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Economic evaluation of benzodiazepines versus cognitive behavioural therapy among older adults with chronic insomnia

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Ce mémoire intitulé:

Economic evaluation of benzodiazepines versus cognitive behavioural therapy among older adults with chronic insomnia

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Résumé

L'insomnie, commune auprès de la population gériatrique, est typiquement traitée avec des benzodiazépines qui peuvent augmenter le risque des chutes. La thérapie cognitive-comportementale (TCC) est une intervention non-pharmacologique ayant une efficacité équivalente et aucun effet secondaire. Dans la présente thèse, le coût des benzodiazépines (BZD) sera comparé à celui de la TCC dans le traitement de l'insomnie auprès d'une population âgée, avec et sans considération du coût additionnel engendré par les chutes reliées à la prise des BZD. Un modèle d'arbre décisionnel a été conçu et appliqué selon la perspective du système de santé sur une période d'un an. Les probabilités de chutes, de visites à l'urgence, d'hospitalisation avec et sans fracture de la hanche, les données sur les coûts et sur les utilités ont été recueillies à partir d'une revue de la littérature. Des analyses sur le coût des conséquences, sur le coût-utilité et sur les économies potentielles ont été faites. Des analyses de sensibilité probabilistes et déterministes ont permis de prendre en considération les estimations des données.

Le traitement par BZD coûte 30% fois moins cher que TCC si les coûts reliés aux chutes ne sont pas considérés (231$ CAN vs 335$ CAN/personne/année). Lorsque le coût relié aux chutes est pris en compte, la TCC s'avère être l'option la moins chère (177$ CAN d'économie absolue/ personne/année, 1,357$ CAN avec les BZD vs 1,180$ pour la TCC). La TCC a dominé l'utilisation des BZD avec une économie moyenne de 25, 743$ CAN par QALY à cause des chutes moins nombreuses observées avec la TCC. Les résultats des analyses d'économies d'argent suggèrent que si la TCC remplaçait le traitement par BZD, l'économie annuelle directe pour le traitement de l'insomnie serait de 441 millions de dollars CAN avec une économie cumulative de 112 billions de dollars canadiens sur une période de cinq ans. D'après le rapport sensibilité, le traitement par BZD coûte en moyenne 1,305$ CAN, écart type 598$ (étendue : 245-2,625)/personne/année alors qu'il en coûte moyenne 1,129$ CAN, écart type 514$ (étendue : 342-2,526)/personne/année avec la TCC.

Les options actuelles de remboursement de traitements pharmacologiques au lieu des traitements non-pharmacologiques pour l'insomnie chez les personnes âgées ne permettent pas d'économie de coûts et ne sont pas recommandables éthiquement dans une perspective du système de santé.

Mots clés : benzodiazépines, thérapie cognitive-comportementale, insomnie, population âgée vivant en communauté, évaluation économique.

Abstract

Insomnia is common in the geriatric population, typically treated with benzodiazepine drugs which can increase the risk of falls. Cognitive behavioral therapy (CBT) is a non-pharmacological intervention with equivalent efficacy and no adverse events. This thesis compares the cost of benzodiazepines versus CBT for the treatment of insomnia in older adults, with and without consideration of the additional cost of falls incurred by benzodiazepine use. A decision tree model was constructed and run from the health payer's perspective over 1 year. The probability of falls, ER visits, hospitalisation with and without hip fracture, cost data and utilities were derived from a comprehensive literature review. Cost consequence, cost utility and potential cost saving analyses were performed. Both probabilistic and deterministic sensitivity analyses were conducted to account for uncertainty around the data estimates.

Benzodiazepine treatment costs 30% less than the price of CBT when the costs of falls are not considered (CAN $231 vs. CAN $335 per individual per year). When the cost of falls is considered, CBT emerges as the least expensive option (absolute cost-saving CAN$ 177 per person per year, CAN $1,357 with benzodiazepines vs. $1,180 for CBT). CBT dominated benzodiazepines, with a mean cost saving of CAN $ 25,743 per QALY gained with CBT due to fewer falls. The cost savings analysis shows that if the CBT were to completely replace benzodiazepine therapy, the expected annual direct cost savings for the treatment of insomnia would be $ 441 million CAD dollars, with a cumulative cost savings of $112 billion CAD dollars over 5-years. The PSA report shows that even at different varying parameters, benzodiazepines cost CAD$ 1,305, S.D $ 598 (range 245-2,625) on average / person / year vs. CAD$ 1,129, S.D $ 514 (range 342-2,526) on average / person / year for CBT.

