skegg et al (1979). The authors matched, for age and gender, 57 drivers injured or killed in a motor vehicle accident with 25 controls each. Drugs prescribed in the three months prior to the accident were identified from medical records. The odds ratio associated with use of minor tranquillizers (including benzodiazepines) was estimated as 4.9 (95% CI 1.8-13.0). In this study exposure was classified simply as present or absent, with no assessment made of dose or duration of use. Alcohol, a known risk factor for motor vehicle accidents in this age range (two-thirds of the subjects were less than 30 years old) was also not taken into account. In addition, no attempt was made to determine if controls were in fact eligible to drive. Despite these limitations, this has become one of the landmark studies in identifying a potential association between drug use and risk of motor vehicle crashes.

In contrast, Jick et al (1981), found no association between use of sedating drugs and automobile accidents resulting in admission to hospital. The study was conducted using drug exposure and outcome data from the Group Health Cooperative of Puget Sound, as well as a review of the clinical records. Among 244 individuals hospitalized following a MVC, there was no difference in the use of sedating drugs by drivers presumed at fault for the crash, compared to other drivers and passengers. One of the major limitations of this study is the lack of an adequate control group, which

consisted of other drivers not at fault and passengers. In addition, the only potential confounder controlled for in the analysis was gender. Given the wide age range of subjects 15 to 64 years, other factors which should have been controlled for include age, alcohol use and prior history of a crash.

The Benzodiazepine / Driving Collaborative Group (1993) also concluded that benzodiazepines were not a risk factor for road accidents. The authors compared injured drivers responsible for a traffic accident with a control group of injured non-responsible drivers and pedestrians. Exposure was classified on the basis of a positive blood sample for benzodiazepines. After stratifying by blood alcohol levels, injured drivers were no more likely than non-injured drivers to have a positive blood test for benzodiazepines. Although the authors state that there was no difference in age or sex between the two groups, the basic demographic characteristics of the subjects were not presented. Assignment of responsibility for each accident was made by the investigators in conjunction with the police, but it is not clear if they were blinded to the exposure status of the subjects at the time this assignment was made. There is also potential for exposure misclassification. The authors pointed out that the test used to detect blood benzodiazepines measures certain drugs poorly, especially triazolam. It is likely however that this misclassification is non-differential with respect to the outcome, and would therefore bias the results towards the null.

A Canadian study, using the Saskatchewan Health computerized databases, focussed specifically on the use of benzodiazepines and their association to MVCs (Neutel 1993). While the author suggests that the risk of hospitalizations for traffic accidents were higher for users of both triazolam and flurazepam compared to a random sample of the population, the results must be interpreted with caution. The study was based solely on hospitalization and prescription drug data, making it impossible to discern the driving status of the study subjects. The benzodiazepine user may not have been the driver, but simply an occupant, of the vehicle involved in the crash. In addition, the sources of data necessarily restricted the outcome to those accidents which resulted in a hospitalization.

In one of the more recent studies, Ray et al (1992c) used computerized data from the Tennessee Medicaid program, driver's license files, and police reports of injurious crashes to examine the association between psychoactive drugs and MVCs in a cohort of 16,262 elderly drivers. Current use of benzodiazepines was reported to be associated with an increased risk of injurious motor vehicle crashes (RR 1.5, 95% CI 1.2-1.9). A significant dose-response relationship was also reported, with a relative risk of 1.1 (95% CI 0.5-2.2) for the equivalent of 4 mg of diazepam and 2.4 (95% CI 1.3-4.4) for 20 mg equivalent. Although this study is unique in that the focus was on elderly drivers, the source population was limited to individuals enrolled in Tennessee Medicaid, a population which has been shown to possess atypical demographic characteristics (Ray & Griffin, 1989a). Although non-representativeness does not necessarily lead to bias, demographic characteristics of the Medicaid population may be effect modifiers. Further limitations include failure to take into account past history of MVCs and the effect this may have on the relative risk, no assessment of the effects of elimination half-life, and no assessment of the risk associated with the initiation of use or with prolonged use.

The most recent study to address the issue of psychoactive medications and injurious motor vehicle collisions among older drivers was undertaken by Leveille et al (1994). This case-control study was conducted using the Group Health Cooperative of Puget Sound (a health maintenance organization) as the source population. Cases were identified from the state police records, and were defined as drivers who sought treatment for injuries within seven days of their collision, during the study period 1987 to 1988, while controls were selected at random from the Group Health Cooperative enrollment files and matched to cases on age, gender and county of residence. Two-hundred-thirty-four of the 312 (75%) cases and 447 of the 648 eligible controls participated (non-participants were subjects who did not respond to the questionnaire or telephone interview). Although the authors had both exposure and outcome information available on the non-responders from computerized sources, they did not report this data. It is therefore not possible to assess the extent to which selection bias may have influenced the study results. Perhaps drivers who were exposed to psychoactive

medications and experienced a motor vehicle collision were less likely to respond to the questionnaire. In contrast to the previous study by Ray et al (1992c) the authors concluded that current use of benzodiazepines was not associated with an increased risk of motor vehicle collisions (OR 0.9, 95% C.I. 0.4-2.0). These results, however, may be an underestimate of the true risk as a consequence of misclassification of the exposure variable. An inability to determine duration of drug use from the computerized pharmacy database forced the authors to develop methods to estimate the likelihood of exposure on the index date, including construction of a probability quotient and assessing the recency of the last prescription dispensed prior to the index date. The probability quotient, which is influenced by frequency of doses per day, would result in a misclassification of the unexposed as exposed for benzodiazepines prescribed in divided daily doses. It appears that the controls were more likely to be prescribed benzodiazepines in this manner, which would have resulted in a reduction in the estimate of risk. Even if the misclassification was nondifferential with respect to the outcome, a reduction in the estimate of the risk would also result. In addition, the number of outcome events available (only 22 cases and 40 controls exposed to benzodiazepines), seriously limited the analyses which could be performed, and prevented the authors from addressing important issues with respect to exposure including that of elimination half-life, and risk among new-users as opposed to long-term users of these drugs. The authors suggest that the discrepancy between findings in their study, and that of Ray et al (1992c) may be related to the variation in the study populations, as well as the drug distributions between these populations. Members of the Group Health Cooperative were from a more advantaged socioeconomic group than the low-income Medicaid enrollees in the study by Ray.

In summary, although only a limited number of epidemiologic investigations have been conducted in this topic area, the evidence regarding use of benzodiazepines and risk of MVCs remains inconclusive. Evidence is even further limited with respect to the risk among elderly drivers, despite the high prevalence and long duration of benzodiazepine use among the elderly, and the ever increasing number of elderly licensed drivers.

2.3 Issues Related to Exposure Characterization

The unwanted central nervous system depression associated with benzodiazepine use appears to be influenced by duration of use, drug dose, and elimination half-life. These topics, as well as that of patient compliance, an important issue to consider when computerized prescription records are used as the source of exposure data, will be addressed in the following section.

2.3.1 Duration of Use - Development of Tolerance

Details surrounding the issue of pharmacodynamic tolerance have been discussed in a previous section of this chapter. To summarize, although evidence from the literature suggests that some degree of tolerance or adaptation develops to the psychomotor impairing effects of benzodiazepines at some point following the initiation of treatment, the results are inconclusive, particularly as they relate to elderly long-term users and the use of long and short half-life benzodiazepines specifically. Ray et al (1989b), in a study of benzodiazepines and the risk of hip fractures, found that new-users of long half-life benzodiazepines (defined as persons whose first prescription was filled in the 30 days preceding the index date) had a higher risk of hip fractures (RR 2.2, 95% CI, 1.5 - 3.4), compared to other current users (RR 1.6, 95% CI, 1.4 - 1.9). However, results of a more recent study, which focussed on benzodiazepines as a class, suggests that risk does not decrease with prolonged use (Ray et al 1992c). Although the risk of MVC did not vary significantly with duration of benzodiazepine use in this study, the highest and only significantly increased risk was reported for a duration of current use greater than 90 days. The conflicting nature of these results may be related to the difference in the distribution of short and long half-life benzodiazepines by duration of use. Although the distribution of exposure by elimination half-life was not provided, the use of short half-life benzodiazepines for short-term exposure, and long half-life products for longer durations of use, may account for the results observed.

2.3.2 Benzodiazepine Dose

Drug dose has been identified as a critical issue in determining unwanted daytime sedation (Roth & Roehrs 1991, Gillin et al 1989). In a review of 52 studies of sedative-hypnotic use and human performance, dose level was the most important factor in performance decrement, with higher doses resulting in increased impairment (Johnson & Chernik 1982). The elderly are also more sensitive to the central nervous system effects of benzodiazepines (Cook 1986, Swift 1990, Greenblatt et al 1991, Teboul & Chouinard 1991).

Earlier studies of hospitalized patients receiving benzodiazepines showed that the most common unwanted side effect symptoms of central nervous system depression such as drowsiness, fatigue, confusion, and ataxia not only increased significantly with age (Boston Collaborative Drug Surveillance Program 1973, Greenblatt et al 1977), but the most striking effect of these drugs among the elderly occurred at higher doses. The increased risk of central nervous system side effects associated with increases in age and dose have been demonstrated in other studies of community-dwelling elderly subjects as well (Castleden et al 1977, Greenblatt et al 1977, Greenblatt et al 1981, Consensus Conference 1984, Pomara et al 1984, Gillin & Byerley 1990).

The impact of benzodiazepine dose on the risk of specific outcomes has produced slightly differing results. In the assessment of benzodiazepines as a risk factor for hip fracture, Ray et al (1987) observed a dose-response relationship for current users of long, but not short, half-life benzodiazepines, while no dose-response relationship was observed for either half-life benzodiazepine in a later study (Ray et al 1989b). The effect of benzodiazepine dose was also evident in a recent study of MVCs (Ray et al 1992c) where there was a pronounced increase in risk with increasing dose to benzodiazepines as a class.

Despite treatment prescribing recommendations (Consensus Conference 1984, American Psychiatric Assoc. 1990, Canadian Pharmaceutical Assoc 1992), results of surveys of benzodiazepine hypnotic use among non-institutionalized elderly in both the U.S. (Swift et al 1984) and Canada (Baker & Oleen 1988) revealed that more than half of the subjects were receiving doses greater than that recommended for the elderly.

2.3.3 Short Versus Long Elimination Half-life Benzodiazepines

As discussed in a previous section on pharmacokinetics, the half-life of benzodiazepines in the elderly are generally prolonged because of reduced clearance and resultant accumulation, an increased volume of distribution, or both (Greenblatt et al 1989). Not only are long half-life products more likely to accumulate, but the elderly also have an increased sensitivity to the psychomotor impairing effects of these drugs (Greenblatt et al 1977, Castleden et al 1977, Dement 1991). It has also been shown that the frequency of psychomotor impairment among users of long half-life benzodiazepines is greater than that for comparable users of short half-life drugs (Carskadon et al 1982, Bliwise et al 1983, Salzman et al 1983, Greenblatt et al 1984), and their use in elderly subjects has been associated with prolonged delirium, an increased risk of falls and hip fractures, and excessive sedation (Pomara et al 1984, Foy et al 1986, Ray et al 1987, Ray et al 1989b, Cummings et al 1995).

Short half-life benzodiazepines are less likely to accumulate and to cause cumulative sedation when multiple daily doses are taken (Shader & Greenblatt 1993), supporting their apparently greater safety. It has been suggested, however, that short half-life benzodiazepines may lose their sedative efficacy over the first few weeks of use (Kales et al 1987, Gillin et al 1989), and are therefore not recommended for long term treatment. In addition, short acting benzodiazepines are more likely to produce symptoms of recurrence, such as rebound insomnia, following their abrupt discontinuation compared to long half-life benzodiazepines (Kales et al 1983, Lucki et al 1986b). The use of rapidly eliminated (short half-life) benzodiazepines are therefore recommended for short term use, while low doses of slowly eliminated (long half-life) benzodiazepines are more appropriate for more prolonged use (Teboul & Chouinard 1991).

2.3.4 Patient Compliance

Another important issue to consider when characterizing exposure using automated databases as the source of information is patient compliance of drug consumption. One of the assumptions made when using databases for exposure

assessment is that prescriptions dispensed from the pharmacies are taken by the subjects as prescribed. Noncompliance would reduce the accuracy of exposure classification. However, if the misclassification is nondifferential, the result would be a conservative bias (Kleinbaum et al 1982).

Estimates of compliance rates in the elderly vary. Spagnoli et al (1989), in a survey of 800 elderly outpatients, reported overall compliance rates of 81.5%, with the most common form of noncompliance being reduced drug use. Other estimates of compliance have ranged from 40% to 75% (Ostrum et al 1988).

Noncompliance in the elderly can be classified into three forms: overuse, forgetting, and alterations of schedules and doses. The most common noncompliant behavior is alterations in schedules with deliberate underuse of the drug (Salzman 1995). These patterns of noncompliance however would vary according to the type of medication, as well as the number of medications the elderly patient is currently taking (Lamy et al 1992). Evidence suggests that for benzodiazepines, elderly patients strictly adhere to their prescribed dose, and do not increase their dose without their doctor's advice (Lamy 1986).

Only a few studies have examined patient compliance and regularity of benzodiazepine use. Baker and Oleen (1988) studied patient-reported use of three benzodiazepine hypnotics among outpatients age 65 years and older in Canada. The study was a convenience sample using pharmacy-based enrollment, with participant follow-up through a 3-day diary and a telephone interview. Potential for selection bias in a sample of such a nature is evident, although the impact of this on the results is difficult to assess. Bearing this in mind, the results suggest that despite receiving prescriptions that allowed discretion as to frequency of use, the majority of participants reported daily rather than episodic use. Reports by continuing users regarding the frequency of use indicated that 57% were taking a hypnotic every day, 20% indicated regular use between one and six times per week, and 22% reported that they took the drug only when necessary or a few times per month, that is, not on a regular schedule. Further, as age increased, the proportion reporting daily use of benzodiazepines also increased gradually.

Swift et al (1984) also reported regular use of benzodiazepine hypnotics among a group of 248 elderly subjects (81.3% of the subjects took regular nightly doses). Compliance with prescribed treatment was also evident; 76% of subjects were taking the drug as prescribed, while 18% were taking smaller and 6% larger than the prescribed doses. Nollan et al (1988) also reported that in the United Kingdom, 70% of benzodiazepine users took their medication as prescribed.

In summary, although the evidence is limited, it appears that regular daily use of benzodiazepines, particularly of hypnotics, is common among elderly long term users of these drugs.

2.4 Risk Factors for MVCs - Potential Confounders

Chronic medical conditions - health status: The evidence regarding the relationship between chronic medical conditions and risk of MVC, although limited, has been inconsistent. One of the initial and frequently cited studies addressing this issue was undertaken by Waller (1965), in which 2672 drivers with chronic medical conditions known to the Department of Motor Vehicles (conditions included diabetes, epilepsy, cardiovascular disease, alcoholism and mental illness), were compared to drivers without any reported chronic conditions. After adjusting for age and driving mileage, drivers with a chronic medical condition experienced a crash rate almost twice that of the control group. No adjustment was made however for the severity of the disease condition. It is likely that drivers who had reported medical conditions would have a more severe and debilitating illness, potentially increasing their risk of a crash.

These results have not been replicated in more recent studies. A study by Koepsell et al (1994) found no association between medical conditions that impair sensory, cognitive, or motor function, including cardiovascular and cerebrovascular disease, and the risk of motor vehicle collisions in older drivers. Similar results were reported by Gresset et al (1994) based on data from elderly Quebec drivers.

Diabetes mellitus and epilepsy are the two conditions studied most frequently in terms of their association with traffic mishaps. Research focussing on diabetes mellitus specifically have also produced conflicting results. While an earlier report suggested an

increased risk of MVCs among diabetics under age 55 (de Klerk & Armstrong 1983), studies which followed reported either no risk (Stevens et al 1989), or only a small risk interpreted by the authors as being of little or no importance (Songer et al 1988, Hansotia & Broste 1991).

Earlier studies have found drivers with epilepsy to be at an increased risk of experiencing a MVC (Waller 1965). More recent studies have observed only slightly increased risks, judged to be insignificant to warrant further restrictions on driving privileges (Hansotia & Broste 1991). The decreased risk may be related to laws restricting the ability of patients with an epileptic-seizure disorder to obtain a driver's license.

Dementia: Evidence from the literature suggests that dementia, with resultant cognitive impairment, may be associated with an increased risk of crash involvement (Kaszniak 1991, Dubinsky et al 1992, Hunt et al 1993), and may also be associated with an increased or decreased potential for exposure to benzodiazepines, depending on the stage of the illness and the prevailing symptoms. Among subjects with dementia, Gilley et al (1991) reported that MVCs were independently associated with the use of sedative medications, even after controlling for the severity of dementia.

Driving history: Driver's characteristics, including prior traffic violations, have also been reported to be associated with the risk of MVCs. Perneger et al (1992), using the Fatal Accident Reporting System in the United States, found that the risk of initiating a fatal crash was increased for drivers with prior traffic violations, including prior offense for driving while intoxicated, prior suspension, and a prior crash (within 12 months). Other risk factors included elevated blood alcohol levels, not wearing a seat belt, and driving without a valid driver's license.

Demographic characteristics: Both age and gender have the potential to confound the relationship between benzodiazepine use and risk of MVC (Underwood 1992, Retchin & Anapolle 1993). Age and gender are both risk factors for crash involvement, as well as associated with benzodiazepine use. It is not clear from the

literature whether age and gender may also act as an effect modifier in this group of elderly drivers.

Other age-related physiologic changes have been identified as potential risk factors for crash involvement among the elderly. These include age-related visual changes, decreased auditory acuity, as well as declines in cognition and functional status (Underwood 1992). However it is unlikely that these factors are associated with the use of benzodiazepines, and therefore should not confound the association between benzodiazepines and risk of MVCs.

2.4.1 Confounding by Indication

The issue of confounding by indication, whereby the risk of experiencing the outcome event is believed to be an effect of the indication for which the drug is prescribed, rather than an independent effect of the drug itself, frequently plagues epidemiologic studies of this nature. However, it appears that the two primary indications for which benzodiazepines are prescribed are unlikely to impair performance in-and-of themselves, and thus are unlikely to act as confounders.

In a study exploring the risk factors for falls among elderly living in the community, the use of benzodiazepines, phenothiazines and antidepressants were associated with falling independently of the disease conditions for which they were prescribed (Tinetti et al 1988).

The impaired performance observed in the study by Golombok et al (1988) was present even after the effects of anxiety had been accounted for, evidence that the impairment is a side effect of the drug, as opposed to being a consequence of the disease condition.

In most patients with chronic insomnia actual sleep loss is slight, excessive daytime sleepiness is rare, and daytime performance is normal (Consensus Conference 1984). This is consistent with the results of studies showing a dose-dependent impairment rather than improvement of performance during the administration of hypnotic agents (Johnson et al 1990). Experimental studies provide further evidence of an independent drug effect in both subjects treated for anxiety (de Grier et al 1981,

Linnoila et al 1983, van Laar et al 1992) and insomnia (Volkers & O'Hanlon 1986, Chen et al 1990, Moskowitz et al 1990).

2.4.2 Alcohol as a Potential Confounder or Effect Modifier

The co-administration of benzodiazepines and alcohol causes greater depression of the central nervous system than either given alone (Sellers & Busto 1982). The extent of this interaction is not known but is believed to be small and vary according to the specific drug, with chlordiazepoxide and oxazepam showing a milder interaction with alcohol than diazepam (Linnoila 1976, Seppala et al 1979, Linnoila 1990). It has also been demonstrated that the time course of benzodiazepine and alcohol interaction is relatively short. Peak effects are seen during the first hour after ingestion of the agents, and after 3 hours the effects are no longer significant (Linnoila & Mattila 1973).

The extent of the interaction and confounding effects of benzodiazepines and alcohol is believed to be minimal among elderly drivers for a variety of reasons. First of all, alcohol itself does not appear to be a major risk factor for MVC in older drivers as it is for younger drivers (Wells-Parker et al 1983, Copeland 1989, Wolf & Rivara 1992). Waller (1985) in a review of the literature concluded that older driver's crashes are less likely to involve alcohol. Both cross-sectional (Sulsky et al 1990) and longitudinal (Adams et al 1990) data show that the frequency and amount of alcohol intake tend to decrease with age. Secondly, the decision to drive after having consumed alcohol also decreases with age. A national survey conducted in 1985 indicates that the proportion of men who drive after drinking was 35% for men aged 25-44 in comparison to 5% for men aged 65 and over (Health & Welfare Canada 1987). Similar results were reported in Quebec from the 1989 National Alcohol and Other Drugs Survey (Health & Welfare Canada 1992).

2.4.3 Driving Frequency

It has been suggested that the opportunity of experiencing a MVC increases with an increase in driving frequency, or total mileage accumulated (Risk & Shaoul 1982). However it has also been proposed that increase in driving frequency results in

enhanced experience with more developed driving skills, and therefore a decreased risk of MVC (Chipman 1982, Brorsson 1989). Driving frequency as a measure of exposure risk becomes particularly pertinent when studying crash rates for drivers in general, as driving frequency varies by age (drivers less than 25 and older than 65 report lower distances travelled than middle-aged drivers). However, this was less of an issue in the current study as our population was restricted to drivers 67 to 84 years of age, where surveys of driving frequency in the United States show a gradual decrease in the number of miles driven for subjects 65 years of age and older (National Research Council 1988).

2.5 Summary

Benzodiazepines are one of the most frequently prescribed class of medications in the elderly population, with both age and female gender strongly associated with an increased prevalence and duration of use. There is convincing evidence available from experimental studies of the performance impairing effects of benzodiazepines, however the association between benzodiazepine use and risk of MVCs from non-experimental studies, particularly among elderly drivers, remains inconclusive. Ray et al (1992c) reported a 50% increased risk of injurious MVCs among elderly drivers currently exposed to benzodiazepines, while Leveille et al (1994) found no association.

The exposure in both these studies was that of benzodiazepines as a class, despite evidence indicating that long, as opposed to short, half-life benzodiazepines are associated with an increased risk of adverse events such as hip fractures. In addition, none of the previous epidemiologic studies have attempted to determine the risk of an injurious event following the initiation of use. Evidence from the literature suggests that some degree of tolerance or adaptation develops to the psychomotor impairing effects of benzodiazepines within the first few weeks of initiating treatment, with the sedative effects highest after initiating treatment, and reduced with continued use. Exploration of benzodiazepine use as a risk factor for MVCs must take into account these important drug characteristics.

Table 2.1 **Prevalence of psychotropic drug use among elderly subjects, by country**

Author	Age of subject	N	Exposure	Exposure period	Prevalence (% of population) Male	Female	Location
Balter et al, (1984)	65+ strata	1500	tranquillizer sedative	prior 12 months	24.1	28.9	Belguim
					17.3	17.8	France
					9.8	18.9	Germany
					5.1	14.9	Great Britain
					7.1	9.7	Italy
					5.8	14.8	Netherlands
					15.2	19.0	Spain
					7.9	24.1	Sweden
					13.4	23.3	Switzerland
					7.4	17.9	USA
Morgan et al (1988)	65+	1020	hypnotic drugs (primarily benzodiazepines)	"ever"	10.0	20.0	England
Dunbar et al (1989)	65+ strata	766	benzodiazepines	prior 12 months	7.0	14.5	Great Britain
Ried et al (1990)	65+	278	psychotropic drugs *	one year	16.8	24.5	Washington
Swartz et al (1991)	55-74 strata	1414	benzodiazepines	prior 12 months	14.0 (male & female)		North Carolina
	75+ strata	425	benzodiazepines	prior 12 months	13.6 (male & female)		North Carolina

* includes antidepressants

Table 2.2a **Percentage of Canadian population using selected licit drugs in the prior month, results from the National Alcohol & Other Drugs Survey, 1989**

	Age 15+			Age 65+		
	males	females	total	males	females	total
sleeping pills	2.5	4.6	3.6	10.3	11.6	11.1
tranquillizers	1.8	4.3	3.1	3.5	6.8	5.4

Table 2.2b **Percentage of Canadian population using selected licit drugs in the prior 12 months, results from the 1990 Health Promotion Survey**

	Age 15+			Age 65+		
	males	females	total	males	females	total
sleeping pills	6	8	7	17	20	19
tranquillizers	4	6	5	12	11	11

Table 2.3* **Randomized trials of the effects of benzodiazepines on psychomotor related skills**

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect**	Comments
Saario et al (1976)	45 anxious outpatients	30.2	diazepam 15 mg	- reactive & co-ordinative skills - attention	2 1	2 week tx. period
Cook et al (1983)	58 inpatients	79	nitrazepam 5 mg temazepam 20 mg	- choice reaction time / letter elimination - choice reaction time / letter elimination	2 2	7 night-time doses
Linnoila et al (1983)	40 anxious outpts. 30 healthy	29 28.7	diazepam 15 mg diazepam 30 mg diazepam 15 mg diazepam 30 mg	- all psychomotor tests - tracking and divided attention only - all psychomotor tests - tracking and divided attention only	0 2 0 2	3 week tx. for anxious pts. 1 day tx. for healthy
Pomara et al (1984)	12 elderly	70.4	diazepam 2.5 mg diazepam 5 mg diazepam 10 mg	- memory and psychomotor performance - memory and psychomotor performance - memory and psychomotor performance	2 2 3	testing 1 & 3 hours after single dose
Hoehn-Saric et al (1986)	20 healthy women	34.7	diazepam 15 mg	- Digit Symbol Substitution Test (DSST) - choice reaction time - drowsiness	0 2 2	6 week tx. period

Table 2.3 con't Randomized trials of the effects of benzodiazepines on psychomotor related skills

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect**	Comments
Chen et al (1990)	107 insomniacs	37.9	midazolam 15 mg	- psychomotor performance	1	14 day tx. period
				- cognitive tasks	0	
				- mood and symptoms	0	
			flurazepam 15 mg	- psychomotor performance	1	
				- cognitive tasks	0	
				- mood and symptoms	0	
			flurazepam 30 mg	- psychomotor performance	3	
				- cognitive tasks	2	
				- mood and symptoms	0	
Nakra et al (1992)	45 insomniacs	72.2	triazolam 0.125 mg	- psychomotor performance	0	testing the morning after a single dose
				- cognitive skills	0	
			triazolam 0.25 mg	- psychomotor performance	0	
				- cognitive skills	0	
			temazepam 15 mg	- psychomotor performance	0	
				- cognitive skills	0	
			temazepam 30 mg	- psychomotor performance	0	
				- cognitive skills	0	

* Tables 2.3 to 2.6 developed using approach adopted from Ray et al (1992a)

** 0 = no effect
1 = non-significant effect
2 = mild effect
3 = marked effect

Table 2.4 Randomized trials of the effects of benzodiazepines on cognitive impairment

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect*	Comments
Roth et al (1980)	11 adult males	19-30	flurazepam 30 mg lorazepam 4 mg triazolam 0.5 mg	- recall tasks - recall tasks - recall tasks	2 3 3	cross-over design with 2 week tx. period
Spinweber et al (1982)	20 male insomniacs	21	triazolam 0.5 mg	- morning performance and mood - memory recognition task	0 2	6 day tx. period
Healey et al (1983)	10 healthy adults	21-40	lorazepam 1 mg lorazepam 2 mg diazepam 5 mg diazepam 10 mg clorazepate 7.5 mg clorazepate 15.0 mg	- word recall - word recall - word recall - word recall - word recall - word recall	3 3 1 1 1 1	cross-over design with testing after a single dose
Scharf et al (1984)	74 healthy adults	24.2	clorazepate 7.5 mg clorazepate 15 mg lorazepam 1 mg lorazepam 2 mg	- immediate word recall - delayed word recall - immediate word recall - delayed word recall - immediate word recall - delayed word recall - immediate word recall - delayed word recall	1 1 1 1 1 1 2 2	testing after a single dose
Scharf et al (1985)	43 nonanxious elderly	60-74	clorazepate 3.75 mg clorazepate 7.5 mg	- immediate recall - delayed recall - immediate recall - delayed recall	1 1 1 1	testing after a single dose

Table 2.4 con't Randomized trials of the effects of benzodiazepines on cognitive impairment

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect*	Comments
Greenblatt et al (1991)	26 healthy young	30	triazolam 0.125 mg	- digit symbol substitution test	2	cross-over design with testing after a single dose
			triazolam 0.25 mg	- digit symbol substitution test	2	
	21 healthy elderly	69	triazolam 0.125 mg	- digit symbol substitution test	3	
			triazolam 0.25 mg	- digit symbol substitution test	3	

* 0 = no effect
1 = non-significant effect
2 = mild effect
3 = marked effect

Table 2.5 Randomized trials of the effects of benzodiazepines on daytime sleepiness

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect*	Comments
Carskadon et al (1982)	13 insomniacs	64-79	triazolam 0.25 mg	- daytime sleepiness; vigilance	0	3 day tx. period
				- performance testing	0	
			flurazepam 15 mg	- daytime sleepiness; vigilance	3	
				- performance testing	0	
Bliwise et al (1983)	23 insomniacs	36.8	triazolam 0.5 mg	- daytime sleepiness (MSLT)	0	cross-over design with 6 day tx.
			flurazepam 30 mg	- daytime sleepiness (MSLT)	2	
Salzman et al (1983)	24 elderly	60-76	diazepam 6 mg	- visual analogue scale rating sedation	2	14 day tx. period
				- visual analogue scale rating fatigue	2	
			oxazepam 30 mg	- visual analogue scale rating sedation	2	
				- visual analogue scale rating fatigue	2	
Roehrs et al (1986)	12 healthy adults	21-35	flurazepam 30 mg	- daytime sleepiness (MSLT) early	2	9 day tx. period
				- daytime sleepiness (MSLT) late	2	
				- performance measures - early	2	
				- performance measures - late	0	
			temazepam 30 mg	- daytime sleepiness (MSLT) early	2	
				- daytime sleepiness (MSLT) late	0	
				- performance measures - early	0	
				- performance measures - late	0	

* 0 = no effect
1 = non-significant effect
2 = mild effect
3 = marked effect

Table 2.6 Randomized trials of the effects of benzodiazepines on driving performance

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect*	Comments
Betts et al (1972)	113 students	18-30	librium 10 mg	- weaving; parking - gap estimation	2 2	5 - 10 mg doses over 36 hours
Hindmarch & Gudgeon (1980)	12 females	34	lorazepam 3 mg	- driving performance	2	cross-over design with 3 day tx. period
de Ger. et al (1981)**	22 males	43	diazepam 15 mg	- driving performance	2	1 day tx. period
Betts & Birtle (1982)	12 women	not reported	flurazepam 15 mg temazepam 20 mg	- weave test - gap test - weave test - gap test	2 3 1 3	cross-over design with testing after a single dose
O'Hanlon et al (1982)	9 males	24-34	diazepam 5 mg diazepam 10 mg	- lateral position control at night - lateral position control at night	0 2	cross-over design with testing after a single dose
Moskowitz & Smiley (1982)	48 adults	21-40	diazepam 15 mg	- driving performance	3	9 day tx. period
O'Hanlon et al (1986)	11 female insomniacs	26-38	temazepam 20 mg nitrazepam 10 mg	- lateral position control - lateral position control	0 2	cross-over design with 8 day tx. period

Table 2.6 con't Randomized trials of the effects of benzodiazepines on driving performance

Reference	Subjects	Age mean or range	Drugs mg/day	Outcome	Effect*	Comments
de Ger. et al (1986)	18 anxious adults	36	lorazepam 3 mg bromazepam 4.5 mg	- driving performance - driving performance	1 1	2 week tx. period
Volkerts et al (1986)	24 female insomniacs	25-40	flurazepam 15 mg flurazepam 30 mg	- driving performance - driving performance	2 3	cross-over design with
	16 female insomniacs	25-40	loprazolam 1 mg loprazolam 2 mg	- driving performance - driving performance	2 3	testing after 2 nights of tx.
	16 female insomniacs	25-40	nitrazepam 5 mg	- driving performance	0	
Brookhuis et al (1990)	16 insomniacs	26-41	lormetazepam 1 mg lormetazepam 2 mg flurazepam 30 mg	- lateral position control - lateral position control - lateral position control	0 2 3	7 day tx. period
van Laar et al (1992)	12 outpatients with anxiety	40	diazepam 15 mg	- lateral position control	3 (weeks 1-3) 0 (week 4)	4 week tx. period
O'Hanlon et al (1995)	16 adults 18 adults	25-43 22-34	diazepam 15 mg lorazepam 1.5 mg	- lateral position control - lateral position control - car following test	3 3 3	8 day tx. 9 day tx.
	56 anxious adults	24-64	lorazepam 4 mg	- lateral position control	3	8 day tx.