Current treatment reimbursement options that fund pharmacologic therapy instead of non-pharmacologic therapy for geriatric insomnia are neither cost-saving nor ethically recommendable from the health system's perspective.

Keywords: Benzodiazepines, cognitive behavioural therapy, insomnia, community dwelling elderly, economic evaluation.

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Abbreviations

BZD: Benzodiazepines

CBT: Cognitive Behavioural Therapy

QALY: Quality Adjusted Life Years

CUA: Cost Utility Analysis

CCA: Cost Consequence Analysis

PIM: Potentially Inappropriate Medication

ADE: adverse drug event

NORGEP: The Norwegian General Practice Criteria

ACOVE: Assessing Care of Vulnerable Elders Project

MAI: Medication Appropriateness Index

GABA: Gamma-Amino Butyric Acid

DSM: Disease State Management

OTC: Over the Counter

WASO: Wake after Sleep Onset

CNS: Central Nervous System

BBTI: Brief Behavioural Therapy for Insomnia

ICUR: Incremental Cost Utility Ratio

EQ5: Euro Quality of life 5

QOL: Quality Of Life

PSA: Probabilistic Sensitivity Analysis

To my beloved family, and to the dearest of all: Mota, Shreya and Rohit

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Foreword

Previous economic evaluations assessing the cost-effectiveness of pharmacologic treatment for insomnia have not considered the cost and loss of quality of life associated with a drug-related increased risk of falls in older adults. The goal of this Master's thesis was to conduct an economic evaluation of benzodiazepine treatment for geriatric insomnia, taking into account the hidden costs associated with an increased risk of drug-induced falls in the elderly. The full cost of benzodiazepine treatment compared to cognitive behavioural therapy, a non-pharmacologic treatment alternative that exhibits equal effectiveness for treating insomnia over the short-term, was assessed.

This MSc thesis consists of twelve chapters including an introduction, the objectives of the study, the methods, the results, discussion, limitations, conclusion and future direction. The introduction provides background on inappropriate prescribing in older adults, with benzodiazepines as a prototype medication. Insomnia, as a prototype non-life-threatening chronic disease in the community dwelling elderly is also introduced.

The objectives of the study include the overall as well specific research questions of our research project. The methodology chapter details information about the cost-minimization, cost-utility analysis and potential cost saving analysis we conducted. This information explains the study design, modelling, and the source of model input parameters such as cost and utilities, the target population, and the types of sensitivity analyses to check the uncertainty around the different parameters used for the cost utility, cost minimization and potential cost saving analysis.

The results chapters present the findings from the analysis and interpretation of the results, as well as the effects of change of the input parameters using a sensitivity analysis. It also projects the effects on government for preferentially reimbursing pharmacologic versus non-pharmacologic therapy for insomnia. The limitations chapter reveals several limitations of our analysis, including assumptions for the model.

The discussion highlights the strengths of our project, and the contribution of our results to the literature in the field of insomnia for the growing elderly population in Canada. Finally, we outline further research recommendations for geriatric pharmaco-economic studies, such as the current analysis on insomnia and falls. The endnote section contains all articles, books, and reports cited in this thesis.

Chapter 1. Inappropriate prescribing

1.1. Inappropriate prescribing in older adults

Much attention has been devoted to the quality of prescribing over the past two decades. The reasons for this are twofold; first, inappropriate prescribing increases the occurrence of adverse drug events and second, it incurs a higher risk of drug-drug interactions. So, inappropriate prescribing not only escalates health care costs but also impacts the health and quality of life in older adults. This thesis will focus on benzodiazepines as a prototype of inappropriate prescribing in older adults.

1.2. Definition

The term potentially inappropriate medication (PIM) refers to medications where the associated risks of consumption outweigh the therapeutic benefits (1). Inappropriate prescribing encompasses the use of medications that introduce a significant risk of an adverse drug event (ADE) when there exists evidence for an equally or more effective but lower-risk alternative therapy for treating the same medical condition (2). Appropriate prescribing is a general phrase encompassing and comprising a range of values and behaviors aimed at reflecting the quality of prescribing.