* 0 = no effect
1 = non-significant effect
2 = mild effect
3 = marked effect

** non-randomized

CHAPTER 3
METHODS

This chapter describes the study design and details of the methods used to determine the association between the use of benzodiazepines and risk of motor vehicle crashes (MVCs) in the elderly. Following a brief overview of the study a description of the computerized databases used as the sources of data will be provided. Details of the methods including identification of the study population, description of the study variables, characterization of exposure and an outline of the analysis will constitute the remainder of the chapter.

3.1 Overview of the Study

A nested case-control design was used to address the study objectives, with computerized databases from three agencies of the Quebec government providing the necessary data. The study population and outcome were identified from the Société de l'assurance automobile du Québec (SAAQ). Drug exposure and medical service data were obtained from the Régie de l'assurance maladie du Québec (RAMQ), and details regarding hospitalizations were obtained from the Ministère de la Santé et des Services sociaux (MED-ECHO). Data from all three sources were linked using a unique identifier, the individual's health care number (numéro d'assurance maladie).

The study period spanned three years, from June 1, 1990 to May 31, 1993. Study subjects were drivers from the province of Quebec who were between the ages of 67 and 84 inclusive on June 1, 1990. The outcome event was defined as involvement of a cohort member as a driver in a motor vehicle crash in which at least one victim (not necessarily the driver) sustained bodily injury, while exposure was new use of short and long half-life benzodiazepines of increasing duration, as well as current use irrespective of duration. The short half-life benzodiazepines included alprazolam, bromazepam, lorazepam, oxazepam, temazepam and triazolam while the long half-life products included clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam

and nitrazepam. For both short and long half-life benzodiazepines the rate ratio of crash involvement was estimated from logistic regression models controlling for demographic characteristics, a measure of health status, exposure to other central nervous system drugs and previous injurious crashes.

3.2 Sources of Data

3.2.1 Société de l'assurance automobile du Québec (SAAQ)

Identification of the cohort and ascertainment of all cases, as well as the formation of the sub-cohort, was undertaken with the Société de l'assurance automobile du Québec (SAAQ). The SAAQ is a provincial government agency responsible for driver's license registration, vehicle registration, recording reports of motor vehicle traffic accidents, as well as administering the universal insurance system which provides financial compensation to those residents of the province who are injured in MVCs. Since it was created in March 1978 the SAAQ has maintained driver, vehicle and accident information for administrative purposes in computerized databases. These databases have been used for research purposes to describe characteristics of crashes (Maag et al 1993), determine prognostic factors for whiplash injuries sustained in a crash (Harder 1993, Suissa et al 1995) as well as to evaluate interventions such as seatbelt use (Laberge-Nadeau et al 1988).

Motor vehicle accident report forms are completed by Quebec police and contained in the "Fichier Accident" computerized files of the SAAQ. According to Quebec law, police who are notified of a crash must, within eight days following the crash, complete and submit an accident report form to the SAAQ. This form is completed for all crashes involving bodily injury, as well as those with material damage only valued at $500 or more. The present version of the accident report form (revised September 1, 1988) contains information concerning the crash (date, time and location of crash, type of crash, weather and road conditions, number and type of vehicles involved, estimated amount of vehicle and property damage), as well as persons involved (vehicle occupied, position in car, seatbelt use, nature of injuries, health care

number, and hospital to which injured were transported). Police are not required to report to the SAAQ those crashes involving material damage only in which the value of the damage was less than $500.00, and for which no crime or offense was committed.

3.2.2 Régie de l'assurance maladie du Québec (RAMQ)

The RAMQ is responsible for administering insured health-care services for the province. Residents of Quebec are eligible for health care coverage once they have established residence and registered with the RAMQ for a health card. Visitors, non-Canadian students, and individuals residing outside of Quebec for more than 183 days in the year are not eligible for coverage. As a result of the various health service programs provided, the RAMQ have three computerized databases that contain a variety of health-care information. The ***demographic database*** contains the name, date of birth, gender and address including postal code of all individuals registered as a medicare card holder in Quebec. The ***medical services database*** contains details regarding the medical services program, including information on the nature of the service rendered, specialty of treating and referring physician, date and location of the service, as well as the diagnostic code of the service (ICD-9 code). This program is universal for all Quebec residents and is fee-for-service (the physician claims reimbursement for the medical service rendered). The ***prescription database*** contains information on out-patient prescription medications. This universal program is restricted to individuals 65 years of age and older and welfare recipients and is fee-for-service (the pharmacy claims reimbursement for the drugs dispensed). The pertinent variables in this database include:

1) patient identification (12 digit health care number)

2) date of dispensing

3) drug class (categorized by the American Hospital Formulary System)

4) drug code - an eight digit drug identification number (DIN)

- this code identifies the name of the product, the unit dose, the form, the manufacturer, and the unit cost

5) quantity dispensed

6) duration of treatment prescribed

7) new prescription or refill

The prescription database contains medications dispensed by a pharmacist to out-patients. Only drugs identified in the RAMQ formulary, a provincial formulary of insured drugs published every six months, are contained in this database. Drugs available over-the-counter are not recorded on the prescription database, unless they have been specifically prescribed by a physician.

The unit of observation is the medical service in the medical services database, and the prescription in the prescription database. This data can be linked using the individual's unique health care number, to obtain a longitudinal record of medical service and drug exposure information.

3.2.3 Ministère de la Santé et des Services sociaux (MED-ECHO)

At the initial stages of the study we had intended to use the SAAQ and RAMQ as our primary sources of data. Dates of hospital admission and discharge, which are not directly available from these two sources, were to be created from the RAMQ Medical Services database using variables from physician billing including date and location of the visit (in-patient versus out-patient setting). However, after reviewing the RAMQ Medical Services data it became obvious that date of admission and discharge reconstructed from this source would be imprecise. Details regarding hospitalizations for all study subjects were thus obtained from a third government

agency, the MED-ECHO hospitalization database. Since 1981 MED-ECHO, which is the hospital discharge database of the Quebec Ministry of Health and Social Services, has collected information on hospitalizations from all acute care hospitals in the province of Quebec. For every hospital admission, a form is completed which contains demographic and personal identification information, dates of admission and discharge, as well as further details of the hospitalization including the discharge diagnoses. This information is collated on the MED-ECHO computerized database.

3.3 Choice of Study Design

The choice of study design was influenced by the size of the cohort of elderly drivers in the province of Quebec, which was approximately 225,000 in 1990. This cohort was too large to be manageable for the purposes of data analysis, and it was therefore necessary to consider sampling designs within cohorts, namely the case-cohort or the nested case-control design. We had initially decided upon the case-cohort approach, primarily to simplify the estimation of absolute rates and rate differences. However, the size of the study population, combined with the complexity of the time-dependent exposure assessment, made it virtually impossible to obtain the relative risks estimates with the necessary case-cohort variance adjustments, even when running the computer-intensive Epicure program on a fast and efficient UNIX-based workstation. We therefore decided to employ a nested case-control design within a case-cohort study population, with a ratio of 10 controls per case, to address the study objectives. The nested case-control design enabled us to classify the time dependent exposure on a daily basis, as well as to define other time dependent covariates, in a much more efficient manner. The validity of this nested case-control design within a case-cohort sample was assessed, and is addressed in chapter 5 of this thesis.

3.4 Identification of Study Population

The identification of the study population took place in a series of four steps performed by the SAAQ, under our direction and supervision. The first step involved

the formation of the cohort. The second step was identification of all outcome events from within the cohort and the third step, which occurred independently of step two, was the process of obtaining a random sample from the full cohort to form a "sub-cohort". The fourth and final step was that of combining all outcome events (step two) and the sub-cohort (step three) to form the case-cohort study population.

3.4.1 Step One - Formation of the Cohort

The source population consisted of all subjects who, on June 1, 1990, were between the ages of 67-84 inclusive, possessed a valid class 5 driver's license (authorized to operate a two-axle passenger vehicle), and had resided in Quebec for at least the previous two years. The universal prescription drug program in the province of Quebec is restricted to residents of the province 65 years of age and over. Thus, in order to obtain a complete two-year history of drug exposure necessary for exposure classification, subjects must have been 67 years of age and older, and residents of Quebec for at least two years prior to their entry into the cohort. We applied an upper age restriction of 84 because subjects beyond this age are less likely to be driving, and therefore would not be candidates for the outcome.

Entry into the cohort was June 1, 1990, and the exit date was the earliest of May 31, 1993, age 85, the date of the event, the date of death, or the date of emigration from the province at which time the Quebec driver's license was no longer valid. Each subject, therefore, had the potential to be followed for three years. The SAAQ "fichier permis de conduire" (driver's license file) was used to identify this cohort.

3.4.2 Step Two - Identification of Outcome Events

The study outcome was defined as involvement of a cohort member as a driver in a motor vehicle crash in which at least one victim (not necessarily the driver) sustained bodily injury. Those crashes which resulted in property damage only were not included for two primary reasons. First of all, from a public health perspective, MVCs which result in property damage only are of less relevance and importance than

those with bodily injury. Secondly, crashes with property damage only are more likely to be under-reported, although this does not affect estimates of the incidence density ratio, unless differentially associated with benzodiazepine use. Thus, for the sake of relevance and validity, we focussed on crashes with bodily injury, as identified from the police recorded accident report forms.

Outcome Ascertainment: Potential events were identified from the source population throughout the three year study period of June 1, 1990 to May 31, 1993. The accident report forms, "rapport d'accident de véhicules routiers", contained in the SAAQ "Fichier Accident" were linked to the source population of eligible drivers defined above using the driver's license number. All crashes in which the cohort member was a driver and at least one victim (not necessarily the driver) sustained bodily injury were identified.

It was possible that an individual may have been involved in more than one MVC resulting in bodily injury during the study period. Only the first eligible event during this period was identified and used.

3.4.3 Step Three - Identification of the Sub-cohort

From the entire cohort defined above, we obtained a random sample of subjects to form the "sub-cohort". Cases were <u>not</u> excluded from the cohort prior to sampling, and had equal opportunity to be sampled as other cohort members. This type of design therefore results in an overlap of a certain number of subjects who are both cases and members of the sub-cohort. It was necessary to identify these subjects by a special variable for the purposes of the calculation of the variance adjustment in the case-cohort analysis, and the formation of risk sets in the nested case-control analysis.

The sub-cohort can in fact be viewed as a smaller version of the full cohort, in that it contains the same proportion of cases, and distribution of subjects by age gender and region of residence, as the full cohort.

3.4.4 Step Four - Formation of the Study Population

The combination of all subjects with the outcome event identified in step two, and the sub-cohort members identified in step three, resulted in the formation of the study population.

3.5 Record Linkage

Record linkage between the three government agency databases occurred in two stages, linkage between the SAAQ and the RAMQ, followed by linkage between RAMQ and MED-ECHO.

Although the SAAQ, RAMQ and MED-ECHO are all provincial government agencies, their computerized databases are administered separately. While linkage within the RAMQ prescription and medical services databases is done routinely, and linkage between the RAMQ and MED-ECHO databases has been undertaken a limited number of times in the recent past, linkage between SAAQ and RAMQ databases is unprecedented. The logistics to undertake this linkage were therefore developed accordingly, using the health care number as a unique identifier.

The health care number is acquired at birth, or at the time of residency, and remains unchanged throughout the life of the individual. This unique identifier is used for record linkage within the RAMQ databases, and ideally would serve as the link between the SAAQ and the RAMQ. However the health care number is not routinely recorded by the SAAQ. Only subjects involved in a MVC have their health care number recorded on the accident report form completed by the police - all members of the study population without a MVC would therefore not have this unique identifier available. It is possible, however, to reconstruct the first 10 digits of the 12 digit health care number using basic information which is available for all subjects with a driver's license. The health care number is composed of the following information:

Digits 1-3	First 3 letters of the surname
Digit 4	First initial of the given name
Digits 5-6	Year of birth

Digits 7-8	Month of birth, for males
	Month of birth + 50, for females
Digits 9-10	Day of birth
Digits 11-12	Numerical code assigned by RAMQ

Using the information available, a 10 digit health care number was reconstructed for ***all*** subjects identified by the SAAQ (all cases and the sub-cohort). This 10 digit number was then linked to the health care number in the RAMQ files.

Subjects for whom a match could not be obtained were then linked by one of two procedures: use of the Social Insurance Number, or a probability match using details of the individuals name, address and date of birth. Although the Social Insurance Number is available in the RAMQ files, since the early 1980's the SAAQ no longer requires that drivers submit their Social Insurance Number. However for all drivers registered in Quebec prior to the 1980's, the Social Insurance Number was available as a means of linkage.

Attempts were made to link the remainder of the subjects using details of the name, address, and date of birth. For each subject remaining in the SAAQ file the combination of information in the following order of priority was constructed:

- first line of address and postal code
- second line of address and postal code
- date of birth (month and day) and address
- date of birth (month and year) and address
- date of birth (year and day) and address
- first initial and date of birth (year, month and day)

Subjects from the RAMQ file corresponding to any component of the above information were identified, resulting in a 1 to "n" match. Each subject from the SAAQ and their "n" potential RAMQ matches were manually reviewed to identify matches. Every subject linked at this stage was verified as a correct match through a

manual check using all details of the name, address and date of birth. The reason the subject had not been linked previously using the 10 digit health care number was also identified. The most common reason for a non-match at this stage was the use, by female subjects, of a different surname in the two files. In Quebec, women are legally required to retain their maiden name on their health insurance card, however the same requirement does not apply to their driver's license. Other reasons were related to typographical errors, including a different spelling for the surname, a different first initial, or a single digit in the date of birth not corresponding between the two files (ie October 30 vs. October 31).

3.6 Exclusion Criteria

The following exclusion criteria were applied equally to all study subjects:

1) Residence in a chronic care setting during the study period.
2) Prior hospitalization, defined as being in hospital in the 60 days prior to the index date, regardless of the length of hospitalization, OR, admitted to hospital in the year prior to the index date, for a duration of 30 days or more.

These exclusion criteria were applied because of their potential influence on both exposure and outcome. Subjects living in a chronic care setting are less likely to drive and hospitalized patients would not be driving, and therefore would not be considered candidates for the outcome.

A further reason these exclusion criteria were applied was to reduce the potential for exposure misclassification. The RAMQ does not record prescription data for institutionalized patients, therefore, regardless of their exposure status, all subjects living in a chronic care setting would be classified as unexposed. Two aspects of the hospitalization were also taken into consideration to prevent potential misclassification of exposure: the length of the hospitalization and the recency of the hospitalization prior

to the index date. Individuals admitted to hospital for long durations would have extensive data truncation; for this reason, all subjects admitted to hospital in the year prior to the index date for a duration of 30 days or more were excluded. With respect to the recency of hospitalization prior to the index date, all subjects who were in hospital in the 60 days prior to the index date were also excluded. We had developed an algorithm of determining exposure status which took into account each of the 60 days prior to the index date. A hospitalization during this period, regardless of the length, would disrupt this algorithm and result in a potential misclassification of exposure.

Dates of hospital admission, discharge and length of stay were identified from the MED-ECHO database. A case or control who was in hospital in the 60 days prior to their index date, regardless of their length of stay, was excluded. The subject may have been admitted prior to the 60 day period before the index date, but the duration of the hospitalization must have lasted into the 60 day period prior to the index. As well, subjects who were admitted to hospital in the year prior to the index date for a duration of 30 days or more, were excluded.

Residence in a chronic care setting was determined from the RAMQ Medical Services file. Any member of the cohort who had at least one physician visit in a chronic care setting (indicated by a facility location code of long term care, long term accommodation, rehabilitation centre, government funded accommodation and private accommodation for the elderly) during the study period was excluded.

3.7 Sample Size Considerations

Sample size calculations were performed a priori on the basis of estimates of the prevalence of exposure and outcome for the province of Quebec. In 1991 there were 314,768 licensed drivers 65 years of age and older in the province of Quebec, (Société de l'assurance automobile du Québec 1992a) and a total of 3,057 drivers in this age category who were involved in a MVC resulting in bodily injury (a rate of 9.7 per 1,000 licensed drivers). Limiting the number of accidents to those which occurred in

the age range of interest (67-84), and assuming that each year 10% of MVCs with bodily injury occur among drivers with previous history of an accident, we had calculated the number of first events in the three year study period to be 6642.

Based on the estimated prevalence of benzodiazepine use in the Quebec population 65 years of age which is around 32%, (Tamblyn et al 1994) an alpha=0.05, two sided test, with 6642 events, and a case-control ratio of 1:2, this study would have 99% power to detect a relative risk of 1.2. We therefore decided to obtain a sub-cohort size approximately 2-3 times the number of events.

Our estimates used to determine the size of the sub-cohort were based on the prevalence of exposure to benzodiazepines in the population in a one year period, and not on the much lower prevalence of "first" use among elderly drivers, which was one of the objectives of our study. Since this prevalence was unknown to us, we elected to sample 10 controls per case.

3.8 Application of Exit Dates

Exit dates were assigned to study subjects prior to the selection of the risk sets. The exit date used was the earliest of: May 31, 1993, age 85, date of the event, date of death or date of emigration from the province. Date of death was obtained from three sources, in the following order of priority according to availability: MED-ECHO, SAAQ and RAMQ. Date of emigration from the province was obtained from the SAAQ driver's license file.

3.9 Formation of Risk Sets

Using incidence density sampling, a random sample of 10 controls were matched to each case on the date of the event. Using this criterion, the potential controls were required to have been at risk for the outcome at the time of the event in the case subjects, a date we refer to as the index date. Hospitalization eligibility criteria previously applied to cases were also applied at this stage in the selection of controls. Subjects were not eligible if they had been in hospital in the 60 days prior to

the index date, regardless of the duration of the hospitalization, or if they had been hospitalized in the year prior to the index date for a period of 30 days or more.

Risk sets were formed on each day that an outcome event occurred. If more than one event occurred per day, then the number of controls selected was 10 times the number of events. For example, if three events occurred on June 15, 1991, then 30 controls were matched to the three cases, for a total of 33 subjects in the risk set (three cases, 30 controls). The number of risk sets was equal to the total number of days in the three year period in which there was at least one outcome event.

As is typical in case-control sampling, a case could serve as a control prior to becoming a case. However a further restriction had to be applied which allowed only cases who were part of the sub-cohort to be eligible as potential controls. Since we had identified all cases from the cohort, inclusion of cases who were not sub-cohort members may result in an over-representation of case subjects serving as controls.

3.10 Selection of Variables

In accord with the SAAQ, RAMQ, and Commission d'accès à l'information confidentiality regulations, the type and detail of the variables made available to us were decided upon only after considerable negotiation. Because of the detail of information which could be obtained by linking SAAQ and RAMQ data, careful scrutiny of each variable was undertaken to ensure that the confidentiality and anonymity of the study subjects was maintained. In addition, following the linkage of the data files the health care number was removed and each study subject was left with a unique identifier originally assigned by the SAAQ.

Outlined below are the modifications which were made to the original variables requested:

SAAQ Original Variables	**Variable Provided**
1) subject's date of birth	1) year of birth
2) exact location of accident	2) regrouped:

· street number or name	1 = urban community of Outaouais
· autoroute number	2 = urban community of Quebec
· intersection	3 = Montreal, Champlain, Laval
	4 = Sherbrooke
	5 = all other regions
3) age of victims	3) eliminated

In addition, the five digit variable in the RAMQ medical services database which defines the exact location of a physician visit (both ambulatory and in-hospital) was modified to ensure confidentiality. Only the first digit, which indicates the type of health care agency, and the last digit, which provides the unit of care within the agency, was requested. The three central digits which specify the exact location of the agency were masked with an "X".

3.11 Classification of Exposure

As discussed in chapter two, the risk of experiencing a MVC may vary depending on specific aspects of benzodiazepine exposure including duration of use, elimination half-life and dose. In addition, the influence of past use as a confounder and/or effect modifier must also be addressed. Each of these dimensions were taken into account in the characterization of exposure. The description of the classification of exposure will be divided into two sections, "new use" and "current use", corresponding to the two types of analyses conducted. Within new use the exposure groups included benzodiazepines as a class, short half-life benzodiazepines and long half-life benzodiazepines. For current use the exposure groups were short and long half-life benzodiazepines.

The following points were taken into account in the classification of exposure:

3.11.1 Exposure on the Index Date

Previous studies suggest that exposure to benzodiazepines on the date of the adverse event results in the highest risk of injuries related to psychomotor impairment (Ray et al 1987, Ray et al 1989b, Ray et al 1992c). The risk for former users was either small or no different that nonusers. Based on this evidence, and the pharmacodynamic properties of the drug, it was determined that the classification of "exposed" must include exposure on the index date. The prescription must have been dispensed ***prior*** to, and not on, the index date, and have been of sufficient duration to extend up to, or beyond, the index date. As will be discussed in chapter 5 of this thesis, benzodiazepines dispensed on the index date were not included in the definition of exposure. This is related to a number of factors including the acuteness of the exposure-outcome relationship, the fact that the outcome event may be an indication for the exposure and the inability to differentiate the temporality of exposure-outcome within a given day.

3.11.2 Initiation and Termination of Exposure

In this study exposure took into account the total length of time an individual was continuously exposed, based on the date of dispensing and prescribed duration of treatment. It was assumed that initiation of exposure began on the day the drug was dispensed. The corresponding start and stop dates for each prescription were thus defined as:

start = date of dispensing

stop = (date of dispensing + duration) - 1

3.12 New Use

3.12.1 Duration of Use

Evidence from the literature suggests that some degree of tolerance or adaptation develops to the psychomotor impairing effects of benzodiazepines within the first few weeks of initiating treatment. It has been suggested that the risk of experiencing an adverse event as a consequence of these sedative effects is highest after

initiating treatment and is subsequently reduced and even returned to baseline, with continued use. Our first objective therefore was to determine the risk associated with "new use" of benzodiazepines, and determine the shape of the rate ratio curve for new use as a function of increasing durations. We sought to determine the risk of experiencing an event within the first seven days of new use, as well as the subsequent 8-30, 31-60 and 61-365 days of continuous new use. Each interval represented an increasing duration of new use. For example, the interval 1-7 indicated at least 1, and up to seven days of new use. In the same manner, 8-30 indicated more than seven and up to 30 days of continued new use, 31-60 indicated more than 30 and up to 60 days of continued new use and 61-365 indicated more than 60 and up to 365 days of continued new use. The four intervals were mutually exclusive. We obtained a rate ratio curve by plotting the rate ratio by the duration of use. The shape of the curve enabled us to determine when, after initiating treatment, the risk of experiencing an adverse event was the greatest, as well as whether or not there was a continued risk with prolonged use.

As a first step in defining exposure we had to define new use, and new use of increasing durations, to draw the rate ratio curve. Guided by the principles of occurrence research (Miettinen, 1993), the scale of time in this case-control design was anchored to the outcome event. Thus T_o was the index date (the date of the event for cases and matching index date for controls), and history of benzodiazepine exposure with respect to the referent point, T_o, was identified.

However in drawing the rate ratio curve associated with first use of benzodiazepines, and in its interpretation, it may be helpful to think of exposure initiation as T_o (cohort T_o), with the task of subsequently identifying the time from exposure initiation until the event. The result is in fact analogous to that described above. The time interval remains the same, whether you view it "backward" as benzodiazepine exposure in number of days prior to the event, or "forward" as time from initiation of exposure to the outcome event. We will refrain from implying a sense of directionality in this study, as is often done in a contrast of case-control and

cohort study design, and as such avoid use of terms such as "backward" and "forward". Case-control studies explicitly involve follow-up of a source population over time. To document occurrence of the outcome you need population experience, which, by definition, requires following a study population (Miettinen 1993).

In summary, regardless of the focus taken to view the relationship between the exposure and outcome, the key feature is the history of benzodiazepine exposure in temporal relationship to the outcome event. Therefore, for the purposes of clarity, in descriptions of the characterization of exposure we shall define benzodiazepine exposure history as the time prior to the index date. However, in addressing the rate ratio curve, and in interpreting the results, we shall refer to time as that being from the initiation of exposure to the outcome event.

3.12.2 Issues in Characterizing New Use - Length of Washout Period

Ideally, a study of the effects of new use of benzodiazepines should be based on first-time ever users. Unfortunately, such subjects are rare when studied against MVCs. It was therefore impossible to focus solely on first-time users. Instead, we defined "new users" to include subjects who may have used benzodiazepines at some time in the past, stopped using the product for a certain washout period, and subsequently started again. This corresponded to a much larger group of subjects.

The challenge in defining this new use was to establish a "washout period", or a period of non-exposure prior to being dispensed a benzodiazepine, which would enable the exposure to be classified as "new use". We found that a three day period with no exposure prior to the initiation of therapy was sufficient to define the washout period. This three day period included no exposure to either half-life benzodiazepine. For example when the focus of analysis was on short half-life exposure, the washout period was non-exposure to short or long half-life benzodiazepines. The validity of this three day washout period was assessed by calculating, for each subject, the time interval since they were last exposed to a benzodiazepine of either half-life, and then assessing

by an interaction term in the model whether the length of the washout period modified the effects of current exposure.

The length of the washout period ranged from 4 to 365 days. A subject meeting the exposure definition of first seven days of use (with no exposure on day 8, 9 or 10) but whose previous benzodiazepine exposure ended day 11 prior to the event would have an interval of 4 days for the length of the washout period. A subject with no prior exposure would have an interval of 365 days.

3.12.3 Characterization of New Use

Utilizing the three day washout period described above, new use of benzodiazepines, defined by the time from exposure initiation to the index date, was characterized in the following manner:

1) First seven days of use:

Exposed: prescription dispensed within 1 to 7 days prior to the event; exposed on the index date; no exposure on days 8, 9 and 10 prior to the event.

Unexposed: no exposure day 0 to 10 prior to the index date.