Many other words are used to describe the quality of prescribing, such as good, poor, appropriate or inappropriate, optimal or suboptimal (3). Additionally some terms are specific to some types of inappropriateness- e.g., under-prescribing refers to failure to prescribe drugs that are needed, overprescribing refers to prescribing more drugs than are clinically needed and mis-prescribing refers to incorrectly prescribing a drug that is needed (3). Three of the most important sets of values in judging appropriateness are what the patients want, scientific rationalism (including clinical pharmacology of the drugs), and the societal and family- related consequences of prescribing. A judgement of appropriateness will therefore depend on consideration of the facts and circumstances in all three domains (3). However much of the published literature has condensed the notion of appropriateness to simple pharmacological appropriateness (4).

1.3. The Elderly Population

The chronological age of 65 is widely accepted to define the elderly or older persons in developed countries. It is recognized that this classification is somewhat arbitrary and may not be appropriate in all world populations. The term 'elderly' in fact describes a heterogeneous population in terms of constitution, health and functional performance, quality of life, and life expectancy.

Older adults represent a large segment of the Canadian population. In 2010, an estimated 4.8 million Canadian were 65 years of age or older, a number that is expected to double in the next 25 years to reach 10.4 million seniors by 2036. By 2051, about one in four Canadians is expected to be 65 years of age or over (5).

Medication is a fundamental component of the health care of older adults. Heterogeneity within the older population renders the selection of appropriate pharmacotherapy for each individual more difficult. Some older adults will be more fit and others vulnerable and frail. Variations in health status often lead to altered pharmacokinetic and enhanced pharmacodynamic sensitivity to specific drugs. A higher prevalence of geriatric syndromes such as cognitive impairment and dementia may also impede older adults' ability to make autonomous decisions and correctly adhere to drug dosing schedules (3).

1.4. Measure of appropriateness in older adults

Inappropriate prescribing in older adults can be assessed by explicit criteria or implicit criteria. Explicit criteria are criterion based and are usually developed from published literature, expert opinions, or consensus techniques (6). Expert opinion is usually needed in geriatric medicine because evidence-based aspects of treatments are frequently absent. Explicit measures are drug-oriented or disease-oriented, alternatively termed "lists of drugs to avoid", and can be applied with little or no clinical judgment.

1.4.1. Explicit criteria

Researchers in the United States were early developers of criteria to evaluate inappropriate prescribing in older adults; the first criteria were developed in the early 1990s by Beers et al. and revised thrice in the year 1997, 2003 and 2012 (1, 7, 8) (Table 1). In Europe, the first consensus-validated criteria were developed in France more than a decade later by Laroche et al. in 2007 (9) followed by Gallagher et al. in 2008 (10) in Ireland. Of the criteria resulting from the literature search (n=8), four (50%) were developed in the Europe (9-12), two (25%) in Canada(13, 14), and one (12%) in the United States(8) and Thailand (15).

Table 1 **Explicit Criteria**

	McLeod	**Beers (Modified)**	**Rancourt**	**Laroche**	**STOPP**	**Winit-Watjana**	**NORGEP**	**PRISCUSS LIST**	**Updated Beers Criteria**
Year of publication	1997	2003	2004	2007	2008	2008	2009	2010	2012
Country	Canada	United States	Canada	France	Ireland	Thailand	Norway	Germany	United States
Number of statements	38	68	111	34	65	77	36	131	68
No. of experts (no. of Delphi rounds)	32 (2)	12 (2)	4 (2)	15 (2)	18 (2)	17 (3)	47 (3)	26 (2)	11 (2)
Applicable age groups (years)	≥ 65	≥ 65	≥ 65	≥ 75	≥ 65	Not Specified (Older)	≥ 70	≥ 65	≥ 65
Long-acting benzodiazepines listed as	✓	✓	✓	✓	✓	✓	✓	✓	✓

PIMs									
Tricyclic antidepressant listed as PIMs	✓	✓	✓	✓	✓	✓	✓	✓	✓

Although the number of experts in Delphi rounds differ and range from 4 (14) to 47 (11) but contents of all the eight criteria (8-15) have been validated in two or three rounds of Delphi technique. The Norwegian General Practice (NORGEP) criteria (11) was designed for persons aged 70 and older and the French criteria (9) for people aged 75 and older. No specific age was mentioned in the criteria developed in Thailand (15) while all remaining (8,10,12,13,14) were designed for persons aged 65 and older.