2) Up to 30 days of continuous use:

Exposed: prescription dispensed within 8 to 30 days prior to the event; continuously exposed until the index date; no exposure on days 31, 32 and 33.

Unexposed: no exposure day 0 to 33 prior to the index date.

3) Up to 60 days of continuous use:

Exposed: prescription dispensed within 31 to 60 days prior to the event; continuously exposed until the index date; no exposure on days 61, 62 and 63.

Unexposed: no exposure day 0 to 63 prior to the index date.

4) Up to 365 days of continuous use:

Exposed: prescription dispensed within 61 to 365 days prior to the event; continuously exposed until the index date.

Unexposed: no exposure day 0 to 365 prior to the index date.

As noted previously, each of the above categories were mutually exclusive, and a subject may contribute to only one of the above exposure categories. Each category of first use was compared to that of non-use within a time interval of the same duration. The relevance of this reference group, and a comparison with current epidemiologic views, will be discussed in chapter 5 of this thesis.

3.12.4 Modifications for the Analysis of Short and Long Half-life Exposure

When the focus of analysis was short half-life benzodiazepines, first use was defined as use of a short half-life benzodiazepine in the appropriate time intervals, as discussed above, irrespective of their exposure to a long half life benzodiazepine. However, the three day washout period was defined as no exposure to either half-life (absence of exposure entirely). Unexposed, the reference group, was also defined as no exposure to either half-life (the absence of exposure) for the duration of the first use interval, as defined previously.

The length of the washout period was taken as the duration since last exposed to a benzodiazepine of either half-life, and was calculated as described previously. Similar definitions were used to classify long half-life exposure.

3.13 Current Use

3.13.1 Exposure on the Index Date Irrespective of the Duration of Use

Following the assessment of new use a second analysis was conducted which focussed only on current use of short and long benzodiazepines, with current use characterized as exposure on the day of the event, irrespective of the duration of that exposure.

Current use of short half-life benzodiazepines was defined as:

Exposed: Prescription for a short half-life benzodiazepine dispensed prior to the index date, lasting up to, or beyond, the index date.

Unexposed: No exposure to benzodiazepines of either half life (absence of exposure) in the 365 days prior to the index date.

3.13.2 Other Half-life Exposure

A substantial number of subjects were currently exposed to both a long and a short half-life benzodiazepine. In order to obtain the independent effect of current short half-life exposure, exposure to a long half-life benzodiazepine in the 60 days prior to the event was also determined and included in the model.

The same definitions were applied in defining long half-life exposure.

3.14 Additional Assessment of Drug Characteristics

Further analyses were undertaken to determine the risk of MVC associated with particular aspects or characteristics of drug exposure. These analyses were conducted for "the first seven days" of benzodiazepine use, as well as for "current use".

3.14.1 Benzodiazepine Dose

For both the first seven days of use and current use, an analysis was conducted to assess whether there was a relationship between benzodiazepine dose and risk of MVC. Dose was divided into three categories to reflect the recommended initial average daily dose schedules for the elderly. Use of these dose categories enabled individual products to be compared without having to rely upon dose equivalencies between products.

The average daily dose for each benzodiazepine prescription was estimated using three variables from the prescription database: the unit dose of the drug, the quantity dispensed, and the prescribed duration of treatment as follows:

$$\text{average daily dose} = \frac{\text{dose per unit} * \text{quantity}}{\text{prescribed duration of treatment}}$$

The average daily dose for the most recent prescription was then categorized as a percentage of the recommended initial average daily dose for the elderly, based on the Compendium of Pharmaceuticals and Specialties (Canadian Pharmaceutical Assoc 1990-

1992) for 1990-1992. The following dose categories were created (Appendix A contains the breakdown of categories):

- recommended average daily dose or less
- 101 - 200% of recommended average daily dose
- > 200% of recommended average daily dose

For the first seven days of use, each dose category was compared to the reference category of non-use in days 0 to 10. For current use, each dose category was compared to the reference category of non-use in days 0 to 365 prior to the event.

If more than one benzodiazepine was prescribed as the most recent prescription prior to the event, that which corresponded to the highest dose category was used in the analysis.

3.14.2 Individual Drugs

An analysis was undertaken to determine the rate ratio of MVC associated with the first seven days of use of individual benzodiazepine drugs, as well as that associated with current use of individual drugs. The distribution of individual products which characterized the first seven days of use were reviewed, and all drugs with a five percent or greater prevalence of use in cases and controls were included in the analysis. The same criteria were applied to determine individual drugs for inclusion in the current use analysis.

3.14.3 Exposure to Multiple Benzodiazepines

First seven days of use: The rate ratio of MVC associated with the first seven days of benzodiazepine use, by the number of different benzodiazepines received, was the focus of a further analysis. The reference category for each was non-use in days 0 to 10 prior to the event, with the exposure categories defined as follows:

1) Only one benzodiazepine: only one benzodiazepine prescribed which characterized the first seven days of use.

2) Two or more different benzodiazepines: two or more different benzodiazepines prescribed, regardless of their half-life, which characterized the first seven days of use.

3) At least one long and one short half-life benzodiazepine: at least one long and one short half-life benzodiazepine prescribed which characterized the first seven days of use.

These categories were not mutually exclusive, in that a subject who was exposed to at least one long and one short half-life benzodiazepine would also be included in the category of two or more different benzodiazepines.

Current use: Similar definitions of exposure to multiple benzodiazepines were applied for current use, with the reference category being no exposure in the 365 days prior to the event. In addition, the following two categories were added:

1) At least two or more short half-life benzodiazepines: At least two or more different short half-life benzodiazepines prescribed which characterized current use.

2) At least two or more long half-life benzodiazepines: At least two or more different long half-life benzodiazepines prescribed which characterized current use.

3.14.4 Independent Effects of Short and Long Half-life Benzodiazepines

To assess the independent effects of the first seven days of use of short and long half-life benzodiazepines, as well as to assess the potential interaction between the two, a model was fit which included both these terms as separate variables.

In summary, the following variables were used to characterize new use and current use:

New Use: for benzodiazepines as a class, short half-life and long half-life

- first seven days of use
- more than seven and up to 30 days of continuous use
- more than 30 and up to 60 days of continuous use
- more than 60 and up to 365 days of continuous use

- time since last exposed: 3 categories:
  - 4 to 30 days
  - 31 to 90 days
  - 91 to 365 days

Current Use: for short half-life and long half-life benzodiazepines

- current use
- other half-life exposure

Both First Seven Days of Use and Current Use:

- dose: 3 categories:
  - recommended average daily dose or less
  - 101-200% of recommended average daily dose
  - > 200% of recommended average daily dose

- individual drugs

- exposure to multiple benzodiazepines:
  - only one benzodiazepine (first seven days of use only)
  - two or more different benzodiazepines (both first seven days of use and current use)

· at least one long and one short half-life (both first seven days of use and current use)

· at least two or more short half-life (current use only)

· at least two or more long half-life (current use only)

3.15 Other Study Variables

3.15.1 Potential Confounders and/or Effect Modifiers

Other variables included in the study because of their potential confounding and/or effect modifying influence are described below.

Age at index date: Age of the subject on the index date was determined from the SAAQ files. As noted previously, age was based on the year of birth only. This variable was reconstructed by the SAAQ based on the age of the subject as of June 1, 1990, the date of entry into the cohort. Since the month and day of birth were unknown, subjects were assumed to remain their current age as of June 1, 1990 until June 1, 1991. This can be thought of as all subjects having their birthday on June 1, with all subjects advancing one year of age as of June 1. Without having the month and day of birth, this resulted in an underestimate, from 0 to 12 months, of the age of all subjects.

Gender: Gender was also obtained from the SAAQ files, with female gender used as the reference group.

Residence: Details regarding residence were limited to that of the region of residence, as determined from the SAAQ files. The 16 administrative regions for the province of Quebec were subsequently categorized into "urban" and "rural". Urban residence included the administrative regions of Québec, Montréal, Laval and Montérégie, while rural residence included Bas-Saint-Laurent, Saguenay/Lac-Saint-

Jean, Mauricie/Bois-Francs, Estrie, Outaouais, Abitibi-Témiscamingue, Côte Nord, Nord du Quebec, Gaspésie/Iles-de-la-Madeleine, Chaudière-Appalaches, Lanaudière and Laurentides. Urban residence was the reference category.

History of previous injurious MVC: The two year period June 1, 1988 to May 31, 1990 was used to determine the history of an injurious MVC. This was defined as involvement of a cohort member as a driver in a MVC in which at least one victim (not necessarily the driver) sustained bodily injury, and was obtained from the SAAQ accident file. The variable was dichotomized, with no prior MVC being the reference category.

Exposure to other drugs with central nervous system effects: Exposure to other drugs with central nervous system effects was defined as having a prescription dispensed for any one of the following drugs in the 60 days prior to the index date: opioid analgesics, partial opioid analgesics, other analgesics, antidepressants, tranquillizers, other sedatives/hypnotics, lithium, or centrally acting skeletal muscle relaxants. The RAMQ prescription database was used to determine this variable, with non-use serving as the reference category. The use of anticonvulsants were not included in this variable since their use was a component of the chronic disease score.

Chronic Disease Score: A measure of chronic disease status, based on patterns of use of selected prescription medications in the year prior to the index date, was calculated using the chronic disease score (Von Korff et al 1992). This score can be used as an indicator of an individual's morbidity and overall health status.

The chronic disease score has been shown to possess strong evidence of validity, including a high correlation with physician ratings of physical disease severity ($r=0.57$) and high year to year stability ($r=0.74$). After controlling for age, gender and health care visits the score was also found to be a significant predictor of hospitalization and mortality in the following year. Further tests of the reliability and the construct and

predictive validity have since been provided (Johnson et al 1994). A copy of the scoring rules applied in the calculation of the chronic disease score are provided in Appendix B. The chronic disease score ranges from 0 to 35.

Driving frequency: As discussed previously, although driving frequency is not believed to vary significantly within this group of elderly drivers, we realized that it may still act as a confounder if distance travelled varied according to use or non-use of benzodiazepines. Since we did not have individual data on driving frequency for study subjects, we sought to determine the extent to which this confounding may exist using an external source of data. This did not allow us to directly control for driving frequency in the present study, but did permit an assessment of the potential to which confounding may exist.

The 1987 Santé Québec Survey (Lévesque 1989) was used to examine whether there was a difference in the number of kilometers travelled annually for users and non-users of "tranquillizers, sedatives or sleeping pills". The Santé Québec Survey was a cross-sectional survey undertaken for the entire province using a multistage sampling strategy. The province was divided into geographic areas in which private households were selected at random. Data were obtained by interviews to 13,885 households and completion of self-administered questionnaires for individuals 15 years of age and older, for which the response rate was 81%. Relevant data from the questionnaires utilized for this analysis included the reported number of kilometers driven in the past year as well as the use of tranquillizers, sedatives or hypnotics in the past 48 hours. The analysis was restricted to subjects 67 to 84 years of age who responded that they were drivers.

3.16 Data Analysis

Univariate analyses were used initially to provide descriptive characteristics of the study population, the exposure and the outcome. When appropriate, the continuous variables (age at index and chronic disease score) were categorized to enable a

comparison between groups to be made. These variables were left in their continuous form in multivariate analyses, and the assumption of linearity of the logit was tested. Logit plots for age at index and chronic disease score showed that the assumption of linearity was met. To aid in the interpretation of the beta coefficient and resultant rate ratio in the multivariate analyses, the unit used for age at index was a decade.

A bivariate analysis was conducted as an initial assessment of confounding. As noted by Rothman (1986), examining whether the potential confounder is associated with exposure among the non-diseased, and with disease among the non-exposed, is an initial step only at determining the presence of confounding. The extent of the confounding is a function of both of these associations, and should also be assessed conditional on other confounding factors. Therefore the bivariate analyses was only an initial assessment of confounding, with the true confounding effect of these variables determined in a multivariate model.

Multivariate analyses were performed using the logistic regression model, which is based on a logit transformation of the dependent variable and a binomial distribution which describes the distribution of the errors as well as the statistical distribution upon which the analysis is based (Hosmer & Lemeshow 1989).

The estimate of the odds ratio obtained from the logistic regression can be interpreted as an estimate of the rate ratio, despite the outcome being relatively rare. The rare disease assumption is not necessary in the interpretation of the odds ratio because of the incidence density sampling which was undertaken (Miettinen 1976).

Since the controls were matched to cases on the date of the event a conditional logistic regression analysis was conducted as time trends in exposure and outcome may confound the rate ratio estimates. Conditional logistic regression was performed with the PHREG procedure (SAS/STAT software release 6.07) by using the discrete logistic model and forming a stratum for each matched set, which was the date of the event. We also performed an unconditional logistic regression analysis for unmatched data. Given the similarity in the estimates of effect obtained from both the conditional and

unconditional analysis, suggesting lack of confounding by time trends, only the simpler unconditional analyses will be reported.

A backward multivariate logistic strategy was adopted in fitting the models, with the deviance used as a measure of the goodness-of-fit. The significance of a parameter was assessed by the Likelihood Ratio Test (difference in the deviances of the model without the variable and the model with the variable). All variables with a significant effect on the outcome were retained in the final model.

A stratified analysis was conducted to further explore potential effect modification by age at index and chronic disease score. The Breslow-Day test was used to assess the homogeneity of the odds ratio; a significant test suggesting heterogeneity of the odds ratio across levels of the stratifying variable.

For the analysis of driving frequency from the 1987 Santé Québec Survey, we used a multiple regression analysis to determine if there was a difference in the mean number of kilometers travelled annually for users and non-users of "tranquillizers, sedatives or sleeping pills", adjusting for both age and gender.

3.17 Validity of the Data

3.17.1 Validity of Exposure Data

Given the universal nature of the RAMQ prescription database, exposure ascertainment was available for all subjects independent of their outcome status. Any misclassification of exposure therefore is expected to be non-differential with respect to the outcome. The issue of exposure misclassification will be addressed in further detail in the discussion of the study results.

One of the important strengths of the RAMQ computerized prescription databases is the accuracy and completeness of the information collected, which is influenced by RAMQ policies regarding reimbursement. Prior to receiving reimbursement pharmacist claims must have all mandatory fields completed and within range. Errors in recording information about drugs dispensed are further reduced through the use of billing agencies by the pharmacies, or special software. Most claims

are processed quickly, with 99% completeness obtained within a six month period (verbal communication - Jacques Barry, RAMQ).

In addition to the internal audits which are routinely undertaken by the RAMQ, the accuracy and comprehensiveness of the prescription claims database have been more extensively evaluated by Tamblyn et al (1995). In a review of almost two million records of prescriptions dispensed to the elderly, values in key fields were missing or out of range in less than one percent. The accuracy of data was further assessed by comparing the prescriptions written for 311 elderly patients, as identified in their files from an outpatient clinic, with the prescription claims for these same patients in the RAMQ drug database. The quantity and duration, two variables used in the calculation of average daily dose, were accurate in 69% and 72% of prescription records respectively. The authors reasoned that since 88% of all errors were for less than the prescribed quantity and duration the most likely explanation for the discrepancy may be related to the pharmacist splitting a 60 or 90 day prescription into two-to-three 30 day supplies. If this is the case, then the accuracy of these variables would increase to 94.3%.

3.17.2 Validity of Outcome Variable

The outcome variable, involvement in a MVC in which at least one subject sustained bodily injury, was obtained from the accident file of the SAAQ. Quebec police are required by law to complete a motor vehicle accident report form for all crashes involving bodily injury or those crashes with material damage only of $500 or more. Although it is possible that some crashes with minor injuries were not reported to the police, and therefore were not included in the accident file, it is unlikely that this under-reporting would be differential with regard to exposure.

The accuracy and completeness of the SAAQ accident data has been previously assessed (Laberge-Nadeau et al 1984), with a low overall error rate between the accident report forms and the computerized data (3% error overall). However this only represents differences between the hard copy of the accident report and the

computerized data; differences between the actual facts of the accident and the information recorded by police were not assessed.

3.17.3 Validity of the Covariates

The covariates considered in this study were obtained from both the SAAQ and RAMQ. Age at index, gender, residence and history of a previous injurious MVC were retrieved from the SAAQ. Data on concomitant medications were obtained from the RAMQ and used to create two variables, exposure to drugs with central nervous system effects in the 60 days prior to the index date, and a chronic disease score.

The validity of the drug exposure data from RAMQ was expected to be similar to that discussed above for benzodiazepines.

3.17.4 Validity of MED-ECHO Data

MED-ECHO data files were used to obtain the dates of hospital admission and discharge for all study subjects. The validity of this data is expected to be high given that number of beds occupied and length of stay are key components in calculating workload and budgetary considerations for these institutions. This has been further confirmed by a study in which 1275 hospital admissions identified from the MED-ECHO files were re-abstracted from 14 Montreal hospitals (Delfino 1993), in which the agreement level for the date of admission was 99.5%.

3.18 Ethical Approval

As discussed previously, special measures were undertaken to ensure that the anonymity and confidentiality of study subjects was maintained. Approval to conduct the research was received from the Commission d'accès à l'information du Québec. The study was also approved by the Ethics Committee of the Department of Epidemiology and Biostatistics, McGill University.

CHAPTER 4
RESULTS

This chapter, which contains the study results, is divided into four main sections. The first section focuses on details of the study population, including its identification and description. The second section provides descriptive details of both the study outcome, motor vehicle crashes (MVCs), and exposure, benzodiazepines, while sections three and four consist of the analysis of the risk of MVCs associated with the new use and current use of benzodiazepines respectively.

4.1 Identification and Description of Study Population

4.1.1 Identification of Cohort, All Cases and the Sub-cohort

The initial step in the identification of the study population was to define the cohort of eligible drivers from the SAAQ "fichier permis de conduire" (driver's license file). Figure 4.1 outlines the criteria applied to identify this cohort, and the 961 exclusions which resulted. There were a total of 225,695 licensed drivers in Quebec between the ages of 67 and 84 inclusive on June 1 1990. Of these, 408 did not have a valid class 5 permit, and, in the two years prior to June 1 1990, 347 did not possess a Quebec driver's license and 206 were not residents of the province. The final size of the cohort of eligible drivers was 224,734.

Figure 4.2 outlines the identification, from the full cohort, of all cases as well as a random sample of subjects to form the sub-cohort. A total of 6064 accidents in which the driver was a cohort member, and at least one victim sustained bodily injury were identified. It is possible that an individual may have been involved in more than one injurious MVC during the study period. Only the first eligible event during this period was identified and used.

The cohort was sorted by region, gender, and age and a systematic random sample of 14,000 drivers (6.2%) were selected to form the sub-cohort. As discussed in chapter 3, cases had equal opportunity to be sampled as members of the sub-cohort and

serve as controls prior to their becoming a case; a total of 378 cases were found to be members of the sub-cohort.

A total of 19,686 potential study subjects were thus identified [(6064 cases + 14,000 sub-cohort) - 378 cases also in sub-cohort]. However, 192 (<1%) of these subjects, which included seven cases, were subsequently excluded because they had undergone a change in their driver's license number during the course of the study. This change in driver's license number, which was primarily related to a change in their marital status and surname, resulted in an inability to reconstruct the health care number for linkage with the health insurance files. Due to time and financial constraints the SAAQ were not able to link these subjects back to their old driver's license number, or to a previous version of the driver's license file, therefore it was not possible to extract the variables to reconstruct the 10 digit health care number. The total number of subjects available for linkage with the RAMQ was therefore 19,494.

4.1.2 Linkage Between SAAQ and RAMQ Databases

The three methods undertaken to link the SAAQ and RAMQ files included, in order of priority:

1) the 10 digit reconstructed health care number
2) the Social Insurance Number, and
3) a probability match using details of the name, address and the date of birth

A total of 18,945 subjects (97.2%) were thus linked. As outlined in table 4.1, the majority of subjects were linked using the reconstructed health care number (80.0%). A further 15.1% were linked using the Social Insurance Number, and 2.1% using a probability match with manual verification.

A comparison of the subjects available for linkage, and the 549 (2.8%) who were not linked is provided in table 4.2. The majority of the subjects not linked were female (87.8%), and is related to the use of a different surname in the two agencies.

By Quebec law women are required to use their maiden name on their health insurance card, but the same requirement does not apply to their driver's license. The distribution of subjects by age and residence were similar, although a smaller proportion of subjects not linked were cases (24.6%), compared to the proportion of case subjects available for linkage (31.1%).

4.1.3 Description of Study Population

Reasons for exclusion: A total of 455 of the 18,945 potential study subjects were subsequently excluded. The reasons for exclusion are outlined in table 4.3, and described below in further detail.

*1) **nursing home residents:*** Any subject who had at least one physician visit in a chronic care setting (as indicated by the service location code on the billing record) during the study period was excluded. This corresponded to 15 cases, and 84 subjects in total.

*2) **cases with their only injurious crash before June 1 1990:*** The fiscal year for SAAQ data in the driver's license file was June 1 to May 31. However, the fiscal year for data in the accident file corresponded to the calendar year - January 1 to December 31. Linkage of the driver's license and accident files therefore resulted in the inclusion of accidents between January 1 1990 and May 31 1990, prior to the actual study period. As a consequence 38 subjects whose only injurious crash was between January 1 1990 and May 31 1990 were subsequently excluded (none of these cases were members of the sampled sub-cohort).

*3) **cases 85 years of age or older on the date of their accident:*** The application of exit dates, including that related to age, took place after data was received from the SAAQ. As a result, 50 of the cases identified who were 85 years of age or older on the date of their first injurious crash were excluded. However

two of these 50 cases were also members of the sub-cohort, and were therefore included in the analysis as potential controls prior to their exit age of 85.

4) cases ineligible due to prior hospitalizations: A total of 235 cases were excluded either because they were in hospital in the 60 days prior to the index date, or they had been admitted to hospital in the year prior to the index date for a duration of 30 days or more. This eligibility criteria was also applied equally to controls in the selection of the risk sets.

5) cases with date of death preceding the date of the crash: Upon merging data from the SAAQ, RAMQ and MED-ECHO, it was discovered that five cases had a date of death (as indicated on RAMQ or MED-ECHO files) which preceded the date of their crash. For these five cases the SAAQ verified the date of the crash as being correct from micro-fiche copies of the accident report forms, and the RAMQ verified the date of death as being correct from their computerized records. The most likely explanation for this discrepancy therefore is an error in the recording of the crash date by the police on the accident report form. However, there was no available data with which to confirm this, and therefore these five cases were excluded.

6) noncases with date of death before June 1 1990: Forty-five noncases were excluded because their date of death, as obtained from the RAMQ and MED-ECHO files, occurred prior to June 1 1990. The SAAQ had not been notified of the deaths and these subjects were still listed on the driver's license file as valid drivers.

In summary, a total of 455 subjects (2.4%) were excluded, which included 343 of the 5922 cases initially identified. The final size of the study population was 18,490, and was comprised of 5579 cases and a sub-cohort of 13,256 subjects, with 345 of the cases also serving as members of the sub-cohort.

Characteristics of cases and controls: As described in chapter 3, a random sample of 10 person-time controls selected from the sub-cohort were matched to each case on the date of the event. Characteristics of the 5579 cases and 55,790 controls are presented in table 4.4. Cases were similar to controls with respect to age, residence and chronic disease score, but were more likely to be male, exposed to other central nervous system drugs in the 60 days prior to the event and have had a previous injurious MVC.

A comparison of age and gender distributions for the study subjects and the population of Quebec, using 1991 census data, are provided in table 4.5. There was a dramatic difference in the ratio of males to females both within the study population, and compared to the general Quebec population. The male to female ratio was higher both within the controls (2.6:1) and cases (4:1) and reflects the fact that males are more likely to possess a driver's license, and also experience a higher rate of MVCs than females. In contrast, the male to female ratio was lower in the Quebec population (0.7:1) and is a result of the higher life expectancy of females.

Compared to the distribution in the Quebec population, females who possess a driver's license are much more likely to be less than 75 years of age, while the distribution of age for male drivers is similar to that of the population as a whole.

4.2 Description of Study Outcome and Exposure

4.2.1 Description of the Outcome

The fact that we were able to identify the cohort of elderly drivers in the province of Quebec, as well as all injurious MVCs occurring within the cohort, enabled us to estimate the cumulative incidence of injurious MVCs for the three year study period. The number of subjects at risk, or the denominator of the cumulative incidence, was estimated by multiplying the number of subjects in each strata by the sampling fraction (the fraction of the cohort that was sampled as the sub-cohort). Estimates of the three year cumulative incidence of injurious MVC per 1,000 drivers, stratified by gender and age, are presented in table 4.6. The overall three year

cumulative incidence was 26.2 per 1,000 drivers, with a considerably higher incidence in males than females (28.6 versus 19.7 per 1,000 drivers respectively). For each of the age categories the cumulative incidence in males was consistently higher than in females. Of note is the increase in cumulative incidence with increasing age, for both males and females. For males, the cumulative incidence was 21.3 per 1,000 drivers for ages 67-70, with a doubling to 44.2 per 1,000 drivers for the oldest age category of 80-84.

We were also able to estimate the rates of MVC for subjects currently exposed to benzodiazepines (exposed on the day of the event) based on the prevalence of exposure in the controls. The controls were a random sample of the cohort, and therefore the prevalence of exposure in these subjects could be extrapolated to the full cohort to obtain the prevalence of exposure in the cohort. The rate of MVC for subjects currently exposed to long half-life benzodiazepines was 22.9 per 1,000 licensed drivers, while current exposure to short half-life products was associated with a lower rate of 18.9 per 1,000 licensed drivers.

The descriptive characteristics of the 5579 injurious MVCs are outlined in table 4.7. In terms of the severity of the crash, most were of minor severity (82.6%), defined as a crash in which no individual required hospitalization. A small proportion were of major severity, with at least one victim hospitalized, and only 178 (3.2%) of the crashes involved a fatality.

Information concerning the crash itself indicated that the majority occurred in regions other than the large urban centres (58.2%), during daylight hours between 6am and 6pm (87.1%), involved two or more vehicles (83.6%), with travel straight ahead (55.0%) and at a posted speed limit of 50 km per hour or less (65.9%). Details regarding weather and road conditions reflect that most crashes took place during the summer (41.8%), with clear weather (64.1%) and on dry road surfaces (67.2%).

4.2.2 Description of Benzodiazepine Prescriptions in the One Year Exposure Window

Individual products: A total of 182,827 prescriptions for benzodiazepines were dispensed to the 5579 cases and their 55,790 person-time controls in the year prior to their index date. The distribution of individual products are provided in table 4.8. This table reveals that the greatest proportion of prescriptions for both cases and controls were for the short half-life benzodiazepine lorazepam (36.3% and 38.3% respectively). Flurazepam, a long half-life benzodiazepine, was prescribed next in frequency to cases, accounting for 17.4% of their prescriptions and 11.3% of prescriptions to controls. Triazolam, another short half-life product, was also prescribed relatively frequently to both cases and controls (10.4% and 12.2% of prescriptions respectively). Other products appeared to be dispensed less frequently, and in equal numbers between cases and controls.

Elimination half-life: Table 4.9 provides a summary, by elimination half-life, of all benzodiazepine prescriptions dispensed to cases and controls during the year prior to the index date. Almost three-quarters of the prescriptions to cases and controls were for short half-life benzodiazepines. However, the proportion of prescriptions for long half-life products was higher for cases (31.6%) than for controls (25.9%).

Duration: As indicated in table 4.10, almost 80% of all benzodiazepines dispensed in the year prior to the index date were prescribed for a treatment duration of 30 days. The prescribed treatment duration was similar for cases and controls.

4.3 Analysis of Initiation and Duration of Benzodiazepine Use

This third section of the results chapter contains details of the analysis of the effects of initiation and duration of benzodiazepine use. The rate ratio curve of MVC as a function of the initiation and duration of use was the primary focus of this analysis. The shape of the rate ratio curve enabled us to assess when, following the initiation of

exposure, the risk of experiencing a MVC was the greatest. Four mutually exclusive categories of duration of use were included in this analysis. We focussed much of the analysis on the category of use in which the rate ratio was the highest - within the first seven days after initiating exposure. Both univariate and multivariate analyses are presented. Additional analyses by dose, individual drug, and multiple drug combinations are also included. Where applicable the analysis of the duration of use was undertaken for three types of exposure: benzodiazepines as a class, short half-life benzodiazepines and long half-life benzodiazepines. The analysis of benzodiazepines as a class was included for comparison with previous research in this area.

Both conditional and unconditional logistic regression analyses were conducted. Given the similarity in the estimates of effect obtained from both analyses, suggesting lack of confounding by time trends, only the simpler unconditional analyses are presented.

4.3.1 Prevalence of Exposure to Benzodiazepines

Table 4.11 provides the distribution of benzodiazepine use by various categories of exposure, including the categories of the duration of first use. A higher proportion of cases (38.5%) than controls (36.2%) were exposed to benzodiazepines at least once during the year prior to the index date. The proportion of cases and controls exposed to short half-life products was similar (28.9% and 28.2% respectively), while a higher proportion of cases than controls were exposed to long half-life products (15.9% and 12.8% respectively). Cases were also more likely than controls to be exposed on the index date (20.4% and 19.0% respectively).

When exposure was defined as the initiation of use within seven days prior to the index date the prevalence of use was considerably lower at 1.9% and 1.6% for cases and controls respectively. Once exposure was initiated, subjects were likely to be exposed for long durations, as reflected by a prevalence of 12.7% for cases and 12.1% for controls for exposure initiated 61 to 365 days prior to the index date and continued

to, or past, the index date. A slightly higher proportion of cases than controls were exposed in each of the categories.

Each of the exposure categories for the initiation and duration of use were mutually exclusive, with algorithms developed to ensure the continuity of use. For example, the interval 1-7 days indicated at least 1, and up to seven days of new use. In the same manner, 8-30 indicated more than seven and up to 30 days of continued new use, 31-60 indicated more than 30 and up to 60 days of continued new use and 61-365 indicated more than 60 and up to 365 days of continued new use. A three day washout period with no exposure was necessary to meet the requirements set for the initiation of use in each of these categories, except for that of 61-365 days, which reflected continuous use.

"Other exposure" includes exposure to benzodiazepines which did not meet the criteria for the initiation of use (for example no three day washout period, no exposure on the index date etc.).

Exposure in the two years prior to the index date confirms the long term use of these drugs; 32.9% of cases and 31.1% of controls were exposed at least once in both the one year and two year period prior to the index date.

4.3.2 Relationship Between Duration of Use and Risk of MVC

The initial focus of the analysis was directed at the risk of MVC associated with continuous benzodiazepine use of increasing durations (duration of seven days, up to 30 days, up to 60 days and up to 365 days). This analysis was undertaken for benzodiazepines as a class, as well as for short and long half-life benzodiazepines, with the results displayed in tables 4.12 to 4.14.

As presented in table 4.12, for benzodiazepines as a class there was no increased risk of MVC regardless of the duration of continuous use. The highest adjusted RR was associated with a duration of use of seven days or less (RR 1.15, 95% CI 0.94-1.41), however this progressively decreased as the duration of use increased, with the

lowest adjusted RR reported for continuous use of up to one year prior to the event (RR 0.99, 95% CI 0.91-1.09).

Similar results are presented in table 4.13 for short half-life benzodiazepines. For a duration of use of seven days or less, the adjusted RR was essentially no different from the null value (RR 1.04, 95% CI 0.81-1.34). Both crude and adjusted RRs decreased with an increasing duration of use, to a low adjusted RR of 0.91 (95% CI 0.82-1.01) for up to 365 days of continuous use.

In contrast, for long half benzodiazepines (table 4.14) the adjusted RR within the first seven days of initiating treatment was significantly increased (RR 1.45, 95% CI 1.04-2.03). For up to 30 days and up to 60 days of continuous use, the RRs were 1.16 and 1.22, respectively, and non-significant, while the risk for use lasting up to 365 days was also increased and significant (RR 1.26, 95% CI 1.09-1.45).

Graphical representation of the crude and adjusted results are presented in figures 4.3 and 4.4 respectively. The increased risk of MVC associated with the first seven days of use, and continuous use of up to one year for long half-life benzodiazepines, as well as the lack of an increased risk for short half-life products are evident in graphs of both the crude and adjusted results.

In summary, for long half-life exposure the greatest risk of an adverse event occurred within the first seven days of initiating treatment. This risk was significantly increased for continuous use of up to one year duration. This significant increase in risk for continuous use suggests that the sedative side effects associated with this exposure may persist, even with long term use. These results remained significant even after adjusting for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crash. In contrast, there was no increase in risk associated with exposure to benzodiazepines as a class, or short half-life benzodiazepines, regardless of the duration of new use.

Justification for further analyses: Based on the results obtained for the duration of benzodiazepine use and risk of MVC, further analyses were focussed in two directions: 1) the first seven days of short and long half-life benzodiazepine use, and 2) current use of short and long half-life benzodiazepines, irrespective of the duration of their use.

The first seven days of exposure was the object of further analyses to enable a more detailed exploration of the peak in the risk of MVC that was observed for long half-life use during this time interval. Given the difference in risk observed for short and long half-life benzodiazepines, a separate analyses was conducted for each of these elimination half-lives. The effect of benzodiazepines as a class was not included in further analyses as these results were simply a mixing of the effects of short and long half-life exposure.

As is evident in figures 4.3 and 4.4, following the first seven days of use the effect of long half-life benzodiazepines on the risk of MVCs remained relatively constant over prolonged periods of exposure. Therefore a further objective of this analysis was to study the effect of benzodiazepine exposure regardless of the length of time the drug had been used. The method by which we proposed to undertake this assessment was to focus on current use of benzodiazepines, that is exposure on the day of the event, irrespective of the duration of use. The less restrictive classification of exposure in this analysis resulted in an increase in the number of exposed subjects, which enabled us to explore potential effect modification by relevant variables.

4.3.3 Description of Benzodiazepine Exposure Characterized as the First Seven Days of Benzodiazepine Use

Individual products: The distribution of prescriptions dispensed which characterized the first seven days of benzodiazepine use for the 108 exposed cases and 924 exposed controls are presented in table 4.15. This distribution contains certain similarities to the distribution of benzodiazepines dispensed in the year prior to the index date (table 4.8). Lorazepam was the most common benzodiazepine used to

initiate therapy for cases and controls (36.8% and 38.6% respectively), followed by flurazepam for cases (14.5%) and diazepam for controls (12.6%). However, as was shown in table 4.8, there was a much higher proportion of prescriptions for triazolam during the year prior to the event for both cases and controls (10.4% and 12.2% respectively), compared to the number prescribed which characterized the first seven days of use (2.6% and 8.8% respectively).

Elimination half-life: Slightly more than one-third of the benzodiazepine prescriptions to cases in the first seven days of use were for a long half-life benzodiazepine (table 4.16). Long half-life benzodiazepines were dispensed less frequently to controls, and accounted for 27.9% of the prescriptions.

Duration: As displayed in table 4.17, approximately three-quarters of benzodiazepines depicting the first seven days of use were dispensed for a treatment duration of 30 days. The prescribed treatment duration was similar for cases and controls.

4.3.4 Association Between Potential Confounders and Exposure

The distribution of potential confounders among controls by the first seven days of exposure to short and long half-life benzodiazepines are presented in table 4.18. As is evident in table 4.18 for short half-life benzodiazepines, a higher proportion of the females were exposed (2.1%) compared to males (1.3%). The prevalence of exposure increased only slightly with age, except for the older age category of 80-84 years. Exposed subjects were more likely to live in a rural area, have a history of exposure to central nervous system drugs, and have a higher chronic disease score. Exposed subjects were less likely to have had a previous injurious MVC.

On the other hand, for long half-life exposure the proportion of subjects exposed did not vary by gender or age. However, as seen with short half-life exposure, a greater proportion of subjects exposed to long half-life benzodiazepines lived in a rural

setting, had a history of exposure to central nervous system drugs and had a higher chronic disease score.

4.3.5 Association Between Potential Confounders and Outcome

The distribution of potential confounders among the unexposed (defined as no use of benzodiazepines days 0 to 10 prior to the index date) and their association with the risk of a MVC are shown in table 4.19. The relationship between each of these risk factors and the outcome (MVC) are described below:

Gender: Male gender was one of the strongest risk factors for MVCs; 81.5% of cases were male compared to 73.4% of controls. Males had 1.6 times the risk of experiencing a MVC compared to females (RR 1.59, 95% CI 1.47-1.73).

Age at index: The risk of experiencing an accident increased with age. Compared to subjects age 67-70, those aged 80-84 had 1.7 times the risk of experiencing a MVC. The crude RR for subjects age 80-84 was 1.66 (95% CI 1.66-1.86).

Residence: Residence in a rural setting was associated with only a slightly increased risk of experiencing a MVC, with a crude RR of 1.13 (95% CI 1.06-1.20).

CNS exposure: Cases were more likely to have a history of exposure to drugs with CNS effects in the 60 days prior to the event than controls (10.4% compared to 7.2% respectively). The crude RR associated with this exposure was 1.51 (95% CI 1.36-1.68).

The distribution of drugs which comprised CNS exposure, as well as their association with risk of MVC, are displayed in table 4.20. The highest prevalence of exposure was for analgesics, followed by antidepressants. Of these CNS drugs, lithium

had the highest risk of MVC (RR 2.32, 95% CI 1.41-3.83), although only 19 cases (0.3%) were exposed. There was also a significant increase in risk of MVC for subjects exposed to centrally acting skeletal muscle relaxants (RR 1.79, 95% CI 1.11-2.88) and to analgesics (RR 1.64, 95% CI 1.49-1.80). A smaller, but significant, increase in risk was also observed for antidepressants (RR 1.19, 95% CI 1.02-1.40). Although not the focus of this study, subsequent exploration of the relationship between these drugs, using relevant time windows and reference groups, will be the object of further research.

Chronic disease score: As indicated in table 4.19, the difference in the chronic disease score between cases and controls was small but significant. Compared to a chronic disease score of zero, subjects with a score greater than three had a 20% increase in risk of MVC. The crude RR for a score of greater than three was 1.22 (95% CI 1.13-1.32).

Previous injurious MVC: The strongest risk factor for a MVC was history of a previous injurious MVC in the two year period prior to the study. Subjects with a previous MVC had 1.9 times the risk of an MVC compared to those with no previous MVC (crude RR 1.91, 95% CI 1.59-2.29).

4.3.6 Risk of MVC Associated with the First Seven Days of Benzodiazepine Use - Independent Predictors and the Effect of Past Use

Short half-life benzodiazepines: The results of the multivariate logistic model for the first seven days of use of short half-life benzodiazepines are presented in table 4.21. The similarity between the crude and adjusted RR for benzodiazepine use (1.08 and 1.04 respectively) suggest that none of the covariates were confounders in the association between benzodiazepine use and risk of MVC. However, each of these covariates were significant independent predictors of the outcome, and their inclusion

improved the goodness-of-fit of the model, therefore they were retained in the final model.

The crude RR associated with the first seven days of benzodiazepine use was 1.08 (95% CI 0.84-1.38). The risk decreased slightly after adjustment, and remained non-significant (RR 1.04, 95% CI 0.81-1.34). Each of the covariates remained significant independent predictors, even after adjustment for all other variables in the model. The highest risk was that associated with previous injurious MVC (adjusted RR 1.79, 95% CI 1.49-2.15), followed by male gender (adjusted RR 1.54, 95% CI 1.42-1.67) and exposure to CNS drugs (adjusted RR 1.49, 95% CI 1.34-1.65). For every 10 year increase in age, the risk of experiencing an MVC, after adjusting for other factors, increased by 30 percent. Living in a rural, as opposed to an urban, setting was associated with a slightly increased risk (adjusted RR 1.12 95% CI 1.05-1.19). The presence of chronic disease conditions, as measured by the chronic disease score, was not associated with any meaningful level of risk (adjusted RR 1.01 95% CI 1.00-1.03).

Long half-life benzodiazepines: Results of the full model for long half-life benzodiazepines are displayed in table 4.22. Both the crude and adjusted analyses revealed a statistically significant association between long half-life benzodiazepines and risk of MVC. The crude RR of 1.53 (95% CI 1.10-2.14) was reduced slightly to 1.45 (95% CI 1.04-2.03) after adjusting for age at index (per decade), gender, residence, chronic disease score, CNS exposure and previous injurious MVC. The independent effects of each of these covariates were similar to that discussed above for short half-life benzodiazepines.

4.3.7 Assessment of Effect Modification by Length of Washout Period

The influence of past use of benzodiazepines as an effect modifier in the association of the first 7 days of exposure to benzodiazepines and risk of MVCs was determined through the use of interaction terms. This analyses provided an assessment

of effect modification by length of the washout period, and the appropriateness of the three-day washout period.

Length of the washout period was defined as the number of days since a subject was last exposed to benzodiazepines of either half-life, categorized into that of 4 to 30 days, 31 to 90 days, and 91 to 365 days.

The results of the assessment of effect modification by length of washout period for short and long half-life benzodiazepines are displayed in table 4.23. For short half-life benzodiazepines the RR increased slightly, but remained non-significant, as the duration of the washout period increased. A washout period of 4 to 30 days was associated with an RR of 0.95, while that of 31 to 90 days and 91 to 365 days were associated with RRs of 1.01 and 1.26 respectively. These results suggest that as the length of the washout period increased, so too did the risk of experiencing a MVC.

The trend, however, was not apparent in the long half-life benzodiazepines. In contrast to short half-life benzodiazepines the lowest risk was observed for the longest washout period. A washout period of 4 to 30 days was associated with an RR of 1.25, while those of 30 to 90 and 91 to 365 were associated with RRs of 1.44 and 1.04 respectively. All results were non-significant.

The marginal increase in risk with the increased duration of the washout period suggests that a three-day washout period was perhaps too short. However, because of the lack of significance and relatively small numbers of subjects with longer washout periods, it was deemed appropriate to define a new episode of exposure by this three day washout period.

4.3.8 Independent Effects of Short and Long Half-life Benzodiazepines

To assess the independent effects of short and long half-life benzodiazepines (exposure is the first seven days of use for each half-life respectively with no exposure in the three day washout period to either half-life benzodiazepine), as well as the potential interaction between these two determinants, a model was fit which included an independent variable for both these terms. The reference group was no exposure to a

benzodiazepine of either half-life in the 0 to 10 days prior to the index date. The adjusted RRs displayed in table 4.24 for short and long half-life benzodiazepines are similar to that previously reported, providing evidence of an independent effect of these drugs. The interaction between short and long half-life benzodiazepines, as assessed by the likelihood ratio test, was not significant (p=0.73).

4.3.9 Analysis of Risk as a Percentage of the Recommended Average Daily Dose

A further analysis was conducted to assess whether there was an association between benzodiazepine dose and the risk of MVC. In this analysis dose of the benzodiazepine in the first seven days of use was categorized as a percentage of the recommended average daily dose for seniors, with the reference category being no exposure in days 0 to 10 prior to the index date. As shown in table 4.25, for short half-life benzodiazepines there was no apparent trend with increasing dose. The highest risk was observed for subjects exposed at the recommended dose, although neither the crude nor adjusted RR results were significant (adjusted RR 1.47, 95% 0.82-2.65). In addition, subjects exposed to benzodiazepines at one-to-two times the recommended daily dose had the lowest risk (RR 0.70, 95% CI 0.46-1.07).

The long half-life analysis of dose corresponds more closely to that which has been suggested in the literature (table 4.26), although none of the results obtained are significant. The lowest risk was observed for the recommended daily dose (RR 1.25, 95% 0.60-2.62), with an increased risk for up to twice the recommended daily dose (RR 1.54, 95% CI 0.99-2.39), and more that twice the recommended dose (RR 1.46, 95% CI 0.72-2.96).

In summary, there was no dose-response relationship observed for either short or long half-life benzodiazepines. Of note is the fact that more than 90% of subjects exposed to lorazepam and oxazepam, the two most frequently prescribed short half-life products, were receiving doses greater than recommended. A similar trend was observed for long half-life products, with 92.1% of subjects exposed to diazepam, and 65.8% of subjects exposed to flurazepam at doses greater than recommended.

4.3.10 Analyses of Individual Drugs

An analysis of the risk of MVC associated with individual drugs was also conducted. The distribution of individual products dispensed as the first seven days of use to cases and controls were reviewed, and all drugs with a five percent or greater prevalence of use in cases and controls were included in the analysis. The short half-life drugs considered were alprazolam, bromazepam, lorazepam and oxazepam, while the long half-life drugs were diazepam and flurazepam (exposure was first seven days of use, as previously defined, with the reference group being no exposure in days 0 to 10). The crude and adjusted RRs obtained are displayed in table 4.27. Lorazepam accounted for over 50% of short half-life exposure, while diazepam and flurazepam accounted for 80% of long half-life exposure. Of the short half-life benzodiazepines, bromazepam was the only drug with a significant increased risk (RR 2.26, 95% CI 1.17-4.37). Among the long half-life products, there was an increased, but non-significant, risk associated with the use of the flurazepam (RR 1.61, 95% CI 0.96-2.70).

4.3.11 Exposure to Multiple Benzodiazepines

The incidence density ratios of MVC for the first seven days of benzodiazepine use, by the number of different benzodiazepines received, are presented in table 4.28. Exposure to only one benzodiazepine was associated with a non-significant crude RR of 1.19 (95% CI 0.96-1.46). When exposure was two or more different benzodiazepines the risk increase slightly, but remained non-significant (RR 1.25, 95% CI 0.49-3.16). The highest RR, although non-significant, was observed for exposure to at least one long and one short half-life benzodiazepine (RR 1.80, 95% CI 0.53-6.16). It must be pointed out that these estimates are based on a small number of exposed cases, and as such are unstable.

4.4 Analysis of Current Use

The analyses presented thus far has focussed only on the first seven days of benzodiazepine exposure. However, as is evident in figures 4.3 and 4.4, the increased risk of MVC remained relatively constant over periods of prolonged use of long half-life benzodiazepines. Therefore the objective of further analyses was to explore the effect of benzodiazepine use irrespective of the duration of exposure. This fourth and final section contains results of this analysis in which exposure was "current use", defined as a benzodiazepine dispensed prior to the index date and of sufficient duration to last up to, or beyond, the index date (i.e. the subject was exposed "currently" on the index date). The reference category was no benzodiazepine exposure in the year prior to the index date. As in the analysis of the first seven days of use, exposure to short and long half-life benzodiazepines were considered separately.

4.4.1 Prevalence of Exposure

The distribution of cases, controls and all subjects by exposure to benzodiazepines, based on the exposure definition of current use, is provided in table 4.29. In the year prior to the MVC, 61.5% of cases and 63.8% of controls had no exposure to benzodiazepines, and served as the reference group. The prevalence of exposure to short half-life benzodiazepines was similar for cases and controls, 14.5% and 14.7% respectively, while cases were more likely to be exposed to long half-life benzodiazepines than controls (6.9% and 5.2% respectively). Subjects who did not meet the criteria for exposure or reference groups are located in the "other" category, and were not included in further analysis. These subjects were exposed to benzodiazepines at some point in the prior year, but were not "currently" exposed.

4.4.2 Association Between Potential Confounders and Exposure

The distribution of potential confounders among controls, by current exposure status to short and long half-life benzodiazepines are provided in table 4.30. The distributions are similar to those observed previously in the presentation of results for

the first seven days of use. Compared to males, a greater proportion of females were currently exposed to short half-life benzodiazepines. The proportion of subjects exposed within each age category also increased slightly with age. A greater proportion of subjects exposed lived in a rural setting, had a history of exposure to central nervous system drugs and had a higher chronic disease score.

Similar proportions are observed when comparing long half-life exposure with unexposed, although for gender and age at index the difference in the proportions are not as remarkable.

4.4.3 Association Between Potential Confounders and Outcome

The distribution of potential confounders among the non-exposed (defined as no exposure in the year prior to the index date) and their association with the risk of MVC are presented in table 4.31. Once again the distributions and measures of effect are similar to those obtained in the assessment of the first seven days of use. Briefly, the strongest risk factor for MVC was history of a previous injurious MVC (RR 1.93, 95% CI 1.58-2.36), followed by male gender (RR 1.62, 95% CI 1.48-1.78) and history of exposure to central nervous system drugs (RR 1.47, 95% CI 1.30-167). There was a significant but small increase in risk for residence in a rural setting as well as for a chronic disease score greater than three (RR 1.10 and 1.22 respectively). The risk also increased with age, with the highest RR observed for the age category 80 to 84 (RR 1.63, 95% CI 1.43-1.85).

4.4.4 Risk of MVC Associated with Current Use of Benzodiazepines - Multivariate Analysis.

Short half-life benzodiazepines: The results of the multivariate analysis for current exposure to short half-life benzodiazepines are presented in table 4.32. Other half-life exposure, defined as use of long half life benzodiazepines in the 60 days prior to the index date, was also included in the model. This variable was added in order to obtain the independent effect of short half-life benzodiazepine exposure.

There was no association between exposure to short half-life benzodiazepines and risk of MVC in either the crude (RR 1.03, 95% CI 0.95-1.11) or the adjusted (RR 0.96, 95% CI 0.88-1.05) analysis. The other covariates remained as significant independent predictors, except for the chronic disease score, with point estimates and confidence intervals similar to that obtained in the first use analysis.

In the assessment of interaction two terms were significant, that of the interaction between short half-life exposure and age ($p=0.03$) and short half-life exposure and the chronic disease score ($p=0.04$). Stratification was used to further evaluate the potential effect modification.

The crude and adjusted RRs for current exposure to short half-life benzodiazepines, by four categories of age, are presented in table 4.33. The highest adjusted RR observed was in the 67 - 70 age category (RR 1.04, 95% CI 0.89-1.22), with a slight reduction in risk as age increased. However, the range in the point estimates was very narrow, from a low of 0.83 to a high of 1.04, with no real meaningful variation in the risk by age. The Breslow Day test for the homogeneity of the odds ratio supported the constancy of the RR over the strata ($p=0.07$).

The crude and adjusted RRs for current exposure to short half-life benzodiazepines, by three categories of the chronic disease score, are presented in table 4.34. The highest risk observed was that restricted to a chronic disease score of zero (adjusted RR 1.13, 95% CI 0.92-1.38). At a score greater than three the adjusted RR was reduced to 0.92 and remained non-significant (95% CI 0.81-1.05). The Breslow Day test for homogeneity of the odds ratio in this instance was significant ($p=0.03$). However, one must question the relative importance of a difference in risk from 0.93 to 1.24 to justify the interaction as being pertinent.

The stratified analysis does suggest however that there may be a particular group of subjects in whom the risk of MVCs are increased, that being the younger age groups and subjects with no chronic disease conditions. A possible interpretation is that perhaps the younger and healthier subjects are driving, and therefore more likely to experience a MVC than older subjects with more chronic disease conditions.

Long half-life benzodiazepines: Table 4.35 contains the results of the multivariate analysis for current exposure to long half-life benzodiazepines. Other half-life exposure in this model was defined as use of short half life benzodiazepines in the 60 days prior to the index date, and was included to determine the independent effect of long half-life benzodiazepines.

There was a significant association between long half-life exposure and risk of MVC with a crude RR of 1.38 (95% CI 1.23-1.54). The adjusted RR was reduced slightly, but remained significant (RR 1.28, 95% CI 1.12-1.45). The point estimates and confidence intervals for the other covariates were similar to those previously reported for short half-life exposure.

The only significant interaction was that between long half-life exposure and age ($p=0.05$). An assessment of this potential effect modification, stratifying by age, is provided in table 4.36. The highest adjusted RR with long half-life exposure was in the age group 71 - 74 (RR 1.49, 95% CI 1.20-1.85). Similar to that reported for short half-life exposure, the adjusted RRs were reduced, and non-significant, in the two oldest age groups (RR 1.05 for ages 75 to 79 and 1.13 for ages 80 to 84). The Breslow day test for the homogeneity of the odds ratio was significant ($p=0.02$). These results also suggest that younger individuals are more likely to be driving, and hence experience MVCs.

4.4.5 Analysis of Risk as a Percentage of the Recommended Average Daily Dose

The association between benzodiazepine dose and risk of MVC was assessed in the same manner as that undertaken with the first use of benzodiazepines described previously. Specifically, the average daily dose of the benzodiazepine prescription which characterized current use was calculated for both short and long half-life benzodiazepines, and categorized into three categories as a percentage of the recommended daily dose. The reference category was no exposure in the year prior to the index date. Results for short and long half-life exposure are presented in tables 4.37 and 4.38 respectively.

From table 4.37, it is evident that of the 9,013 subjects currently exposed to short half-life benzodiazepines, only 12.3% were receiving the recommended average daily dose or less. The majority (49.2%) were receiving up to twice, and a further 38.5% more than twice, the recommended average daily dose. However, despite the increased dose the highest crude RR was observed for the recommended average daily dose or less (RR 1.23, 95% CI 1.01-1.50), which became non-significant after adjustment (RR 1.21, 95% CI 0.99-1.48). A protective effect was observed for the category of up to twice the recommended average daily dose (adjusted RR 0.83, 95% CI 0.74-0.94), with a small and non-significant RR at more than twice the recommended average daily dose (adjusted RR 1.08, 95% CI 0.96-1.22). A possible explanation for this relationship is that subjects who are using benzodiazepines for the first time are exposed at the recommended initial daily dose levels for the elderly, and it is among these first time users that the risk is highest. Long term users of the drug are receiving higher doses, but are not experiencing the same adverse effects.

As with short half-life exposure, the majority of subjects currently exposed to long half-life benzodiazepines (table 4.38) were receiving up to twice the recommended average daily dose (56.4%). However a smaller proportion were exposed at twice the recommended average daily dose (18.9%). A significant increase in the RR was observed at the category of up to twice the recommended average daily dose (adjusted RR 1.33, 95% CI 1.15-1.54). The RR for the recommended dose, and for the level of more than twice the recommended dose, were similar and showed a slightly increased but non-significant RR.

4.4.6 Analysis of Individual Drugs

The criteria for the inclusion of products in the analysis of individual drugs was similar to that undertaken previously for first use. Briefly, all individual products which met the definition of current use with a 5% or greater prevalence of use in cases and controls were selected. The reference category was no exposure to benzodiazepines in the year prior to the index date. The four short half-life products,

bromazepam, lorazepam, oxazepam and triazolam, included in this analysis accounted for 88.6% of all short half-life prescriptions, while the two long half-life products, diazepam and flurazepam, accounted for 79.2% of all long half-life use.

As displayed in table 4.39, bromazepam was the only short half-life product with a significant crude RR (RR 1.36, 95% CI 1.06-1.75), which was reduced somewhat and no longer significant after adjustment for other covariates (RR 1.27, 95% CI 0.99-1.64).

Among the long half-life products, flurazepam was associated with a significantly increased RR, even after adjusting for other covariates (RR 1.47, 95% CI 1.26-1.72). Subjects currently exposed to flurazepam had a 50% increase risk of MVC compared to subjects with no exposure.

4.4.7 Exposure to Multiple Benzodiazepines

The crude and adjusted RR for current exposure to benzodiazepines, by the number of different drugs received, are shown in table 4.40. The significant crude RR for current exposure to two or more different benzodiazepines (RR 1.27, 95% CI 1.06-1.51), was reduced and became non-significant after adjusting for other covariates (RR 1.15, 95% CI 0.96-1.38). The same pattern was observed when the exposure was limited to two or more short half life benzodiazepines (adjusted RR 1.20, 95% CI 0.95-1.52). There was no increased risk for two or more long half-life benzodiazepines, although the small number of exposed cases must be pointed out.

Of note is the fact that 1362 of the 11,741 exposed subjects (11.6%) were currently exposed to two or more different benzodiazepines. This does not include multiple dispensing of the same drug. To meet the criteria of multiple drug exposure, current exposure must have been to two or more *different* benzodiazepines. Three subjects were currently exposed to three different benzodiazepines.

4.4.8 Driving Frequency

Data from the 1987 Santé Québec survey were used as an indirect method to assess the extent to which driving frequency may confound the association between benzodiazepine use and risk of MVC. Exposure in this survey was defined as use of tranquillizers, sedatives or sleeping pills in the prior 48 hours, and driving frequency was reported as the average number of kilometers travelled in the prior year. The analysis, restricted to respondents 67 to 84 years of age, included a total of 549 subjects. As shown in table 4.41, the mean number of kilometers driven in the prior year decreased slightly for each of the age categories, except for the females oldest age category, which included only six subjects and therefore must be interpreted with caution. As reflected by the reported standard deviation there was considerable variability within each age category, which probably also includes error in recalling or estimating distance travelled in the past year.

After controlling for age and gender, there was no significant difference in the number of kilometers driven for subjects exposed and non-exposed to sedatives. Subjects who used sedatives drove 1501 kilometers less per year than those who did not, so that the estimates of effect obtained in this study may under estimate the true risk.

4.4.9 Measures of Potential Impact

Assuming that the association between current use of long half-life benzodiazepines and the risk of MVC is causal, the etiologic fraction among the exposed (also referred to as the attributable proportion or attributable risk) and the population attributable risk (also referred to as the population attributable fraction or population attributable risk percent) can be used to assess the impact of such exposure.

The etiologic fraction, or the proportion of exposed cases for whom the event can be attributable to exposure (Rothman 1986), for current exposure to long half-life benzodiazepines was 21.9%. This was based on an adjusted RR of 1.28 for current long half-life benzodiazepine exposure, with the etiologic fraction = (RR - 1) / RR.

Thus 21.9% of MVCs occurring among drivers exposed to long half-life benzodiazepines can be attributed to their use of these long half-life products. Analogously, 21.9% of MVCs in drivers exposed to long half-life benzodiazepines could be prevented by either eliminating long half-life exposure, or substituting short half-life benzodiazepines.

At the population level, if the association between long half-life benzodiazepines and injurious MVC is causal, then our data suggest that 2.2% of MVCs can be attributable to current long half-life benzodiazepine exposure. This again is based on an adjusted RR of 1.28 for current long half-life exposure, and a prevalence of exposure among cases of 101 per 1,000 (Table 4.29). The population attributable risk = $(RR-1)P_1 / RR$, where P_1 is the prevalence of exposure among cases. Applying this to the province of Quebec, of the 3,000 injurious crashes that occur per year in elderly drivers in Quebec (Société de l'assurance automobile du Québec 1992a), at least 66 of them can be attributable to long half-life benzodiazepine use.

4.5 Summary of Study Results

A brief summary of the study results are enumerated below, and discussed in further detail in chapter 6.

1) The initial seven days of long half life benzodiazepine exposure was associated with a 50% increased rate of involvement in injurious MVCs. Although reduced somewhat, the risk remained significant for continuous use of up to one year duration prior to the event.

2) Current exposure to long half life benzodiazepines, irrespective of the duration of use, was associated with a 30% increased rate of experiencing an injurious MVC. This corresponds to 2.2% of all MVCs, or 66 of the approximately 3,000 annual injurious MVCs in Quebec.

3) There was no increased risk of injurious MVC observed following the initiation of treatment with short half-life benzodiazepines, or with their continued use in the year prior to the event. However, there may be an increased risk with a longer washout period, or with use of one particular drug.

4) Current use of short half-life benzodiazepines, irrespective of the duration of use, was also not associated with an increased risk.

5) The results of the assessment of effect modification by duration of washout period for short half-life benzodiazepines suggests that the three day washout period may perhaps be too short, although this trend was not observed for long half-life products, and was limited due to the small number of subjects initiating treatment.

6) These was no dose-response relationship apparent for either the first seven days, or current use, of short or long half-life benzodiazepines.

7) The individual products associated with a significant increased risk of MVC were bromazepam for the first seven days of short half-life exposure, and flurazepam for current use of long half-life products.

Figure 4.1 **Criteria applied to identify cohort of eligible drivers in the province of Quebec.**

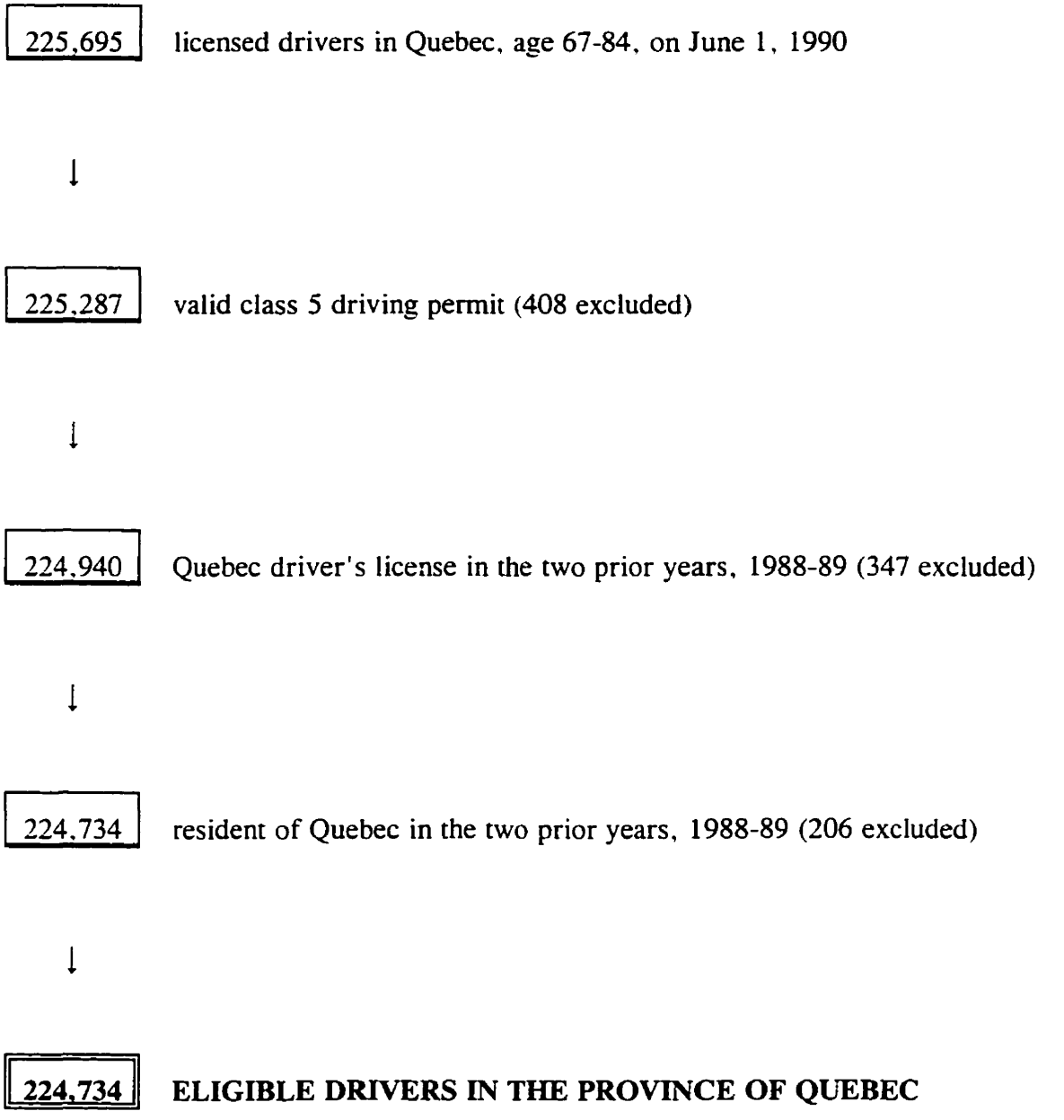

Figure 4.2 **Identification of cases and subcohort from the cohort of eligible drivers**

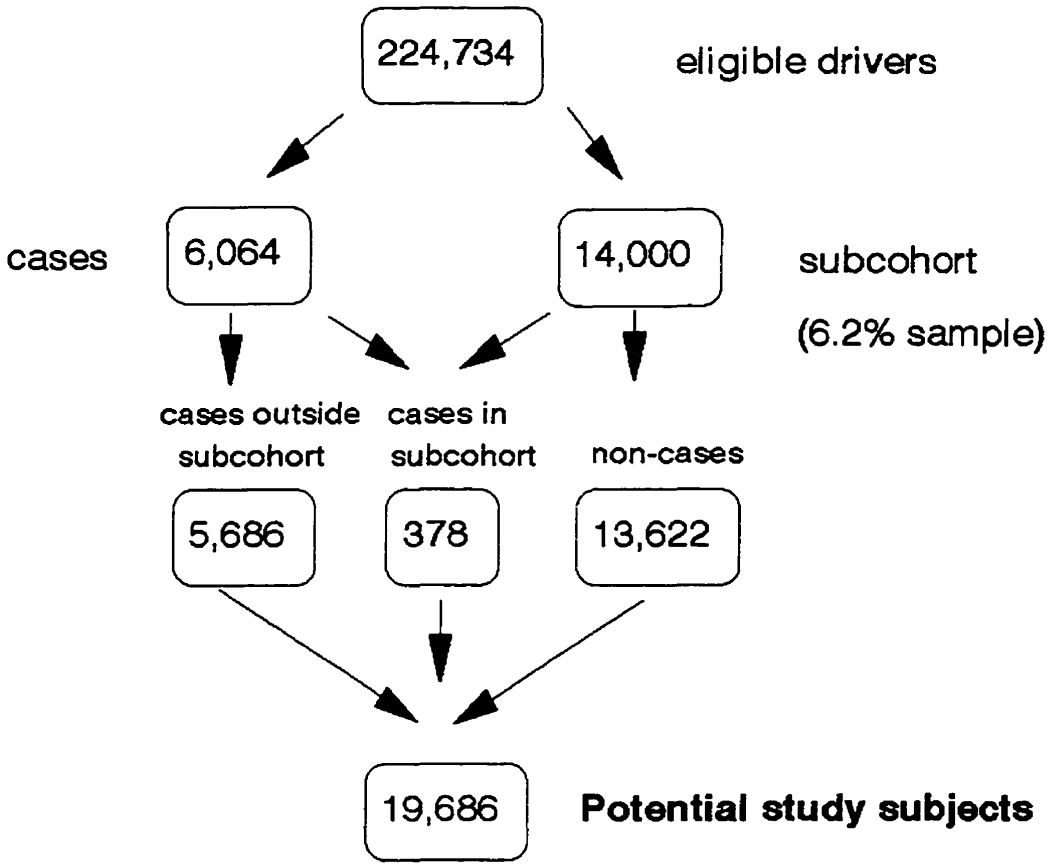

Table 4.1 Distribution of methods used to link study subjects from SAAQ to RAMQ

	Number	%
Total subjects available for linkage with RAMQ	19,494	100.0
Subjects linked using reconstructed health care number	15,596	80.0
Other methods used to link subjects		
Social Insurance Number	2943	15.1
Probability match using name, date of birth and address	406	2.1
Subjects unable to link	549	2.8
Total number of subjects linked	18,945	97.2

Table 4.2 Comparison of the subjects available for linkage and the 549 subjects for whom linkage between SAAQ and RAMQ data was not obtained

Characteristics	Subjects available for linkage (N=19,494)	Subjects not linked (N=549)
Gender: (%)		
Female	26.3	87.8
Male	73.7	12.2
Age at entry: (%)		
67-70	45.0	44.1
71-74	28.5	29.7
75-79	19.9	18.7
80-84	6.6	7.5
Residence: (%)		
Urban	53.7	58.1
Rural	46.3	41.9
Outcome status: (%)		
Case	31.1	24.6
non-case	68.9	75.4

Table 4.3 Reasons for exclusion

	All drivers	Cases
Number of subjects linked	18,945	5922
Reasons for exclusion:		
nursing home residents	84	15
cases with only injurious crash before June 1 1990	38	38
cases ≥ 85 years of age on date of crash *	48	50
cases ineligible due to prior hospitalization(s) **	235	235
cases with date of death before crash	5	5
noncases with date of death before June 1, 1990	45	0
Total number excluded	455	343
Number of subjects available for analysis	18,490	5579

* Two of the 50 cases excluded were also members of the sub-cohort. They were included in the analysis as noncases prior to their exit age of 85.

** See text for description of hospitalization criteria applied to determine eligibility.

Table 4.4 Characteristics of cases and controls

Characteristic	Cases (N=5579)	Controls (N=55,790)
% male	80.0	72.2
Age at index date: (%)		
67-70	33.8	38.0
71-74	32.3	33.0
75-79	24.0	22.0
80-84	9.9	7.0
% rural residence	48.3	45.1
% with CNS drug use *	14.5	10.3
% with previous injurious MVC	3.4	1.7
Chronic disease score (mean ± SD)	2.82 (2.81)	2.62 (2.76)

* Exposure to any of the following drugs in the 60 days prior to the event: opioid, partial opioid or other analgesics; antidepressants; tranquillizers; other sedative/hypnotics; lithium; centrally acting skeletal muscle relaxants

Table 4.5 Comparison of study population and Quebec 1991 census population by gender and age

Characteristic	Cases (N=5579)	Controls (N=55,790)	Quebec Population (N=593,580)
% male	80.0	72.2	40.7
Female, age (%)			
67 - 70	38.9	43.0	32.4
71 - 74	35.0	34.5	25.5
75 - 79	20.2	18.4	25.4
80 - 84	5.8	4.1	16.7
Male, age (%)			
67 - 70	32.5	36.1	37.2
71 - 74	31.6	32.4	26.6
75 - 79	25.0	23.3	23.4
80 - 84	10.9	8.2	12.8

Table 4.6 **Three year cumulative incidence of first injurious motor vehicle crash per 1,000 drivers, by gender and age**

Age	Males	Females	All subjects
67 - 70	21.3	14.3	19.2
71 - 74	32.0	24.5	30.0
75 - 79	33.8	26.1	32.2
80 - 84	44.2	38.6	43.4
TOTAL	28.6	19.7	26.2

Table 4.7 Descriptive characteristics of the 5579 injurious motor vehicle crashes

Characteristic	missing	% of MVCs (N=5579)
Severity of crash:		
Minor - no one hospitalized		82.6
Major - at least one victim hospitalized		14.2
Fatal - at least one fatality within 8 days of crash	0	3.2
Location of crash: (administrative region)		
Montreal / Champlain / Laval		30.3
Outaouais		2.1
Quebec		6.2
Sherbrooke		3.2
all other regions	0	58.2
Time of day:		
6 am - 12 noon		32.8
1 pm - 6 pm		54.3
7 pm - 5 am	38	12.9
Season:		
Spring (April - May)		15.3
Summer (June - September)		41.8
Fall (October - November)		18.0
Winter (December - March)	0	24.9
Weather:		
Clear		64.1
Cloudy		19.2
Rain		10.2
Snow		4.1
Other	47	2.3
Condition of road surface:		
Dry		67.2
Wet		20.5
Snow		6.5
Ice		4.5
Other	0	1.3

Table 4.7 con't **Descriptive characteristics of 5579 injurious MVCs.**

Characteristic	missing	% of MVCs (N=5579)
Number of vehicles:		
Single vehicle		16.4
Two vehicles		68.1
Three or more vehicles	0	15.5
Posted speed limit:		
< 50 km per hour		3.6
50 km per hour		62.3
> 50 km per hour	599	34.1
Movement of the vehicle:		
Travel straight ahead		55.0
Right turn		3.4
Left turn		21.0
Other	84	20.6

Table 4.8 Distribution of benzodiazepine prescriptions dispensed to cases and controls during the year prior to motor vehicle crash

Product	Cases % of prescriptions (N=18,557)	Controls % of prescriptions (N=164,270)	All Subjects % of prescriptions (N=182,827)
Short half-life			
Alprazolam	3.7	4.7	4.5
Bromazepam	5.5	4.3	4.4
Lorazepam	36.3	38.3	38.1
Oxazepam	9.0	11.0	10.8
Temazepam	3.7	3.6	3.6
Triazolam	10.4	12.2	12.0
Long half-life			
Chlordiazepoxide	0.9	1.4	1.3
Clonazepam	2.4	1.3	1.4
Clorazepate	0.5	0.3	0.4
Diazepam	7.7	9.3	9.1
Flurazepam	17.4	11.3	11.9
Nitrazepam	2.7	2.3	2.4

Table 4.9 Distribution of benzodiazepine prescriptions dispensed to cases and controls during the year prior to motor vehicle crash, by elimination half-life

Elimination half-life	Cases No. (%) of prescriptions	Controls No. (%) of prescriptions	All Subjects No. (%) of prescriptions
Short half-life	12,701 (68.4)	121,782 (74.1)	134,483 (73.6)
Long half-life	5856 (31.6)	42,488 (25.9)	48,344 (26.4)

Table 4.10 **Distribution of duration (in days) of all benzodiazepine prescriptions dispensed to cases and controls in the year prior to motor vehicle crash**

Prescribed duration of treatment	Cases % of prescriptions (N=18,557)	Controls % of prescriptions (N=164,270)	All Subjects % of prescriptions (N=182,827)
< = 7 days	6.7	5.0	5.2
8 - 15 days	5.5	4.7	4.8
16 - 29 days	5.0	5.3	5.3
30 days	77.9	79.5	79.3
> 30 days	4.9	5.5	5.4

Table 4.11 Percent distribution of cases, controls and all subjects by exposure to benzodiazepines in the year prior to the motor vehicle crash

Benzodiazepine exposure	Cases (N=5579)	Controls (N=55,790)	All subjects (N=61,369)
Exposed at least once during the year prior to the index date	38.5	36.2	36.4
Short half-life *	28.9	28.2	28.3
Long half-life *	15.9	12.8	13.1
Exposed on index date	20.4	19.0	19.1
Initiation and *duration* of use in the 365 days prior to index date: (time from initiating exposure to index date)			
1 - 7 days	1.9	1.6	1.7
8 - 30 days	3.9	3.6	3.6
31 - 60 days	1.8	1.6	1.6
61 - 365 days	12.7	12.1	12.2
Other exposure:**	18.2	17.2	17.3
Exposure in the two years prior to index date:			
day 0-365 only	5.6	5.0	5.1
day 366-730 only	4.7	4.5	4.5
day 0-365 and day 366-730	32.9	31.1	31.3

* The addition of short and long half-life exceeds the number exposed at least once during the year prior to the index date because subjects may have been exposed to both a short and long half-life benzodiazepine

** Other exposure includes exposure to benzodiazepines which did not meet the criteria for new use

Table 4.12 Crude and adjusted rate ratio of motor vehicle crash by duration of exposure to benzodiazepines as a class

Duration of exposure	Cases		Controls		Crude RR (95% CI)	Adjusted RR* (95% CI)
	Yes	No	Yes	No		
1 - 7 days	108	4268	924	43,639	1.20 (0.98-1.46)	1.15 (0.94-1.41)
8 - 30 days	218	4081	2018	41,827	1.11 (0.96-1.28)	1.08 (0.94-1.25)
31 - 60 days	100	3937	909	40,412	1.13 (0.92-1.39)	1.05 (0.85-1.30)
61 - 365 days	710	3430	6754	35,600	1.09 (1.00-1.19)	0.99 (0.91-1.09)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.13 Crude and adjusted rate ratio of motor vehicle crash by duration of exposure to short half life benzodiazepines

Duration of exposure	Cases		Controls		Crude RR (95% CI)	Adjusted RR* (95% CI)
	Yes	No	Yes	No		
1 - 7 days	71	4268	674	43,639	1.08 (0.84-1.38)	1.04 (0.81-1.34)
8 - 30 days	156	4081	1477	41,827	1.08 (0.91-1.28)	1.06 (0.90-1.26)
31 - 60 days	68	3937	667	40,412	1.05 (0.81-1.35)	0.99 (0.77-1.28)
61 - 365 days	503	3430	5285	35,600	0.99 (0.90-1.09)	0.91 (0.82-1.01)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.14 Crude and adjusted rate ratio of motor vehicle crash by duration of exposure to long half life benzodiazepines

Duration of exposure	Cases		Controls		Crude RR (95% CI)	Adjusted RR* (95% CI)
	Yes	No	Yes	No		
1 - 7 days	40	4268	267	43,639	1.53 (1.08-2.14)	1.45 (1.04-2.03)
8 - 30 days	67	4081	575	41,827	1.19 (0.93-1.54)	1.16 (0.90-1.50)
31 - 60 days	31	3937	234	40,412	1.36 (0.93-1.98)	1.22 (0.84-1.79)
61 - 365 days	235	3430	1725	35,600	1.41 (1.23-1.63)	1.26 (1.09-1.45)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Figure 4.3

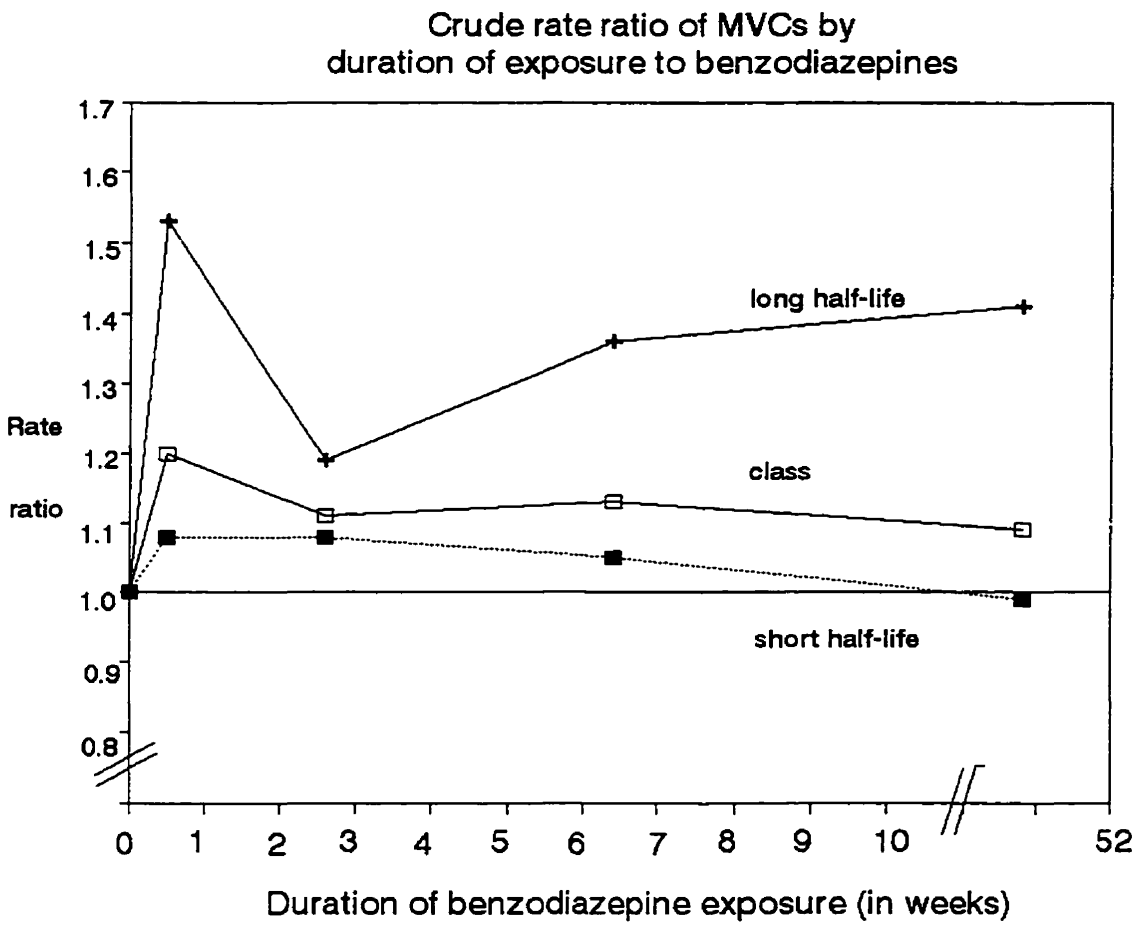
Crude rate ratio of MVCs by
duration of exposure to benzodiazepines
Rate
ratio
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
long half-life
class
short half-life
0
1
2
3
4
5
6
7
8
9
10
52
Duration of benzodiazepine exposure (in weeks)

Figure 4.4

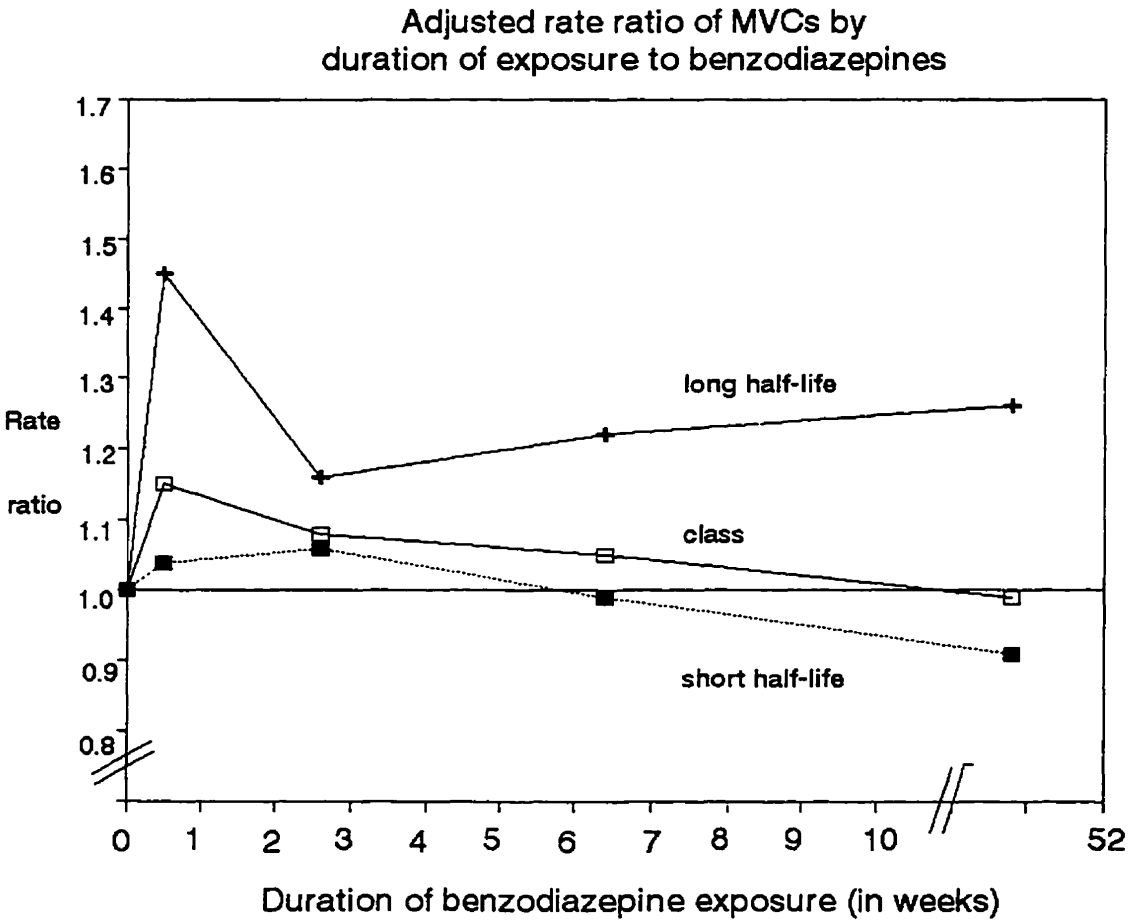
Adjusted rate ratio of MVCs by
duration of exposure to benzodiazepines
Rate
ratio
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
long half-life
class
short half-life
0
1
2
3
4
5
6
7
8
9
10
52
Duration of benzodiazepine exposure (in weeks)

Table 4.15 Distribution of benzodiazepine prescriptions dispensed in the seven days prior to the motor vehicle crash for cases, controls and all subjects

Product	Cases % of prescriptions (N=117)	Controls % of prescriptions (N=981)	All Subjects % of prescriptions (N=1098)
Short half life			
Alprazolam	6.8	5.0	5.2
Bromazepam	9.4	5.1	5.6
Lorazepam	36.8	38.6	38.4
Oxazepam	7.7	11.5	11.1
Temazepam	1.7	3.1	2.9
Triazolam	2.6	8.8	8.1
Long half life			
Chlordiazepoxide	3.4	1.3	1.5
Clonazepam	1.7	1.1	1.2
Clorazepate	0	0.1	0.1
Diazepam	12.8	12.6	12.7
Flurazepam	14.5	9.9	10.4
Nitrazepam	2.6	2.9	2.8

Note: The number of benzodiazepine prescriptions dispensed exceeds the number of exposed individuals because subjects may have had more than one benzodiazepine prescription dispensed in the 7 days prior to the index date.

Table 4.16 Distribution of benzodiazepine prescriptions dispensed in the seven days prior to the motor vehicle crash for cases, controls and all subjects, by elimination half-life

Elimination half-life	Cases No. (%) of prescriptions	Controls No. (%) of prescriptions	All subjects No. (%) of prescriptions
Short half-life	76 (65.0)	707 (72.1)	783 (71.3)
Long half-life	41 (35.0)	274 (27.9)	315 (28.7)

Note: The number of benzodiazepine prescriptions dispensed exceeds the number of exposed individuals because subjects may have had more than one benzodiazepine prescription dispensed in the 7 days prior to the index date.

Table 4.17 Distribution of duration (in days) of benzodiazepine prescriptions dispensed in the seven days prior to the motor vehicle crash for cases, controls and all subjects

Prescribed duration of treatment	Cases % of prescriptions (N=117)	Controls % of prescriptions (N=981)	All Subjects % of prescriptions (N=1098)
< = 7 days	0.0	0.9	0.8
8 - 15 days	11.1	7.7	8.1
16 - 29 days	6.9	10.6	10.2
30 days	76.9	75.7	75.9
> 30 days	5.1	5.0	5.0

Note: The number of benzodiazepine prescriptions dispensed exceeds the number of exposed individuals because subjects may have had more than one benzodiazepine prescription dispensed in the 7 days prior to the index date.

Table 4.18 Distribution of potential confounders among controls by first seven days of exposure to short and long half-life benzodiazepines

Characteristic	Short half-life exposure (%)	Long half-life exposure (%)
Gender:		
Female	2.1	0.7
Male	1.3	0.6
Age at index:		
67-70	1.3	0.6
71-74	1.5	0.6
75-79	2.0	0.6
80-84	1.3	0.4
Residence:		
Urban	1.4	0.5
Rural	1.6	0.7
CNS exposure:		
No	1.3	0.5
Yes	4.0	1.6
Chronic disease score:		
0	0.7	0.3
1 - 3	1.7	0.7
> 3	2.4	1.0
Previous injurious MVC:		
No	1.5	0.6
Yes	0.8	0.5

Table 4.19 Distribution of potential confounders among the unexposed * (n=47,907) and their association with risk of motor vehicle crash

Confounder	MVC		RR	95% CI
	Yes (n=4268) No. (%)	No (n=43,639) No. (%)		
Gender:				
Female	790 (18.5)	11,600 (26.6)	1.00	ref
Male	3478 (81.5)	32,039 (73.4)	1.59	(1.47-1.73)
Age at index:				
67 - 70	1470 (34.4)	17,109 (39.2)	1.00	ref
71 - 74	1355 (31.7)	14,311 (32.8)	1.10	(1.02-1.19)
75 - 79	1015 (23.8)	9216 (21.1)	1.28	(1.18-1.39)
80 - 84	428 (10.0)	3003 (6.9)	1.66	(1.66-1.86)
Residence:				
Urban	2251 (52.7)	24,293 (55.7)	1.00	ref
Rural	2017 (47.3)	19,346 (44.3)	1.13	(1.06-1.20)
CNS exposure:				
No	3823 (89.6)	40,515 (92.8)	1.00	ref
Yes	445 (10.4)	3124 (7.2)	1.51	(1.36-1.68)
Chronic disease score:				
0	1457 (34.1)	16,653 (38.2)	1.00	ref
1 - 3	1460 (34.2)	14,378 (32.9)	1.16	(1.08-1.25)
> 3	1351 (31.7)	12,608 (28.9)	1.22	(1.13-1.32)
Previous injurious MVC:				
No	4126 (96.7)	42,867 (98.2)	1.00	ref
Yes	142 (3.3)	772 (1.8)	1.91	(1.59-2.29)

* Unexposed defined as no use of benzodiazepines day 0 to 10 prior to event

Table 4.20 Distribution of other central nervous system drug use * in the 60 days prior to the event, and their association with risk of motor vehicle crash

CNS drugs	Cases (n=5579) No. (%)	Controls (n=55,790) No. (%)	RR	95% CI
Analgesics	577 (10.3)	3674 (6.6)	1.64	(1.49-1.80)
Antidepressants	179 (3.2)	1508 (2.7)	1.19	(1.02-1.40)
Tranquillizers	20 (0.4)	216 (0.4)	0.93	(0.59-1.47)
Other sedatives	83 (1.5)	707 (1.3)	1.18	(0.94-1.48)
Centrally acting skeletal muscle relaxants	20 (0.4)	112 (0.2)	1.79	(1.11-2.88)
Lithium	19 (0.3)	82 (0.2)	2.32	(1.41-3.83)

* Exposed defined as prescription dispensed for the CNS drug in the 60 days prior to the index date.
Unexposed defined as no prescription for the CNS drug in the 60 days prior to the index date.

Table 4.21 Independent predictors of motor vehicle crashes - first seven days of exposure to short half-life benzodiazepine

Parameter	Crude RR (95% CI)	ADJUSTED			
		Adjusted RR (95% CI)	ß coefficient	Standard error	p value
short half-life BZD use	1.08 (0.84-1.38)	1.04 (0.81-1.34)	0.042	0.127	0.740
age at index*	1.43 (1.33-1.54)	1.34 (1.24-1.45)	0.293	0.039	0.0001
male gender	1.59 (1.47-1.72)	1.54 (1.42-1.67)	0.430	0.041	0.0001
rural residence	1.13 (1.06-1.20)	1.12 (1.05-1.19)	0.109	0.032	0.0006
chronic disease score	1.03 (1.02-1.04)	1.01 (1.00-1.03)	0.013	0.006	0.032
CNS exposure	1.50 (1.36-1.67)	1.49 (1.34-1.65)	0.398	0.053	0.0001
previous injurious MVC	1.89 (1.58-2.27)	1.79 (1.49-2.15)	0.584	0.093	0.0001

* per decade

Table 4.22 Independent predictors of motor vehicle crashes - first seven days of exposure to long half-life benzodiazepines

Parameter	Crude RR (95% CI)	ADJUSTED			
		Adjusted RR (95% CI)	ß coefficient	Standard error	p value
long half-life BZD use	1.53 (1.10-2.14)	1.45 (1.04-2.03)	0.374	0.171	0.029
age at index *	1.44 (1.34-1.55)	1.35 (1.25-1.46)	0.030	0.004	0.0001
male gender	1.60 (1.48-1.73)	1.54 (1.42-1.67)	0.431	0.041	0.0001
rural residence	1.13 (1.06-1.20)	1.11 (1.05-1.19)	0.107	0.032	0.0009
chronic disease score	1.03 (1.02-1.04)	1.01 (1.00-1.03)	0.014	0.006	0.018
CNS exposure	1.50 (1.35-1.66)	1.47 (1.33-1.64)	0.388	0.054	0.0001
previous injurious MVC	1.91 (1.59-2.29)	1.81 (1.52-2.17)	0.592	0.093	0.0001

* per decade

Table 4.23 Adjusted rate ratio of motor vehicle crashes for first seven days of benzodiazepine use: assessment of effect modification by length of washout period

Length of washout period	Cases	Controls	RR *	95% CI
Short half-life benzodiazepines				
4 - 30 days	43	415	0.95	0.67-1.35
31 - 90 days	15	149	1.01	0.53-1.94
91 - 365 days	13	110	1.26	0.64-2.47
Long half-life benzodiazepines				
4 - 30 days	20	140	1.25	0.77-2.04
31 - 90 days	12	62	1.44	0.64-3.21
91 - 365 days	8	65	1.04	0.43-2.53

* adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crash

Table 4.24 Independent effects of short and long half-life benzodiazepines and risk of motor vehicle crash

Determinant	ß coefficient	Standard error	p value	Adjusted RR (95% CI)
short half-life BZD	0.033	0.127	0.796	1.03 (0.81-1.33)
long half-life BZD	0.374	0.171	0.029	1.45 (1.04-2.03)
age at index *	0.297	0.038	0.0001	1.35 (1.25-1.45)
male gender	0.431	0.041	0.0001	1.54 (1.42-1.67)
rural residence	0.109	0.032	0.0006	1.12 (1.05-1.19)
chronic disease score	0.013	0.006	0.029	1.01 (1.00-1.03)
CNS exposure	0.385	0.053	0.0001	1.47 (1.32-1.63)
previous injurious MVC	0.584	0.093	0.0001	1.79 (1.50-2.15)

* per decade

Interactions:

- short half life BZD * long half life BZD: Likelihood ratio test (1df)=0.112 p=0.73

Table 4.25 Crude and adjusted rate ratio of motor vehicle crashes for first seven days of short half-life benzodiazepine use, as a percentage of the recommended average daily dose for seniors

Dose	Cases	Controls	Crude RR (95% CI)	Adjusted RR * (95% CI)
No exposure day 0 to 10	4268	43,639	1.00	ref
Recommended average daily dose or less	13	87	1.53 (0.85-2.74)	1.47 (0.82-2.65)
101-200% of recommended average daily dose	24	340	0.72 (0.48-1.09)	0.70 (0.46-1.07)
> 200% of recommended average daily dose	34	247	1.41 (0.98-2.02)	1.36 (0.98-1.95)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.26 Crude and adjusted rate ratio of motor vehicle crashes for first seven days of long half-life benzodiazepine use, as a percentage of the recommended average daily dose for seniors

Dose	Cases	Controls	Crude RR (95% CI)	Adjusted RR * (95% CI)
No exposure day 0 to 10	4268	43,639	1.00	ref
Recommended average daily dose or less	8	61	1.34 (0.64-2.80)	1.25 (0.60-2.62)
101-200% of recommended average daily dose	23	149	1.58 (1.02-2.45)	1.54 (0.99-2.39)
> 200% of recommended average daily dose	9	57	1.61 (0.80-3.26)	1.46 (0.72-2.96)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.27 Crude and adjusted rate ratio of motor vehicle crashes for first seven days of use of alprazolam, bromazepam, lorazepam, oxazepam, diazepam and flurazepam

BZD exposure	CASES		CONTROLS		Crude RR (95% CI)	Adjusted RR * (95% CI)
	Yes	No	Yes	No		
Short half life:						
Alprazolam	8	4268	46	43,639	1.78 (0.84-3.77)	1.72 (0.81-3.66)
Bromazepam	11	4268	49	43,639	2.30 (1.19-4.42)	2.26 (1.17-4.37)
Lorazepam	39	4268	375	43,639	1.06 (0.76-1.48)	1.04 (0.74-1.45)
Oxazepam	9	4268	111	43,639	0.83 (0.42-1.64)	0.80 (0.41-1.59)
Long half life:						
Diazepam	15	4268	121	43,639	1.27 (0.74-2.17)	1.26 (0.74-2.17)
Flurazepam	17	4268	97	43,639	1.79 (1.07-3.00)	1.61 (0.96-2.70)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.28 Crude rate ratio for motor vehicle crashes for first seven days of benzodiazepine use, by number of different benzodiazepines received

Number of benzodiazepines	Cases		Controls		Crude RR (95% CI)
	Yes	No	Yes	No	
Only one benzodiazepine	101	4268	871	43,639	1.19 (0.96-1.46)
Two or more different benzodiazepines	5	4268	41	43,639	1.25 (0.49-3.16)
At least 1 long and 1 short half-life benzodiazepine	3	4268	17	43,639	1.80 (0.53-6.16)

Note: exposure categories are not mutually exclusive

Table 4.29 Percent distribution of cases, controls and all subjects by exposure to benzodiazepines in the year prior to the motor vehicle crash

Benzodiazepine exposure	Cases (N=5579)	Controls (N=55,790)	All subjects (N=61,369)
No exposure in prior year	61.5	63.8	63.6
Exposed on index date	20.4	19.0	19.1
Short half-life *	14.5	14.7	14.7
Long half-life *	6.9	5.2	5.4
Exposure other than on index date:	18.2	17.2	17.3

* The addition of short and long half-life exceeds the number exposed on the index date because 62 cases and 508 controls were currently exposed to both a short and long half-life benzodiazepine

Table 4.30 Distribution of potential confounders among controls by current short and long half-life benzodiazepine exposure status

Confounder	Short half-life exposure (%)	Long half-life exposure (%)
Gender:		
Female	24.3	9.2
Male	16.8	7.0
Age at index:		
67 - 70	16.1	6.7
71 - 74	19.4	7.9
75 - 79	21.6	8.9
80 - 84	20.8	6.9
Residence:		
Urban	17.9	6.8
Rural	19.7	8.5
CNS exposure	46.1	24.8
Chronic disease score:		
0	7.7	3.2
1 - 3	20.0	8.4
> 3	30.5	12.9
Previous injurious MVC	17.5	8.3

Table 4.31 Distribution of potential confounders among the unexposed (n=39,030) and their association with risk of motor vehicle crashes

Confounder	MVC		RR	95% CI
	Yes (n=3430) No. (%)	No (n=35,600) No. (%)		
Gender:				
Female	557 (16.2)	8515 (23.9)	1.00	ref
Male	2873 (83.8)	27,085 (76.1)	1.62	(1.48-1.78)
Age at index:				
67 - 70	1174 (34.3)	14,116 (39.6)	1.00	ref
71 - 74	1088 (31.7)	11,554 (32.5)	1.13	(1.04-1.23)
75 - 79	831 (24.2)	7436 (20.9)	1.34	(1.22-1.48)
80 - 84	337 (9.8)	2494 (7.0)	1.63	(1.43-1.85)
Residence:				
Urban	1834 (53.5)	19,879 (55.8)	1.00	ref
Rural	1596 (46.5)	15,721 (44.2)	1.10	(1.03-1.18)
CNS exposure:				
No	3140 (91.5)	33,498 (94.1)	1.00	ref
Yes	290 (8.5)	2102 (5.9)	1.47	(1.30-1.67)
Chronic disease score:				
0	1283 (37.4)	14,791 (41.5)	1.00	ref
1 - 3	1154 (33.6)	11,456 (32.2)	1.16	(1.07-1.26)
> 3	993 (29.0)	9353 (26.3)	1.22	(1.12-1.34)
Previous MVC:				
No	3314 (96.6)	34,967 (98.2)	1.00	ref
Yes	116 (3.4)	633 (1.8)	1.93	(1.58-2.36)

Table 4.32 Independent predictors of motor vehicle crashes - current exposure to short half-life benzodiazepines

Parameter	Crude RR (95% CI)	ADJUSTED * Adjusted RR (95% CI)	ß coefficient	Standard error	p value
current short half-life BZD	1.03 (0.95-1.11)	0.96 (0.88-1.05)	-0.042	0.045	0.357
other half-life	1.16 (0.92-1.45)	1.14 (0.90-1.44)	0.129	0.122	0.287
age at index **	1.41 (1.31-1.52)	1.33 (1.23-1.44)	0.285	0.039	0.0001
male gender	1.58 (1.46-1.71)	1.53 (1.41-1.66)	0.423	0.042	0.0001
rural residence	1.12 (1.05-1.19)	1.11 (1.04-1.18)	0.104	0.032	0.001
chronic disease score	1.02 (1.02-1.04)	1.01 (0.99-1.02)	0.008	0.006	0.180
CNS drugs	1.40 (1.26-1.54)	1.41 (1.27-1.56)	0.342	0.052	0.0001
previous injurious MVC	1.99 (1.66-2.38)	1.89 (1.57-2.26)	0.635	0.092	0.0001

* Adjusted for all other variables in the model

** Per decade

Interactions:

- short half life BZD * age at index: LRT(1df)=4.90 p=0.03
- short half life BZD * gender: LRT(1df)=0.52 p=0.47
- short half life BZD * chronic disease score: LRT(1df)=4.42 p=0.04
- short half life BZD * CNS drugs: LRT(1df)=0.617 p=0.43
- short half life BZD * previous injurious MVC: LRT(1df)=0.404 p=0.52

Table 4.33 Crude and adjusted rate ratio of motor vehicle crashes for current users of short half life benzodiazepines, stratified by age.

Age	Cases		Controls		Crude RR (95% CI)	Adjusted * RR (95% CI)
	Yes	No	Yes	No		
67 - 70	252	1174	2713	14,116	1.12 (0.97-1.29)	1.04 (0.89-1.22)
71 - 74	281	1088	2781	11,554	1.07 (0.94-1.23)	1.01 (0.87-1.18)
75 - 79	197	831	2053	7436	0.86 (0.73-1.01)	0.83 (0.70-0.99)
80 - 84	81	337	655	2494	0.92 (0.71-1.18)	0.90 (0.68-1.18)

- Adjusted for age at index, gender, residence, chronic disease score, long half-life benzodiazepine exposure and other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crash

Breslow Day test for homogeneity of the odds ratio: $p = 0.07$

Table 4.34 Crude and adjusted rate ratio of motor vehicle crashes for current users of short half life benzodiazepines, stratified by chronic disease score.

Chronic disease score	Cases		Controls		Crude RR (95% CI)	Adjusted * RR (95% CI)
	Yes	No	Yes	No		
0	132	1283	1229	14,791	1.24 (1.03-1.50)	1.13 (0.92-1.38)
1 - 3	274	1154	2859	11,456	0.95 (0.83-1.09)	0.91 (0.79-1.06)
> 3	405	993	4114	9353	0.93 (0.82-1.05)	0.92 (0.81-1.05)

- Adjusted for age at index, gender, residence, chronic disease score, long half-life benzodiazepine exposure and other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crash

Breslow Day test for homogeneity of the odds ratio: p = 0.03

Table 4.35 Independent predictors of motor vehicle crashes - current exposure to long half-life benzodiazepines

Parameter	Crude RR (95% CI)	ADJUSTED * Adjusted RR (95% CI)	ß coefficient	Standard error	p value
current long half-life BZD	1.38 (1.23-1.54)	1.28 (1.12-1.45)	0.243	0.066	0.0002
other half-life	1.29 (1.03-1.61)	0.95 (0.74-1.22)	-0.052	0.130	0.678
age at index **	1.43 (1.32-1.55)	1.35 (1.24-1.46)	0.297	0.004	0.0001
male gender	1.59 (1.45-1.73)	1.53 (1.40-1.67)	0.425	0.045	0.0001
rural residence	1.11 (1.04-1.19)	1.09 (1.02-1.17)	0.087	0.034	0.011
chronic disease score	1.03 (1.02-1.05)	1.01 (0.99-1.03)	0.011	0.007	0.082
CNS drugs	1.58 (1.42-1.76)	1.50 (1.34-1.68)	0.405	0.057	0.0001
previous injurious MVC	1.95 (1.61-2.36)	1.84 (1.52-2.23)	0.610	0.097	0.0001

* Adjusted for all other variables in the model

** per decade

Interactions:

- long half life BZD * age at index: LRT(1df)=3.89 p=0.05
- long half life BZD * gender: LRT(1df)=0.691 p=0.40
- long half life BZD * chronic disease score: LRT(1df)=1.38 p=0.24
- long half life BZD * CNS drugs: LRT(1df)=1.315 p=0.25
- long half life BZD * previous injurious MVC: LRT(1df)=0.03 p=0.86

Table 4.36 Crude and adjusted rate ratio of motor vehicle crashes for current users of long half life benzodiazepines, stratified by age

Age	Cases		Controls		Crude RR (95% CI)	Adjusted * RR (95% CI)
	Yes	No	Yes	No		
67 - 70	125	1174	1009	14,116	1.49 (1.23-1.81)	1.29 (1.03-1.62)
71 - 74	150	1088	996	11,554	1.60 (1.33-1.92)	1.49 (1.20-1.85)
75 - 79	86	831	722	7436	1.07 (0.84-1.35)	1.05 (0.81-1.38)
80 - 84	26	337	184	2494	1.05 (0.68-1.60)	1.13 (0.72-1.79)

* Adjusted for age at index, gender, residence, chronic disease score, short half-life benzodiazepine exposure and other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crash

Breslow Day test for homogeneity of the odds ratio: p = 0.02

Table 4.37 Crude and adjusted rate ratio of motor vehicle crashes for current users of short half life benzodiazepines, as a percentage of the recommended average daily dose for seniors

Dose	Cases	Controls	Crude RR (95% CI)	Adjusted RR * (95% CI)
No exposure day 0 to 365	3430	35,600	ref	ref
Recommended average daily dose or less	118	994	1.23 (1.01-1.50)	1.21 (0.99-1.48)
101-200% of recommended average daily dose	345	4090	0.88 (0.78-0.98)	0.83 (0.74-0.94)
> 200% of recommended average daily dose	348	3118	1.16 (1.03-1.30)	1.08 (0.96-1.22)

* Adjusted for age at index, gender, residence, chronic disease score, long half-life benzodiazepine exposure and other CNS drugs exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.38 Crude and adjusted rate ratio of motor vehicle crashes for current users of long half life benzodiazepines, as a percentage of the recommended average daily dose for seniors

Dose	Cases	Controls	Crude RR (95% CI)	Adjusted RR * (95% CI)
No exposure day 0 to 365	3430	35,600	ref	ref
Recommended average daily dose or less	89	725	1.27 (1.02-1.59)	1.19 (0.95-1.49)
101-200% of recommended average daily dose	230	1630	1.46 (1.27-1.69)	1.33 (1.15-1.54)
> 200% of recommended average daily dose	68	556	1.27 (0.98-1.64)	1.15 (0.89-1.48)

* Adjusted for age at index, gender, residence, chronic disease score, short half-life benzodiazepine exposure and other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.39 Crude and adjusted rate ratio of motor vehicle crashes for current users of bromazepam, lorazepam, oxazepam, triazolam, diazepam, flurazepam and nitrazepam

BZD exposure	CASES		CONTROLS		Crude RR (95% CI)	Adjusted RR * (95% CI)
	Yes	No	Yes	No		
Short half life:						
Bromazepam	71	3430	542	35,600	1.36 (1.06-1.75)	1.27 (0.99-1.64)
Lorazepam	475	3430	4617	35,600	1.07 (0.97-1.18)	1.02 (0.91-1.13)
Oxazepam	117	3430	1311	35,600	0.93 (0.76-1.12)	0.85 (0.70-1.04)
Triazolam	127	3430	1391	35,600	0.95 (0.79-1.14)	0.87 (0.72-1.05)
Long half life:						
Diazepam	99	3430	1061	35,600	0.97 (0.79-1.19)	0.92 (0.75-1.14)
Flurazepam	212	3430	1338	35,600	1.65 (1.42-1.91)	1.47 (1.26-1.72)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure in the 60 days prior to the event and previous injurious motor vehicle crashes

Table 4.40 Crude and adjusted rate ratio of involvement in motor vehicle crashes for current users of benzodiazepines, by number of different benzodiazepines received

Number of different BZDS	Cases exposed	Controls exposed	Crude RR (95% CI)	Adjusted RR* (95% CI)
Two or more	148	1214	1.27 (1.06-1.51)	1.15 (0.96-1.38)
At least 1 long & 1 short half life	62	508	1.27 (0.97-1.65)	1.17 (0.89-1.54)
At least two or more short half life	82	637	1.34 (1.06-1.69)	1.20 (0.95-1.52)
At least two or more long half life	7	102	0.71 (0.33-1.53)	0.60 (0.28-1.29)

* Adjusted for age at index, gender, residence, chronic disease score, other CNS drug exposure and previous injurious motor vehicle crashes

Table 4.41 **Average number of kilometers driven (per 1,000) in the prior year among Quebec drivers age 67 to 84, by age and gender. Santé Québec Survey, 1987.**

Age	Females		Males	
	No. of subjects	Mean (SD)	No. of subjects	Mean (SD)
67 - 70	67	6.6 (6.6)	200	9.5 (9.1)
71 - 74	30	6.1 (10.5)	124	8.8 (8.4)
75 - 79	8	3.6 (4.7)	85	7.2 (8.2)
80 - 84	6	6.0 (4.7)	29	6.5 (5.2)

CHAPTER 5
METHODOLOGICAL CONSIDERATIONS

This chapter contains details of three specific methodological issues pertaining to the study. Given that exposure consisted of categories of increasing duration of use, the choice of the proper reference category for contrast with these exposure categories was not clear cut. We thus explored the rationale and implications for the reference exposure category utilized in this study, and present the results here. A second issue was related to the characterization of exposure, or more specifically the potential for bias due to error in the temporal sequence of the exposure-outcome relationship. Finally, the validity of the nested case-control design within a case-cohort sample had to be assessed.

5.1 Choice of Reference Category for Exposure Contrast

While the choice of a "control" group in case-control studies has been explored previously in the literature (Wacholder et al 1991a, Wacholder et al 1991b, Wacholder et al 1992), the choice of an appropriate reference category against which exposure is contrasted has received less emphasis. Using the clinical trial as a paradigm, Miettinen et al (1989) explain that the issue is not merely a contrast between exposed and unexposed at the time of the event, but the effect of the treatment group (exposed) in contrast with a comparable group without the agent, often a placebo (reference). This is necessary to ensure comparability between groups with respect to other extraneous risk factors for the outcome. Except for very basic situations, a simple dichotomy of exposed versus unexposed at the time of the event does not follow this experimental paradigm.

Accordingly, the reference category should be similar to the index category on extraneous effects that may influence the outcome (Miettinen 1985), and should not simply be the complement of the exposed group (Rothman 1986). This requires the use of a subdomain of the unexposed as the reference category.

In the present study subjects were not dichotomized into exposed and unexposed, but were in fact categorized into one of three categories: exposed, unexposed, and "other". The exposed and unexposed groups were defined in an attempt to ensure their comparability, while the "other" category included subjects who did not meet the criteria for either of these categories. This "other" category may include, for example, a subject with a prescription dispensed in the month prior to the event, but of insufficient duration to include exposure on the index date, one of the criteria in defining exposure for all categories, or non-exposure of sufficient duration (ie. 10 days). Subjects in the "other" category were not included in the analysis.

The majority of studies with multiple exposure categories typically contrast exposure to a single category of non-exposure. In the present study for the analysis of new use of increasing durations we defined a separate reference category, or a variable as opposed to a constant reference category of non-exposure, for contrast with each of the four exposure categories. The reference category of non-exposure in the present study corresponded to the time interval of exposure, plus the three-day washout period. For example, benzodiazepine exposure defined as seven days of continuous new use was contrasted to that of non-use in the 10 days prior to the index date. Similarly, 30 days of continuous new use was contrasted to that of non-use in the 33 days prior to the index date.

Given the indications for which benzodiazepines may be prescribed, and the fact that among the elderly they may be used for longer treatment of weeks to months, we deemed that reference categories created in this manner were more likely to be comparable to the exposure category with respect to extraneous factors. A reference group which included only subjects with no prior history of exposure would probably be healthier as a whole, and may have a different baseline risk and distribution of extraneous risk factors for the outcome than an exposed group initiating benzodiazepine therapy.

However, when characterizing the reference group in this manner, and including subjects with a prior history of benzodiazepine exposure, a potential for bias exists if

the reason for discontinuing use of the drug is related to the outcome event. For example, if the reference group included subjects who discontinued benzodiazepine use because of symptoms of psychomotor impairment the result would be an under-estimate of the measure of effect. To assess the influence of our choice of a variable reference group, and the extent to which inclusion of subjects with prior benzodiazepine exposure may effect the results, we also conducted an analysis using a constant reference group, defined as no exposure to benzodiazepines in the year prior to the event.

The crude rate ratios obtained from the analyses with variable and constant reference groups, for short and long half-life benzodiazepines, are presented in tables 5.1 and 5.2 respectively. The subjects in the variable reference group for the 61-365 day category, corresponding to no exposure in the year prior to the index date, comprised the constant reference group. As is evident in table 5.1, the crude rate ratios are almost identical for the analysis using a variable or a constant reference group. A similar effect was seen for long half-life benzodiazepines (table 5.2).

The similarities in the estimates of effect obtained, which validates our choice of reference categories, are due to the fact that over eighty percent of the subjects in each of the variable reference categories were in fact subjects with no exposure in the year prior to the index date. Despite the fact that subjects with prior benzodiazepine exposure were included in the reference exposure groups in an attempt to ensure comparability with exposed subjects, the majority of subjects in these reference categories had no benzodiazepine exposure in the prior year. Therefore we can not exclude the possibility that the reference groups were healthier as a whole, with a different distribution of extraneous risk factors for the outcome necessary to control for in the analyses.

5.2 Issues in the Temporality of Exposure and Outcome

One fundamental requirement in assessing drug risks is that exposure precede the adverse event under study. Violations to this requirement have led to the development of various forms of bias. Kramer (1988) refers to "reverse causality bias"

as a simple situation in which outcome precedes exposure, a condition more common in cross-sectional studies, while Feinstein (1985) refers to "protopathic bias" as a more subtle error in the timing between exposure and outcome. Protopathic bias occurs when the outcome event has already taken place, but is not adequately recognized, before the treatment / exposure is allocated or initiated. In pharmacoepidemiology protopathic bias has usually been confined to situations where the outcome event is preceded by unreported early symptoms, and the suspected drug is an indication for these symptoms. One may wrongly conclude that the drug is a risk factor for the event that follows the symptoms, when in fact it was prescribed because of the presence of early symptoms for the event. A classic example is the use of aspirin in children ill with fever, a prodromal manifestation of Reye's syndrome. The validity of the association between use of aspirin and Reye's syndrome has been questioned because of concerns regarding the temporality of exposure and outcome (Daniels et al 1983).

The potential for reverse causality bias or a form of protopathic bias was possible in the present study and was related to two factors, the acuteness of the exposure-outcome relationship and the fact that the outcome event may be an indication for the exposure. The degree of precision of time data from these computerised databases is at most daily, and thus does not permit one to differentiate the temporality of exposure-outcome within a given day. This can be important when studying very acute effects where the outcome event can be experienced within hours of the exposure, as was the case in the present study.

In defining exposure we had established that a subject must have been dispensed a benzodiazepine of sufficient duration to have extended up to, or beyond, the index date. However, having established this criterion, and given the indications for which benzodiazepines are prescribed, another issue that had to be considered was whether prescriptions dispensed on the day of the event were to be included in the exposure definition.

The benzodiazepine and motor vehicle crash (MVC) relationship presents a unique situation in that the outcome event may in fact be an indication for the exposure.

One of the indications for the use of benzodiazepines is the short term treatment of anxiety - such as the anxiety which may result after being involved in an injurious MVC.

Based on the short induction period of benzodiazepines, and the resultant acute nature of the adverse reactions, it may be plausible that an individual obtained a prescription for a benzodiazepine, initiated treatment, and subsequently experienced a MVC, all within a matter of a few hours. However, it may also be plausible that a subject was involved in a MVC and was subsequently prescribed and dispensed a benzodiazepine on the same day. Without information as to the actual time of day that the benzodiazepine was dispensed, it is difficult to determine the sequence of events, and thus the potential for bias due to an alteration in the temporal sequence of exposure and outcome.

In an attempt to clarify the temporal sequence of events, and determine the extent to which this bias may be present, we conducted a further analysis to determine if involvement in an injurious MVC was a predictor of benzodiazepine exposure. The outcome in this analysis was the dispensing of a benzodiazepine on the day following the MVC for the cases, or the matching index date for the controls.

As shown in table 5.3, a total of 444 subjects (51 cases and 393 controls) were dispensed a benzodiazepine on the day following the index date, regardless of their prior exposure to benzodiazepines. Subjects involved in a MVC were 30 percent more likely to be dispensed a benzodiazepine than subjects not involved in a MVC, although this was not statistically significant (RR 1.30, 95% CI 0.97-1.74).

When the analysis was limited to subjects with no benzodiazepine exposure in the 30 days prior to the index date, the risk was increased substantially, and became significant (RR 3.08, 95% CI 1.76-5.40). When a further restriction was applied, and included only subjects with no benzodiazepine exposure in the prior 60 days, the risk of being dispensed a benzodiazepine was over four and-a-half times higher for subjects involved in a MVC, compared to subjects not involved in a MVC (RR 4.65, 95% CI 2.41-8.99).

The restriction of benzodiazepine exposure for a specified period of time prior to the MVC was applied to ensure that the prescription was dispensed as a consequence of the MVC, and not simply as a result of regular use. The increasing rate ratio corresponding to the increasing length of time with no previous benzodiazepine exposure provides convincing support that MVCs may be an indication for benzodiazepine exposure.

It is based on this evidence and the fact that we did not have the exact time of day that prescriptions were dispensed in relation to the MVCs, that benzodiazepines dispensed on the day of the event were not included in the definition of exposure for the study. This corresponded to 14 cases who had been dispensed a benzodiazepine on the day of the crash and had no exposure in the prior 60 days.

5.3 Validity of the Nested Case-control Design with a Case-cohort Sample

As discussed previously in chapter 3, the size of the cohort of elderly drivers initially assembled for the study was too large to be manageable for the purposes of data analysis, and required that sampling designs within a cohort, namely the case-cohort and nested case-control design, had to be considered. Not only are both designs advantageous in that the reduction in size facilitates data management and analysis, but they are also efficient and cost effective since exposure and covariate information is required only for the cases and a subset of the cohort. With the ever increasing use of computerized databases, these sampling designs have received considerable attention (Langholz & Thomas 1990, Wacholder 1991c, Suissa 1994).

The nested case-control design, formalized by Liddell et al in 1977, involves the random selection of a (generally fixed) number of "controls" from all subjects at risk at the failure time of each case, with controls matched to the cases on time. As discussed by Suissa et al (1994), the general rule of a 4:1 control to case ratio is appropriate in the majority of instances, however, there are situations when the ratio may be required to increase to 10 or more controls per case. This could include conditions when exposure to the drug under study is infrequent, such as in the analysis of the initiation

of benzodiazepine use in the present study. Data from a nested case-control study are analyzed using standard techniques for the analysis of matched case-control studies. Advantages of the nested case-control design include ease of analysis using widely available software and the fact that information on time-dependent exposures does not have to be collected for the controls beyond the time of follow-up of the case. There are several examples of the use of the nested case-control design in the literature (Ray et al 1989b, Spitzer et al 1992).

The case-cohort can be viewed as an unmatched variation of the nested case-control design (Wacholder 1991c), or a reduced version of the cohort (Prentice 1986). This design involves the selection of all cases occurring in a cohort over a follow-up period, as well as a random sample (sub-cohort) from the entire cohort (Prentice 1986). The sub-cohort will also include some individuals who become cases. A case who is a member of the sub-cohort is eligible to be included in a risk set prior to their becoming a case. However cases who are not members of the sub-cohort cannot contribute to prior risk sets.

A number of studies using the case-cohort design have recently been published (Boivin et al 1992, van den Brandt et al 1993, Armstrong et al 1994, Boivin et al 1995). The advantages of the case-cohort design include the ability to use the same sub-cohort for several disease outcomes (Prentice 1986, Langholz & Thomas 1990), ease in performing external comparisons (Wacholder & Boivin 1987), and the ability to use multiple time scales (Wacholder 1991c). One of the major disadvantages of the case-cohort design is related to the complexity of data analysis. The analysis must take into account the overlap between successive risk-sets induced by the sampling strategy. A special variance adjustment is required, which is related to the overlap of cases who are also included in the sub-cohort, and a correlation between subsequent risk sets. EPICURE, a statistical software package for the analysis of case-cohort data, involves an adjustment to the variance estimates that takes into account failures among those not included in the risk set (Preston et al 1991). The net effect of the adjustment is to increase the overall variance of the estimate; an unadjusted variance will result in p

values from associated tests that will be too low, and confidence intervals that are too narrow.

The calculation of this adjusted variance does, however, involve considerable computer processing time. This fact, combined with the complexity of the time dependent exposure and covariates in the present study, made it virtually impossible to obtain estimates of effect with the necessary case-cohort variance adjustment. We therefore decided to undertake a nested case-control design within the case-cohort study population, and assess the validity of such a procedure.

The usual steps involved in the nested case-control design are to select all cases from within a predefined cohort, form risk sets corresponding to the cases from the cohort, and then randomly select the required number of controls from each risk set. The same procedure was undertaken in the present study, except that the risk sets were formed from the sub-cohort, rather than from the cohort itself. In essence, this can be viewed as a two step sampling procedure. The first step being a random sample of the cohort to form the sub-cohort, and the second being the selection among risk sets from within the sub-cohort.

Given that there were 5,579 cases, and 13,256 members of the sub-cohort from which to sample controls, one may be concerned that there would be multiple use of the same controls in different risk sets, which may result in induced correlatedness of the risk sets. However we felt that the classification of exposure on a daily basis, and the irregularity of use of benzodiazepines, would help ensure that the exposure profile of a subject would vary sufficiently across risk sets. This assumption would hold true as long as current exposure was not too dependent on prior exposure.

To further assess the validity of the nested case-control design in this situation we conducted both a case-cohort and a series of simulations of the nested case-control analysis on a one and five percent sample of the study population. This analysis was undertaken for the initial seven days and current use of benzodiazepines as a class. Thus four case-cohort analyses were performed: the assessment of new use for both a one and five percent sample, and the assessment of current use for both a one and five

percent sample. For each of these four case-cohort analyses, 20 simulations of the nested case-control analyses were performed. The average of the 20 simulations were taken to obtain the parameters for the case-control analyses, which were then compared to the case-cohort analyses, considered to be the gold standard. The case-cohort analysis was conducted using EPICURE (Preston et al 1991), with the appropriate variance adjustment, and the nested case-control analysis, with 10 controls per case, was conducted using unconditional logistic regression. As noted previously similar estimates of effect were obtained from both the conditional and unconditional analyses, suggesting lack of confounding by time trends, therefore only the unconditional analysis will be reported here.

Results of the analysis for the initial seven days of benzodiazepine use as a class, for both the one and five percent sample, are presented in table 5.4a and 5.4b respectively. The one percent sample consisted of 183 subjects and 60 cases, corresponding to 59 risk sets (more than one event occurring on any one day is considered a single risk set). Contrary to what had been expressed in the literature, the adjusted standard error from the case-cohort analysis was smaller than the unadjusted standard error obtained as the average of the 20 case-control simulations (ratio of adjusted:unadjusted standard error=0.96). A rate ratio of 1.20 (95% CI 0.16-9.05) was obtained for the case-cohort analysis, and 1.26 (95% CI 0.15-10.30) for the average of the 20 case-control simulations. A similar trend was observed in the five percent sample, which consisted of 1009 subjects, 307 cases and 253 risk sets. The ratio of adjusted:unadjusted standard error was 0.95; the rate ratio was 1.92 (95% CI 0.97-3.79) for the case-cohort analysis, and 1.90 (95 % CI 0.92-3.91) for the case-control simulations.

The analysis of current use for the one and five percent samples are displayed in table 5.5a and 5.5b respectively. The adjusted standard error in this instance was increased, with the ratio of adjusted:unadjusted standard error being 1.10. For the one percent sample a rate ratio of 1.03 (95% CI 0.48-2.18) was obtained for the case-cohort analysis, and 1.03 (95% CI 0.52-2.04) for the case-control simulations. The results of

the analysis for the five percent sample showed a similar trend, with an adjusted to unadjusted standard error of 1.11, a rate ratio of 1.54 (95% CI 1.13-2.10) for the case-cohort analysis and 1.54 (95% CI 1.16-2.04) for the case-control simulations.

Contrary to what has been expressed in the literature, for the analysis of new use the adjusted standard error from the case-cohort analysis was slightly smaller than the unadjusted standard error from the nested case-control analysis. This suggests that the results obtained for the analysis of new use in the present study may in fact be conservative. As such, the p values may underestimate the degree of significance, and the confidence intervals may be slightly larger than those obtained from a case-cohort analysis. For new exposure it may be that the case-cohort analysis in fact over-adjusts the estimates of effect, particularly since exposure on a daily basis was considered.

However, for current use, which simply reflects exposure on the day of the event irrespective of duration of use, the adjusted standard error from the case-cohort analysis was slightly larger than the unadjusted standard error from the case-control analysis. The current use analysis in the present study may therefore overestimate the degree of significance, and the confidence intervals may be narrower than those which would be obtained from a case-cohort analysis. However, the similarity in the results obtained, with a slightly larger unadjusted standard error for new use, and a slightly smaller unadjusted error for current use, provides support for the validity of the nested case-control design within a case-cohort sample, as used in the present study.

Of note is the fact that it required seven days of continuous computational time to obtain the parameters for the case-cohort analysis with a five percent sample, using a HP-710 UNIX workstation. The one percent sample was computed within two hours, which suggests there is an exponential increase in computational time as the sample size and number of risk sets increases. Clearly, this analysis with the entire case-cohort study population was infeasible.

Table 5.1 Crude rate ratio of motor vehicle crashes for new use of short half-life benzodiazepines: Comparison of analysis with variable and constant unexposed reference groups

Variable Unexposed Reference Group

Duration of exposure	Cases		Controls		Crude RR
	Yes	No	Yes	No	
1 - 7 days	71	4268	674	43,639	1.08
8 - 30 days	156	4081	1477	41,827	1.08
31 - 60 days	68	3937	667	40,412	1.05
61 - 365 days	503	3430	5285	35,600	0.99

Constant Unexposed Reference Group

Duration of exposure	Cases		Controls		Crude RR
	Yes	No	Yes	No	
1 - 7 days	71	3430	674	35,600	1.09
8 - 30 days	156	3430	1477	35,600	1.10
31 - 60 days	68	3430	667	35,600	1.06
61 - 365 days	503	3430	5285	35,600	0.99

Table 5.2 Crude rate ratio of motor vehicle crashes for new use of long half-life benzodiazepines: Comparison of analysis with variable and constant unexposed reference groups

Variable Unexposed Reference Group

Duration of exposure	Cases		Controls		Crude RR
	Yes	No	Yes	No	
1 - 7 days	40	4268	267	43,639	1.53
8 - 30 days	67	4081	575	41,827	1.19
31 - 60 days	31	3937	234	40,412	1.36
61 - 365 days	235	3430	1725	35,600	1.41

Constant Unexposed Reference Group

Duration of exposure	Cases		Controls		Crude RR
	Yes	No	Yes	No	
1 - 7 days	40	3430	267	35,600	1.55
8 - 30 days	67	3430	575	35,600	1.21
31 - 60 days	31	3430	234	35,600	1.37
61 - 365 days	235	3430	1725	35,600	1.41

Table 5.3 Injurious motor vehicle crashes as a predictor of benzodiazepine exposure

	MVC (cases)		No MVC (controls)		RR (95% CI)
	Yes	No	Yes	No	
Prescription dispensed on day after MVC:					
regardless of prior exposure	51	5528	393	55,397	1.30 (0.97-1.74)
no exposure in prior 30 days	16	5563	52	55,738	3.08 (1.76-5.40)
with no exposure in prior 60 days	13	5566	28	55,762	4.65 (2.41-8.99)

Table 5.4a Crude rate ratio of motor vehicle crashes for first seven days of benzodiazepine use as a class: Comparison of case-cohort and nested case-control analysis using a one percent sample

		case-cohort			nested case-control (average of 20 simulations)			
subjects	cases (risk sets)	ß	SE	RR (CI)	ß	SE	RR (CI)	Ratio of SE
183	60 (59)	0.1855	1.029	1.20 (0.16-9.05)	0.2307	1.0765	1.26 (0.15-10.30)	1.029 / 1.0765 = 0.96

Table 5.4b Crude rate ratio of motor vehicle crashes for first seven days of benzodiazepine use as a class: Comparison of case-cohort and nested case-control analysis using a five percent sample

		case-cohort			nested case-control (average of 20 simulations)			
subjects	cases (risk sets)	ß	SE	RR (CI)	ß	SE	RR (CI)	Ratio of SE
1009	307 (253)	0.6499	0.3489	1.92 (0.97-3.79)	0.6428	0.3680	1.90 (0.92-3.91)	0.3489 / 0.3680 = 0.95

Table 5.5a Crude rate ratio of motor vehicle crashes for current use of benzodiazepines as a class: Comparison of case-cohort and nested case-control analysis using a one percent sample

		case-cohort			nested case-control (average of 20 simulations)			
subjects	cases (risk sets)	ß	SE	RR (CI)	ß	SE	RR (CI)	Ratio of SE
183	60 (59)	0.0274	0.3837	1.03 (0.48-2.18)	0.0296	0.3479	1.03 (0.52-2.04)	.3837 / .3479 = 1.10

Table 5.5b Crude rate ratio of motor vehicle crashes for current use of benzodiazepines as a class: Comparison of case-cohort and nested case-control analysis using a five percent sample

		case-cohort			nested case-control (average of 20 simulations)			
subjects	cases (risk sets)	ß	SE	RR (CI)	ß	SE	RR (CI)	Ratio of SE
1009	307 (253)	0.4306	0.1594	1.54 (1.13-2.10)	0.4304	0.1435	1.54 (1.16-2.04)	0.1594 / 0.1435 = 1.11

CHAPTER 6
DISCUSSION

This sixth and final chapter contains the discussion pertaining to the study. In the initial section we will discuss the main study results which were outlined at the end of chapter four, and compare the results obtained with that of previous research. The second section will include a description of the study outcome, motor vehicle crashes (MVCs) and exposure, benzodiazepines, in terms of their relevance and generalizability, while the third section will contain a discussion of the internal and external validity as well as limitations and strengths of the study. The chapter will end with a summary of the conclusions derived from the study.

6.1 Study Results

6.1.1 Relationship Between Benzodiazepine Use and Risk of MVC

First seven days of benzodiazepine use: The initial seven days of long half-life benzodiazepine exposure was associated with a 50% increased rate of involvement in injurious MVCs (RR 1.45, 95% CI 1.04-2.03). Although reduced somewhat, the risk remained significant for continuous use of up to one year duration. For both 30 and 60 days of continuous long half-life benzodiazepine exposure the risk was increased slightly, but was non-significant (RR 1.16 and 1.22 respectively).

There was no increased risk of injurious MVCs following the initiation of treatment with short half-life benzodiazepines. A rate ratio of 1.04 (95% CI 0.81-1.34) was observed for the initial seven days of short half-life benzodiazepine use. This risk decreased as the duration of use increased, to a low of 0.91 (95% CI 0.82-1.01) for continuous use in the year prior to the event.

Ray et al (1992c) also reported a 50% increased rate of involvement in injurious MVC for current users of benzodiazepines. However, exposure in that study was defined as benzodiazepines as a class, and it can only be hypothesized that the risk reported was in fact limited to use of long half-life benzodiazepines. In contrast,

Leveille et al (1994) found no association between use of benzodiazepines as a class and risk of injurious crashes in elderly drivers. However, as discussed previously, this study was limited by a small number of cases and potential misclassification of exposure.

The increased risk of motor vehicle crashes associated with long half-life benzodiazepine exposure is consistent with previous studies in the elderly in which the outcome was hip fracture (Ray 1987, Ray 1989b, Cummings 1995). As discussed in chapter two the pharmacokinetic properties of absorption, distribution and elimination are altered in the aging process. Among the physiologic changes with aging are decreased plasma albumin levels leading to a higher fraction of unbound and active drug, an increase in the proportion of body fat resulting in an increased volume of distribution, and decreased hepatic function which impairs clearance of the drug. While both short and long half-life benzodiazepines are distributed more widely in the elderly, it is the decreased hepatic function which results in the accumulation of the long half-life products. Long half-life benzodiazepines undergo complicated liver metabolism (through oxidative pathways), leading to the production of active metabolites (Salzman 1992). With delayed elimination both the drug and its active metabolites may accumulate, leading to potential toxicity. This is further enhanced by the fact that the elderly have an increased sensitivity to the psychomotor impairing effects of long half-life benzodiazepines (Castleden et al 1977, Greenblatt et al 1977, Dement 1991). Short half-life benzodiazepines on the other hand undergo less complex hepatic metabolism (by direct conjugation) and do not produce active metabolites, therefore relatively little accumulation takes place and elimination is essentially unaffected by age. This has been demonstrated by a decreased frequency of psychomotor impairment among users of short, in contrast to long, half-life benzodiazepines (Carskadon et al 1982, Salzman et al 1983, Bliwise et al 1983, Greenblatt et al 1984, Volkerts & O'Hanlon 1986, Moskowitz et al 1990). The most likely explanation therefore for the increased risk associated with long half-life

exposure is related to the increased intensity and duration of exposure associated with their prolonged elimination.

The increased risk of injurious MVCs associated with the first seven days of long half-life benzodiazepine exposure is consistent with evidence in the literature which emphasizes the increased psychomotor impairing effects of benzodiazepines following the initiation of their use (Canadian Pharmaceutical Association 1992, Woods et al 1992, American Medical Association 1994). However, in the present study we found that this risk remained elevated for continuous use of up to one year duration, contrary to what has been previously speculated (Greenblatt & Shader 1986, Roehrs et al 1986, Woods et al 1988, van Laar et al 1992, Shader & Greenblatt 1993). These results suggest that tolerance to the sedative and psychomotor effects of these long half-life products may not develop with continued use, or it may be that, as has also been proposed, tolerance may develop for some but not all of the psychomotor skills (Aranko et al 1983, Lucki et al 1986b, Mamelak et al 1989). Lucki et al (1986b), in the assessment of chronic use of benzodiazepines and psychomotor impairment, concluded that tolerance develops selectively to different behavioral and subjective effects of benzodiazepine medications with their continued use, and that complete tolerance does not develop. The increased risk associated with continuous long half-life exposure is further supported by experimental studies which showed an impairment of psychomotor function in healthy volunteers which persisted throughout three- and four-week treatment periods (Volkerts & O'Hanlon 1986, van Laar et al 1992).

Ray et al (1992c) also reported an increased risk of MVC with prolonged benzodiazepine use of greater than 90 days, which included the majority of the exposed elderly subjects in the study. An earlier study in which the outcome was hip fracture also showed a significantly increased risk for both new and continued use of long half-life benzodiazepines (Ray et al 1989b). New use in the hip fracture study was defined as a first prescription (in the year prior to the index date) filled in the 30 days preceding the index date, while continued use was treatment beyond the first 30 days. While these studies by Ray also support an increased risk with new and continued use, the

definition of new use included a relatively large time window of up to 30 days which would obscure any immediate elevation of risk following the initiation of use. The authors also do not address the concept of tolerance, or attempt to define when, following the initiation of use, the risk is the highest.

Woods et al (1992), following an extensive review of the literature, concluded that studies of the development of tolerance to psychomotor impairing effects of benzodiazepines are typically limited to exposure of a few weeks duration, and that the effects of benzodiazepines administered over longer periods have not been adequately studied. The results of the present study represent one of the initial attempts to determine when, following the initiation of treatment, the risk of experiencing an adverse event is elevated, and whether there is a continued risk with prolonged use.

For long half-life exposure both the first seven days, and continuous use of up to one year in duration, were associated with a significant increased risk, while the risk was slightly reduced and non-significant for the 30 and 60 day periods of continuous use. This lack of a significant effect for the 30 and 60 day periods may be due to several factors including the small number of exposed subjects, the short time intervals, as well as potential misclassification of exposure. The categories of the first seven days of use, and continuous use of up to one year duration, were more likely to be accurately classified as exposed. Subjects who had just recently been dispensed a benzodiazepine (i.e. the first seven days of use) were more apt to still be taking their medication on a regular basis and, in the same manner, subjects with continuous use of benzodiazepines of up to one year duration, who were also using the drug on a regular basis, would be accurately classified as exposed. However, the 30 and 60 day periods of continuous use may include subjects who, even though their prescribed duration of treatment includes the index date, may be taking the drug on an irregular as opposed to continuous basis. Noncompliance, or irregular use, would therefore reduce the accuracy of exposure classification. Subjects may be misclassified as exposed if they discontinued the drug prior to the number of days for which it was dispensed. In the same respect, a subject may be misclassified as unexposed if they had initially

consumed the drug on an irregular basis, and were therefore exposed beyond the number of days for which the drug was dispensed. However, any misclassification which may result is likely to be nondifferential with respect to the outcome, and as such would bias the results towards the null (Kleinbaum et al 1982).

Current use: Current use of long half-life benzodiazepines, irrespective of the duration of use, was associated with a 30% increased rate of involvement in an injurious MVC, while current use of short half-life benzodiazepines was not associated with an increased risk (RR 0.96, 95% CI 0.88-1.05).

Although duration of use was not included in the exposure definition of current use, the majority of subjects in this category were long term regular users of benzodiazepines. Of the controls, 19.0% were exposed to a long or short half-life benzodiazepine on the index date, and 12.1% met the definition for continuous use in the year prior to the event. These results, in combination with the results described previously for the duration of use of up to one year prior to the event, provide support for a continued risk with prolonged use.

The current use analysis contained a sufficient number of exposed subjects to enable an assessment of effect modification for relevant variables. For short half-life benzodiazepines age and chronic disease score were identified as significant interaction terms. The stratified analysis revealed a slight reduction in the risk of MVC with both an increase in age and an increase in chronic disease score, although the range in the point estimates were limited. While both older age and higher chronic disease scores were identified as significant independent predictors of MVC, the stratified analysis suggests that there may be a particular group of subjects in whom the risk of MVCs associated with benzodiazepine use is increased - the younger age group and subjects with fewer chronic disease conditions. These younger, healthier subjects are more likely to be driving, and thus experience a MVC.

For long half-life exposure age was also identified as a significant interaction term, with results of the stratified analysis similar to that obtained for short half-life

exposure. These results also suggest that younger individuals are more likely to be driving and hence experience a MVC. These results are consistent with reports in the literature suggesting that the elderly tend to impose self-restrictions on the amount and type of driving they perform. The primary factors associated with a decrease in the amount of driving are age and physical factors, such as diseases affecting neuromuscular and visual function (Retchin et al 1988, Marattoli et al 1993), while it has been suggested that cognitive impairment does not influence driving frequency (Retchin et al 1988).

Assessment of effect modification by duration of washout period: In defining a new episode of benzodiazepine exposure in this case-control study we used a three-day period of non-exposure prior to being dispensed a benzodiazepine to classify the exposure as first use; this is analogous to a "washout period" in experimental designs. The appropriateness of this three-day washout period was assessed by calculating, for each subject, the time interval since they were last exposed to a benzodiazepine and then fitting an interaction term in the model to assess the modifying effects of past exposure. For short half-life benzodiazepines the results suggested that as the length of the washout period increased, so too did the risk of experiencing a motor vehicle crash, although all results were non-significant. The trend, however, was not apparent in the long half-life benzodiazepines.

Given the prolonged half-life of benzodiazepines in the elderly, particularly for the long half-life products such as flurazepam which has a half-life of up to 240 hours in the elderly (Wooten 1992), it may be that the washout period for subjects with previous exposure in the 4 to 30 days prior to the initiation of treatment also included active drug exposure. However, since the risk for subjects with previous exposure in the 4 to 30 days prior to the initiation of treatment was lower than both the first seven days of use, as well as that for subjects with previous exposure in the 31 to 90 days prior to the initiation of treatment, it is unlikely that a carryover of drug effects influenced the results.

Although the assessment of the effect of past benzodiazepine use suggests that there may be effect modification by past use, and that the risk was highest among short half-life users who had no previous exposure in at least the prior three months, the results are limited due to the small number of subjects initiating treatment. The majority of subjects exposed to benzodiazepines are long term users (Woods et al 1992, Ray et al 1992b, Tamblyn et al 1994, Thapa et al 1995). Thus, although this three-day washout period may perhaps be too short, and result in an underestimate of the true risk associated with the initiation of treatment, this statistical analysis suggests that it is quite appropriate.

Assessment of dose response: To permit standardization of dose between different drugs, we expressed the average daily dose of the most recent prescription as a percentage of the recommended initial average daily dose for the elderly (Canadian Pharmaceutical Assoc. 1992). It was hypothesized that the risk of MVCs may increase with an increase in dose of the benzodiazepine, however the analysis for the initial seven days of short and long half-life benzodiazepine exposure did not support a dose-response relationship. The largest rate ratio for short half-life exposure was for an average daily dose within the recommended range (RR 1.47), while the lowest was for one-to-two times the recommended dose (RR 0.70), although all adjusted results were non-significant.

While there was no obvious dose-response relationship for the first seven days of long half-life exposure, the apparent trend was in the direction anticipated. The risk for both one-to-two times and more than twice the recommended dose (RR 1.54 and 1.46 respectively) were larger than that obtained for dose within the recommended range (RR 1.25). Chlordiazepoxide was the only long half-life product in which the majority of subjects (70.6%) were exposed at the recommended dose. For diazepam and flurazepam the majority were exposed at one-to-two times the recommended dose (54.0% and 64.0% respectively).

There was also no dose-response relationship for current use of long or short half-life benzodiazepine exposure. The results for short half-life were similar to those obtained for the initial seven days of use, with the highest risk observed within the recommended dose range, and the lowest at one-to-two times the recommended dose. As in the initial seven days of long half-life benzodiazepine use, the highest risk observed was for one-to-two times the recommended dose.

Although controlled trials of the relationship between an increase in dose and an increase in sedative effects and impaired performance have been described relatively consistently in the past (Pomara et al 1984, Volkerts & O'Hanlon 1986, Smiley 1987, Johnson et al 1990b, Roth & Roehrs 1991), observational studies have produced inconsistent results. An earlier study by Ray et al (1987) observed a dose-response relationship for long half-life benzodiazepines and risk of hip fracture, while no significant dose response relationship was observed for either half-life in a later study (Ray 1989b). A significant dose effect was observed in a recent study of MVCs, although exposure in this instance was to benzodiazepines as a class (Ray 1992c).

The lack of a dose-response relationship may be due to several factors. First of all, for the assessment of the initial seven days of benzodiazepine use, the small number of exposed cases would have limited power to detect a small effect, although this does not explain the lack of a dose response relationship for current use.

A second and more likely factor could be related to the manner in which the elderly patients were taking their medications. The average daily dose was calculated based on the dose per unit of drug administered, the number of units administered, and the prescribed duration of treatment, all variables which are recorded in the RAMQ database, therefore there is unlikely to be an error in the estimation of the average daily dose. However if a subject was not taking the drug as prescribed, using only half the dose for example or taking their drugs on an irregular basis, than their estimated average daily dose would be higher than their actual consumption. The misclassification of dose that would result may obscure any existing trend. For long half-life products the increased risk at higher than recommended doses, although non-

significant, suggest that misclassification of dose is less likely for these drugs, and that they are being consumed on a regular basis.

Assuming the drugs were prescribed for continuous use, the majority of subjects in the present study were receiving up to twice the initial average daily dose recommended for the elderly. This may be related to the fact that these subjects were previously exposed to benzodiazepines, and had their dose increased over time. The recommended initial doses for the elderly reported in the Compendium of Pharmaceuticals and Specialties (Canadian Pharmaceutical Assoc. 1992) and used to form the dose categories for the present study, are consistent with other sources (Gillin & Byerley 1990, Maletta et al 1991).

Other studies in outpatient settings have also shown that, contrary to practice guidelines, the highest rather than the lowest dose of benzodiazepines are often prescribed (Nolan & O'Malley 1988).

Assessment of individual drugs: In the present study lorazepam accounted for more than 50% of the first seven days of short half-life exposure, while diazepam and flurazepam accounted for more than 80% of long half-life exposure. A similar trend was observed for current use.

The assessment of individual drugs for the initial seven days of benzodiazepine use revealed that bromazepam was the only short half-life product associated with a significant increased risk of a MVC, even after adjusting for other factors. Of the long half-life products, flurazepam was associated with a significant crude risk, which became non-significant after adjustment. Similar results were obtained for current use, although the adjusted rate ratio for bromazepam was no longer significant, while the adjusted rate ratio for flurazepam remained significant.

Ray et al (1992c) reported no difference in the risk of crash involvement by individual drugs. However, when the outcome was hip fractures, flurazepam was shown in two separate studies to be associated with a significant increased risk (Ray 1987, Ray 1989b). The increased risk associated with flurazepam is consistent with

previous clinical trials assessing the effects of individual drugs and the impairment in driving performance (Betts & Birtle 1982, Brookhuis et al 1990, Johnson et al 1990b). In fact, the increased central nervous system depression associated with use of flurazepam in the elderly was first reported in 1977 (Greenblatt et al 1977), and has since been replicated (Dement 1991). Despite the knowledge of its increased sedative side effects, flurazepam was the most frequent long half-life benzodiazepine dispensed in the one year period prior to the MVC. The frequency with which flurazepam is used may be related to the fact that it has been available on the Canadian market since 1971 (Teboul & Chouinard 1990). The common long term use of flurazepam in the elderly has also been reported in other outpatient settings in the United States (Schorr et al 1990).

Although no effects were observed in this study, other long half-life products including chlordiazepoxide, diazepam and nitrazepam have also been shown in clinical trials to be associated with an impairment in driving performance (Betts et al 1972, Moskowitz & Smiley 1982, O'Hanlon & Volkerts 1986, Smiley 1987, Brookhuis et al 1990, van Laar et al 1992).

Of the short half-life products, lorazepam (Hindmarch & Gudgeon 1980), temazepam (Betts & Birtle 1982), and alprazolam (Hindmarch 1986) have shown only slight impairment in driving performance. One of the few studies to investigate the effect of bromazepam on driving reported no impairment of performance (de Ger, et al 1986), however the daily dose of 4.5 mg administered to the young healthy subjects was considerably less than the 6 to 18 mg initial daily dose which is recommended for adults (Canadian Pharmaceutical Association 1992). As noted previously, the results of these trials are also limited due to their small sample size, a duration of exposure which was limited to a few days in length, and the characteristics of subjects which limits the generalizability of the results.

The low prevalence of bromazepam use accounts for the fact that although it was associated with a significant increased risk of MVC, the overall rate ratio for short half-life products was non-significant. This may be related to the fact that bromazepam

has only been available on the Canadian market since 1981, while oxazepam and lorazepam, the two most commonly prescribed short half-life products, have been available since 1965 and 1977 respectively (Teboul & Chouinard 1990).

Use of multiple benzodiazepines: For the initial seven days of benzodiazepine use, the risk of injurious MVC increased slightly with multiple drug exposure, but remained non-significant. The small number of subjects exposed to more than one benzodiazepine is expected, as initiating therapy with more than one benzodiazepine is highly unlikely.

However, exposure to multiple benzodiazepines was much more common with current use of any duration. Of the 11,741 exposed subjects, 1362 (11.6%) were currently exposed to two or more different benzodiazepines. After adjustment for other factors, there was no association between exposure to multiple benzodiazepines and risk of injurious MVC. It may be that subjects exposed to multiple benzodiazepines are less likely to be driving, and therefore not eligible for the outcome.

This is in contrast to the results obtained by Ray et al (1992c), with an increase in the relative risk from 1.5 for use of a single benzodiazepine to 4.8 for use of more than one. The estimates of effect for multiple use were very unstable (95% CI 1.6-14.5), and corresponded to only three exposed cases.

6.2 Incidence of MVC and Prevalence of Benzodiazepine Exposure

Both the incidence of injurious MVCs and the prevalence of benzodiazepine exposure obtained in the present study were compared to figures available in the literature for the elderly population. The similarity of the results provide further support for the validity of the study findings.

6.2.1 Study Outcome - Injurious MVCs

Compared to females, elderly males are more likely to possess a driver's license and be involved in a MVC. In 1991, 69.9% of the Quebec male population 65 years of

age and older had a class 5 driver's license, compared to only 21.6% of the female population (Société de l'assurance automobile du Québec 1992a). During that same year, the rate of involvement in an injurious MVC for males was 11.0 per 1000 licensed drivers, and almost 50% less for females at 6.8 per 1000. The highest rates of involvement in injurious MVCs were reported for males age 16-19 (41.2 per 1,000 licensed drivers). The rates were consistently lower among females for all age groups.

Ray et al (1992c) reported similar figures for elderly drivers, with a rate of 10.6 per 1000 person-years for all Tennessee drivers age 65-84, as well as rates of 15.0 for males and 10.1 for females in the Tennessee Medicaid crash study.

In the present study, we found a cumulative incidence of injurious MVCs for the three year study period to be 26.2 per 1000 licensed drivers. This cumulative incidence was higher among males, 28.6 per 1000 licensed drivers, compared to females, 19.7 per 1000 licensed drivers. For both males and females the risk of involvement in an injurious crash increased with age above 65, with the cumulative incidence for the 80-84 age group more than twice as high as the 67-70 age group, which is consistent with previous studies (Perneger & Smith 1991).

Characteristics of the crash itself revealed that the majority occurred in rural as opposed to large urban centres, between 6 am and 6 pm, involved two or more vehicles, with travel straight ahead and at a posted speed limit of 50 km per hour or less. Except for an increased risk of crashes in rural regions, the crash characteristics in the present study are all consistent with those reported for elderly drivers (Graca 1986, Ray 1992c, Retchin & Anapolle 1993). The majority of the crashes in the present study occurred in favorable road conditions, during the summer, with clear weather, and on dry road surfaces.

In summary, the increased rates of MVCs for males and the older age groups observed in the present study, as well as the characteristics of the crash, are consistent with previous research.

6.2.2 Study Exposure - Benzodiazepine Use

The prevalence of benzodiazepine use within this elderly population of drivers was remarkably high, with 36.2% of controls exposed to benzodiazepines at least once in the year prior to the crash. The long term nature of benzodiazepine use was evident by the fact that 31.1% of controls received at least one benzodiazepine in both the one and two year periods prior to the crash. The prevalence among controls was reduced to 19.0% when exposure was restricted to include use on the day of the crash (current use), and reduced even further to 1.6% when exposure was the first seven days of use prior to the event (new use).

Despite the fact that long half-life benzodiazepines are not recommended for use in the elderly, 12.8% of controls were exposed to a long half-life benzodiazepine at least once in the year prior to the crash. This is consistent with results by Tamblyn et al (1994) who reported that an estimated 12.9% of the total Quebec elderly population were exposed to long half-life benzodiazepines in 1990.

For long half-life products the prevalence of use for both initiation of treatment within seven days prior to the crash and current use did not vary by age or gender. Among short half-life products for both the first seven days of use and current use, there was an increasing prevalence of use among females. Except for the oldest age category, the prevalence of use also increased with age. The highest prevalence of current exposure to both short and long half-life benzodiazepines was among the 75-79 age group (21.6% and 8.9% respectively), which decreased slightly in the oldest age group of 80-84 (20.8% and 6.9% respectively).

The increased prevalence of use among females, and with increasing age, is consistent with that reported in the literature. Tamblyn et al (1994) reported that among the elderly in Quebec in 1990, 51% of women and 33% of men had been dispensed at least one prescription for a benzodiazepine. These prevalence rates are at least twice as high as those reported in Saskatchewan (Quinn et al 1990), the United States (Ried et al 1990, Swartz et al 1991), and European countries (Balter et al 1984, Morgan et al 1988, Dunbar et al 1989).

6.3 Internal Validity

6.3.1 Confounding

Potential confounders of the association between benzodiazepine use and risk of MVC were identified a priori and assessed as to their confounding effect using bivariate as well as multivariate analyses. Male gender, older age, rural residence, CNS exposure in the 60 days prior to the event, a positive chronic disease score and history of an injurious MVC in the two years prior to the event were all significant independent predictors of the outcome. When included in the multivariate analysis, these variables did not change the estimate of effect, which suggests that none of the covariates were confounders. However, they were retained in the final model because they were significant independent predictors of the outcome, and their inclusion improved the goodness of fit of the model. The adequacy of the proxy measure used for health status, as well as evidence for the lack of confounding by other variables not measured, are discussed below.

Health status: The chronic disease score (Von Korff et al 1992) was used to obtain an indirect measure of health status, based on patterns of drugs dispensed in the year prior to the event. The score includes diabetes mellitus and epilepsy, two conditions believed to be associated with an increased risk of MVCs. The advantages of this measure include the use of prescription data to provide an objective measure of health status, in comparison to the subjective nature of that obtained from self-reports. The score also has the ability to capture the severity of the medical conditions by the combinations of drug products dispensed, which reflect the stage and complication of a disease. However, the score does not reflect the health status for subjects who do not seek medical care for their condition, or are using over-the-counter or non-drug therapy. Given that prescription medications are commonly used to treat medical conditions, these subjects are unlikely to have major limitations to their health status, and as such their condition would not be a potential confounder in the benzodiazepine - MVC association. The results of the chronic disease score obtained in the present

study, stratified by age and gender, were similar to those reported in two other study populations (Von Korff et al 1992, Johnson et al 1994), which suggests that prescribing practices did not alter the validity of the score, and that drivers have similar scores.

It is important to note that people with more severe medical impairments should already have been eliminated from the population of eligible drivers because of the SAAQ driver's license renewal requirements. According to the Highway Safety Code for the province of Quebec, a medical and visual exam are required prior to driver's license renewal at ages 70, 74, 76, 78, 80 and yearly thereafter (Société de l'assurance automobile du Québec 1992b). In May 1992 an administrative rule was imposed by the SAAQ which decreased the frequency of these exams to ages 75, 80 and every two years thereafter (personal communication - Pierre Fortier, SAAQ). Given that driver's licenses are renewed every two years, and the modified rule was only instituted in the third and final year of our study period, it is likely that the more frequent medical and visual exams would have applied to the majority of the study subjects, and those deemed medically unfit to drive based on these examinations would have had their license suspended.

Dementia: Another potential confounder which we were unable to control for directly was dementia, a condition which has been shown to be associated with an increased risk of MVCs. However, there are two lines of evidence which suggest that the results obtained were not confounded by dementia. Firstly, given the high prevalence of dementia in chronic care institutions, which has been estimated to be almost 45% in the province of Quebec (Canadian Study of Health & Aging Working Group 1994), all subjects residing in a chronic care institution during the study period were excluded. The prevalence of dementia in the community residing elderly is considerably lower at approximately 5%, and therefore is unlikely to be an important confounder. Secondly, the lack of an effect observed with short half-life benzodiazepines, which are more likely to be prescribed to subjects with dementia than long half-life products, provides further support that the results are not confounded by

dementia. It is recommended that agitated behavior in dementia be treated with antipsychotic drugs, or occasionally a short half-life benzodiazepine such as lorazepam for episodic agitation; long half-life benzodiazepines are to be avoided (Roy-Byrne & Cowley 1991). This practice was evident in previous studies in which subjects with dementia were more likely to be prescribed short, as opposed to long, half-life benzodiazepines (Ray 1989b).

Confounding by indication: It is possible that insomnia and anxiety, the two most common indications for which benzodiazepines are prescribed, may have contributed to the increased crash risk. However, as discussed in detail in chapter two, evidence in the literature suggests that, among persons with insomnia and anxiety, drug use independently impairs psychomotor function (Linnoila et al 1983, Moskowitz et al 1990, van Laar et al 1992).

In addition, given that short and long half-life benzodiazepines are prescribed for similar clinical conditions, the lack of an increased risk for short half-life products in the present study provides further evidence against such confounding by indication.

Alcohol as a potential confounder: Evidence of alcohol use is no longer recorded on the accident report forms since their revision in 1988. However, as discussed previously, the extent of the potential confounding or effect modification of benzodiazepines and alcohol is believed to be minimal among the elderly for a variety of reasons. First of all, alcohol is not a major risk factor for MVCs among elderly drivers as it is for younger drivers (Wells-Parker 1983, Wolf & Rivara 1992). Secondly, the frequency and amount of alcohol use decreases with age, as does the decision to drive after having consumed alcohol (Health & Welfare Canada 1987, Adams et al 1990). Finally, previous studies in this area also provide evidence for lack of confounding or effect modification by alcohol use (Ray 1992c).

Driving Frequency: A limitation of the study is the lack of information regarding the driving frequency of study subjects, which would be a confounder if frequency of driving varied according to use or non-use of benzodiazepines. However, using data from the 1987 Santé Québec survey, we were able to demonstrate that there was no significant difference in the number of kilometers driven for subjects exposed and non-exposed to sedatives. Subjects who used sedatives drove 1501 kilometers less per year than those who did not, so that the estimates of effect obtained in the present study may in fact underestimate the true risk.

6.3.2 Selection Bias

The study outcome was restricted to injurious MVCs as identified from accident report forms completed by the police. It is possible that not all MVCs were reported to police, which would result in a bias if MVCs not reported were more or less likely to be exposed to benzodiazepines. An attempt was made to minimize this potential bias by excluding MVCs with property damage only, which are more likely than injurious MVCs to be under-reported. In addition, even with under-reporting of injurious MVCs, there is no reason to believe that this would be differential with respect benzodiazepine use, and therefore would not affect estimates of the rate ratio.

A potential source of selection bias relates to the exclusion of 192 subjects from the 19,686 potential study subjects because of a change in their driver's license number, and therefore an inability to reconstruct their health insurance number. The reason for the change in driver's license number was primarily related to change in marital status and name change, and as such it is unlikely that the benzodiazepine-MVC association in these subjects was any different from that observed in the present study.

Although a further 549 subjects were not linked, primarily due to the use of a different surname in the two agencies, for the reasons discussed above this is unlikely to have induced a selection bias.

6.3.3 Information Bias

Misclassification of exposure: Exposure to benzodiazepines was classified on a daily basis, taking into account the date of dispensing and the prescribed duration of treatment. The duration, which is recorded by the pharmacist dispensing the drug, corresponds to the prescribed treatment duration indicated by the physician. For PRN prescriptions the duration recorded is the minimum number of days required to complete the prescription, assuming that the patient is taking the medication on a regular basis. For example, *triazolam 0.125 mg hs prn, 30 tabs*, would be recorded as 30 days duration.

There are two assumptions inherent in the accuracy of exposure classification in this study: the patient actually took the drug beginning at the time the prescription was dispensed, and the total amount of benzodiazepine prescribed was consumed on a regular basis. As a result, if some patients took only part of the medication, initiated treatment at a time later than the prescription was filled, or took the medication on an irregular basis, there would be exposure misclassification. As discussed previously, subjects may be misclassified as exposed if they discontinued the drug prior to the number of days for which it was dispensed, or, in the same respect, they may be misclassified as unexposed if they were taking the drug on an irregular basis and were actually exposed at various points in time beyond the number of days for which the drug was dispensed.

The most likely misclassification would be related to the irregular use of the medication, and therefore the misclassification of exposed as unexposed. If cases were more likely to consume benzodiazepines on an irregular basis, this differential misclassification would result in a bias of the estimate towards the null value of one, while if controls were more likely to consume the drug on an irregular basis the differential misclassification would result in an overestimate of the effect. The increased risk observed for the initial seven days of treatment, and continuous use of up to one year for long half-life benzodiazepines, with no such risk apparent for short half-life benzodiazepines suggests that the misclassification which may have occurred would

be nondifferential, and as such bias the estimate towards the null. The regularity and duration with which these drugs are used among the elderly (Mellinger et al 1984, Woods et al 1992, Ray et al 1992b, Thapa et al 1995), suggests that the extent of the bias due to irregular drug use would be minimal.

6.4 External Validity

Although there have only been a limited number of epidemiologic studies of the association between benzodiazepine use and risk of MVCs in the elderly, the results of the present study are consistent with previous research suggestive of an increased risk of MVC associated with benzodiazepine use, and an increased risk of adverse events limited to both brief and extended periods of long half-life benzodiazepine exposure. Given the population based nature of the study, and assuming that the sedative and psychomotor impairing effects of benzodiazepines experienced in elderly drivers in Quebec are consistent in other elderly populations of similar driving habits, the study findings may be generalizable to the elderly population of drivers receiving benzodiazepines as outpatients. The results can not be extrapolated to the younger population in whom the drug effects may be different.

6.5 Study Limitations and Strengths

6.5.1 Limitations of the Study

The primary limitations of the study are related to the exclusive use of data from computerized sources, which limits the detail and amount of information available. The inability to obtain measures on potential confounders, namely dementia, alcohol use, driving frequency, and the indications for benzodiazepine use, were discussed previously. The limitations of the study with respect to the RAMQ and SAAQ data sources specifically will be outlined below, as well as the inability to identify subjects with a temporary residence outside of the province.

Limitations of the RAMQ data: Only drugs dispensed to outpatients are recorded on the RAMQ prescription database; drugs prescribed during periods of institutionalization are not recorded. It has been estimated that approximately one-third of elderly individuals are admitted to a health care institution each year for some period of time (Tamblyn et al 1994). Therefore to reduce the potential for exposure misclassification we excluded all subjects living in a chronic care setting during the study period, as well as those with a prior hospitalization (based on both the length and recency of the hospitalization prior to the event).

Use of over-the-counter medications are also not recorded on the RAMQ prescription database. Since benzodiazepines are only available by prescription, this would not have influenced the classification of exposure. However the sedative effects of antihistamines, which are widely available over-the-counter, could not be controlled for.

As discussed previously, a further limitation of the prescription database is the lack of information on drug compliance. In the present study exposure was classified based on the assumption that these drugs were consumed on a regular basis. Noncompliance, or irregular use, would likely result in an underestimate of effect.

Limitations of the SAAQ data: Absence of the health care number in the SAAQ computerized files required that other procedures for linkage of the SAAQ and RAMQ datafiles be developed. The majority of subjects linked were done so using the reconstructed health care number or the Social Insurance Number (97.9%). The remaining 406 subjects were linked using a probability match with manual verification, which proved to be a very labor intensive and time consuming endeavour requiring several months to complete. Although there is potential for error in the linkage of subjects between the two agencies, due to an error in the recording of the birth date in one file for example, this is likely to be nondifferential with respect to both exposure and outcome.

A further limitation of the SAAQ data relates to the potential inaccuracy of the accident report forms completed by the police. A study of the quality of the SAAQ databases (Laberge-Nadeau et al 1984), based on the accuracy of the computerized data entry for accident report forms, found the databases to be very reliable for the variables used in this study. However, this does not address the accuracy in the completion of the forms by the police at the scene of the crash. Although errors are inevitable, it is unlikely that they would be differential with respect to benzodiazepine exposure.

Temporary residence outside the province: A further limitation of the RAMQ and SAAQ databases is the inability to identify subjects who reside outside of the province for a portion of the year, namely the elderly who migrate to Florida for several months in the winter (subjects remain eligible for Quebec medicare coverage as long as they reside in the province for at least 182 days of the year). Although in principle only a single renewal prescription is to be dispensed on the same date, subjects may arrange to have several renewal prescriptions dispensed prior to their departure. A survey of 2046 elderly Canadian seasonal migrants to Florida reported that 86% had visited their family doctor, and 84% had filled prescriptions and stocked up on medications, before leaving Canada (Marshall et al 1989). Therefore there is unlikely to be a misclassification of exposure, however a potential misclassification of outcome arises because only MVCs which occur in the province of Quebec are recorded with the SAAQ. Subjects who obtained their benzodiazepine prescriptions, migrated to Florida, and then experienced a MVC would be misclassified as controls, which could result in an underestimate of the measure of effect. In addition, if other factors related to benzodiazepine use and risk of MVC also influenced winter residence outside the province, such as age or health status, then the information bias could also be differential. It is not possible to estimate the extent of this bias as the number of Quebec elderly who reside outside the province for a portion of the year is not known.

6.5.2 Strengths of the Study

Sources of data: This study represents the first time that computerized data from three agencies in the province of Quebec, the SAAQ, RAMQ and MED-ECHO were linked for research purposes. The combination of these three data sources provided us with sufficient detail on exposure, outcome and potential covariates to undertake a large population based study of benzodiazepine use and risk of MVC in a specific segment of the population, namely the elderly. Given the large scale of the study we were able to focus on the initiation of benzodiazepine use, an exposure considered extremely rare in the elderly. A study of this size would not have been possible had data from subjects themselves, or a manual review of medical records, been required.

The universal nature of the prescription drug program for the elderly in Quebec ensured that the results were generalizable to the elderly population as a whole. The discrepancy in previous research in this area which used members of Medicaid (Ray 1992b) and a health maintenance organization (Leveille 1994), suggests that specific subject characteristics within these populations may be biasing the estimates of effect obtained, and therefore limit the generalizability of the results.

Use of prescription databases for exposure assessment: The exposure data available from prescription databases represent their major strength. Detailed information on timing and duration of drugs dispensed provide a longitudinal record of the prescription drug history for a defined population, independently of the disease condition or particular outcome under investigation. In addition, exposure to prescription medications is obtained without having to rely on patient recall, or the use of proxy informants for subjects who are deceased or too ill to answer questions.

Drug use based on self-report has been shown to result in a significant under ascertainment of exposure, with a greater degree of inaccuracy in subjects 65 years of age and older (West et al 1995). In addition, medication histories recorded by physicians have also been shown to be incomplete (Gurwich 1983). Computerized

records of prescriptions filled at the pharmacy therefore represent an accurate method of assessing drug exposure in the elderly. Obtaining accurate information of psychotropic drug use is a particular concern, especially because of the problem of underreporting of exposure obtained from self-reports of persons involved in a crash (Honkanen et al 1980).

6.6 Conclusions

The following overall conclusions have been derived from the results and discussion of the study findings:

1) The initial seven days of long half-life benzodiazepine exposure was associated with a 50% increased rate of involvement in injurious MVCs (RR 1.45, 95% CI 1.04-2.03). Although reduced somewhat, the risk remained significant for continuous use of up to one year duration prior to the event.

2) There was no increased risk following the initiation of treatment with short half-life benzodiazepines, or with their continued use. However, there may be an increased risk with a longer washout period.

3) Current use of long half-life benzodiazepines, irrespective of the duration of use, was associated with a 30% increased rate of involvement in an injurious MVC. This corresponds to 2.2% of all MVCs, or 66 of the approximately 3,000 annual injurious MVCs among elderly drivers in Quebec. In contrast, current use of short half-life benzodiazepines was not associated with an increased risk.

4) For current use the results of the stratified analysis suggest that the risk of MVC was higher in a particular subset of subjects, the younger age groups and subjects with fewer chronic disease conditions. These results suggest that younger healthier subjects are more likely to be driving and thus experience an MVC.

5) There was no dose-response relationship for either the first seven days, or current use, of short and long half-life benzodiazepine exposure.

6) Of the individual drugs, bromazepam was associated with a significant increased risk of MVC for the first seven days of short half-life benzodiazepine exposure, while flurazepam was associated with a significant increased risk of MVC for current use of long half-life benzodiazepines.

7) Use of multiple benzodiazepines was not associated with a significant increased risk for either the first seven days of benzodiazepine exposure, or current use.

The results of this study suggest that brief or extended periods of exposure to long half-life benzodiazepines are associated with an increased risk of motor vehicle crash involvement in the elderly, while there appears to be no such risk for short half-life benzodiazepines. These results reinforce current recommendations that long half-life benzodiazepines should be avoided, or prescribed sparingly, in the elderly population.

Many elderly people regard driving as critical to maintaining their independence. Physicians should therefore inquire as to the driving habits of elderly patients when prescribing these medications, or choose a short half-life product which was not associated with an increased risk of adverse events including hip fractures or MVCs. The elderly are the fastest growing segment of the population, and comprise an increasing proportion of our licensed drivers. With the recognition of the increased risk of MVCs associated with the use of long half-life benzodiazepines, appropriate management of elderly patients can be adopted in clinical practice. Only then can the independence that driving offers the elderly be maintained without jeopardizing their safety, or the safety of others.

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APPENDIX A

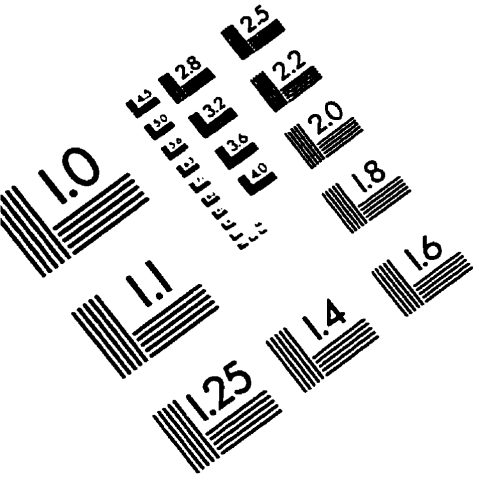
Benzodiazepine dose categories. Categories created as a percentage of the recommended average daily dose for seniors.

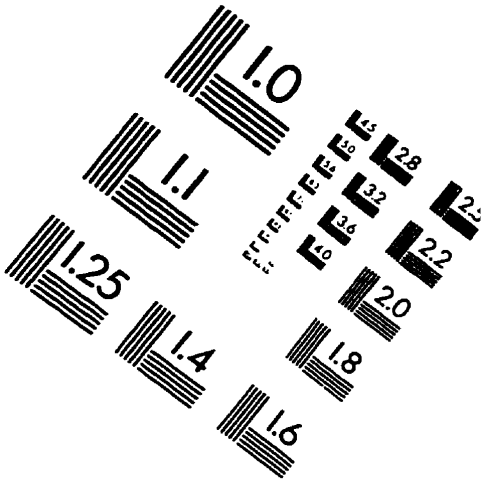
	Dose categories - % of average daily dose		
	maximum recommended or less	**101 - 200%**	**> 200%**
Alprazolam	≤ 0.5 mg	0.5 < dose ≤ 1.0	> 1.0
Bromazepam	≤ 3.0 mg	3.0 < dose ≤ 6.0	> 6.0
Chlordiazepoxide	≤ 20.0 mg	20.0 < dose ≤ 40.0	> 40.0
Clorazepate	≤ 3.75 mg	3.75 < dose ≤ 7.5	> 7.5
Diazepam	≤ 4.0 mg	4.0 < dose ≤ 8.0	> 8.0
Flurazepam	≤ 15.0 mg	15.0 < dose ≤ 30.0	> 30.0
Lorazepam	≤ 0.5 mg	0.5 < dose ≤ 1.0	> 1.0
Nitrazepam	≤ 2.5 mg	2.5 < dose ≤ 5.0	> 5.0
Oxazepam	≤ 10.0 mg	10.0 < dose ≤ 20.0	> 20.0
Temazepam	≤ 15.0 mg	15.0 < dose ≤ 30.0	> 30.0
Triazolam	≤ 0.125 mg	0.125 < dose ≤ 0.25	> 0.25
Clonazepam	≤ 1.5 mg	1.5 < dose ≤ 3.0	> 3.0

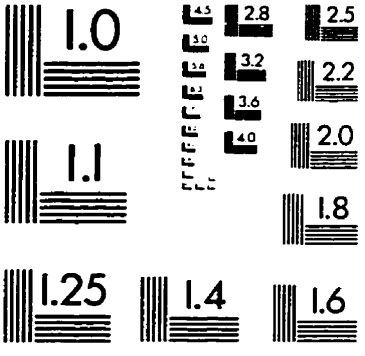
APPENDIX B
Scoring Rules for the Chronic Disease Score (Von Koroff et al 1992)

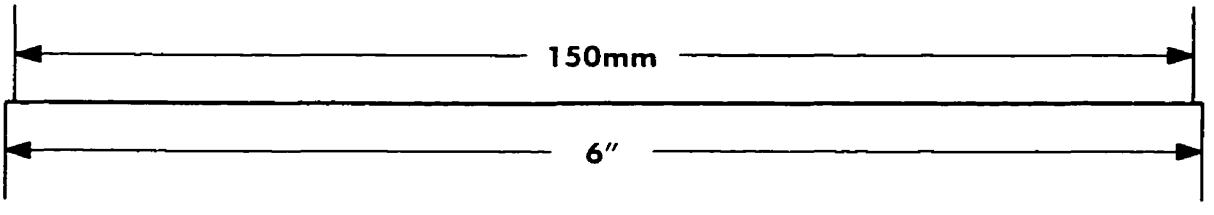
Chronic disease	Medication class(es)	Scoring rules
Heart disease	1) Anticoagulants, hemostatics 2) Cardiac agents, ACE inhibitors 3) Diuretic loop	One class = 3 Two classes = 4 Three classes = 5
Respiratory illness	1) Isoproterenol 2) Beta-adrenergic, misc. 3) Xanthine products 4) Respiratory products including bronchodilators and mucolytics but excluding cromolyn 5) Epinephrine	One class = 2 Two or more classes = 3
Asthma, rheumatism	Glucocorticoids	Score = 3
Rheumatoid arthritis	Gold salts	Score = 3
Cancer	Antineoplastics	Score = 3
Parkinson's	L-Dopa	Score = 3
Hypertension	1) Antihypertensives (except ACE inhibitors) or calcium channel blockers 2) Beta blockers, diuretics	If class (1) = 2 If class (2) & not (1) = 1
Diabetes	Insulin Oral hypoglycemics	Score = 2
Epilepsy	Anticonvulsants	Score = 2
Asthma, rhinitis	Cromolyn	Score = 2
Acne	1) Antiacne tretinoin 2) Topical macrolides	Either class with 2+ Rx. filled = 1
Ulcers	Cimetidine	Score = 1
Glaucoma	Ophthalmic miotics	Score = 1
Gout, hyperuricemia	Uric acid agents	Score = 1
High cholesterol	Antilipemics	Score = 1
Migraines	Ergot derivatives	Score = 1
Tuberculosis	Antitubercular agents	Score = 1

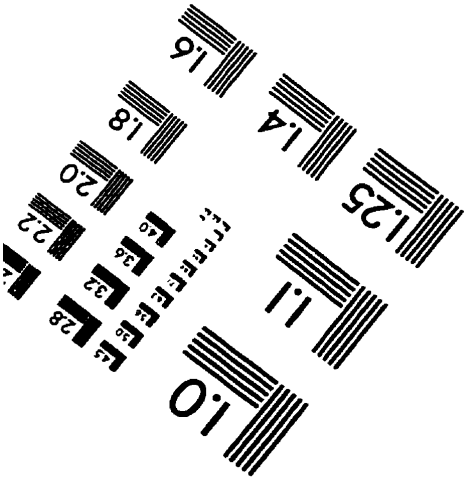
IMAGE EVALUATION
TEST TARGET (QA-3)

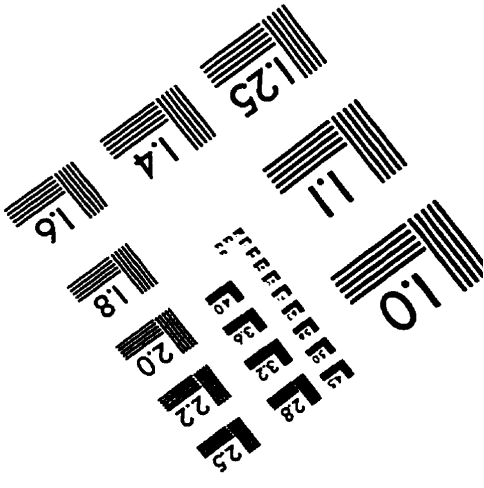












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