The Beers 1991 criteria (7) were generated for a vulnerable subgroup of individuals aged 65 and older. Most criteria were applied to non-hospitalized people aged 65 years and older. All the explicit criteria (8-15) include long-acting benzodiazepines and tricyclic antidepressant as potential inappropriate medication in older adults. The expert panels were composed of gerontologists and physicians whose practices concentrate on older adults.

In 2012, a panel of 11 experts updated the beers criteria. The 2012 Beers Criteria is an important and improved update of previously established criteria widely used by healthcare providers, educators, and policy-makers and as a quality measure. In earlier beers criteria, as many as 40% of older adults received one or more medications on this list, were depending on the care setting.

The new criteria are based upon methods for determining best-practice guidelines that included a rigorous systematic literature review, the use of an expert consensus panel, and grading of the strength of evidence and recommendations. This criterion recommends avoiding benzodiazepines in older adults for the treatment of insomnia. The

drug selection has been modified according to the developing country's drug selection. The association with the Beers criteria (1, 7, 8) can also be an advantage.

It means that these criteria comprise certain basic items that have been proven valid through many consensus panels and offer, to some extent, transnational comparability of the process. United States researchers lead by being the only ones who have been updating their criteria (1, 8) and by publishing a new set of explicit criteria for determining preferred (rather than potentially inappropriate) medications for individuals aged 65 and older in 2009 (16). Explicit criteria cannot capture the clinical details of the patient accurately; hence do not take into account all factors that define high quality health care for the individual.

For example in the Assessing Care of Vulnerable Elders Project (ACOVE) proposes quality-of-care markers for chronic diseases and geriatric syndromes in frail older adults and recognizes that the goals of care and preferences affect definitions of quality. Patient-reported measures of quality of care address access, continuity, coordination, communication, and empowerment for patient and family involvement (17). They generally do not address the burden of comorbid disease and patients' preferences(18). Additionally, consensus approaches have little evidence of validity or reliability (19).

1.4.2. Implicit criteria

In implicit approaches, a clinician or clinical pharmacist uses information from the patient's chart and scientific evidence on outcomes to make judgments about appropriateness. The focus is usually on the patient rather than on drugs or diseases. These approaches are potentially the most sensitive and can account for patients' preferences, but they are time-consuming, depend on the user's knowledge and attitudes, and can have low reliability (3).

Reliability can be improved with detailed specifications, instrument to obtain data, and by training data collectors (20), as done with the Medication Appropriateness

Index (MAI) (21). Some of the criteria are developed in randomized controlled trials of individuals aged 65 and older, their validity has been demonstrated using medical records of the participants in these trials (22, 23). The Assessment of Underutilization of medication (AOU) has been validated in a small case study in a long-term care facility (24).

Existing measures of medication inappropriateness using implicit criteria include pharmacological appropriateness of prescribed drugs (23, 25, 26). Although much of the published work on medication inappropriateness has been conducted using explicit process measures, there is no ideal measure. Rather, the strengths and weaknesses of both approaches should be considered (3).

1.5. Prevalence of potentially inappropriate medications in older adults

The prevalence of potentially inappropriate medications in older adults is provided in Table 2. Recent data indicate that the majority of older persons takes at least one prescribed drug, with more than one-third of patients taking four drugs or more (27). The following review of the literature indicates that the use of medicines in elderly people is often inappropriate. One of the first reports of inappropriate prescribing in the elderly, more than 20 years ago, quoted that one quarter of older patients admitted to the general medical and geriatric beds of a teaching hospital were prescribed a contraindicated or adversely interacting drug, and that at least 65.5% of adverse drug reactions could have been avoided (28).

Table 2 **Prevalence of potentially inappropriate medications in older adults**

Author, year	*Country, setting*	*Sample size*	*Study design, population*	*PIM Criteria*	*Prévalence/incidence of PIM*	*% of BZP (overall/*	*Outcome, Yes/No*
Wilcox et al. 1994	United States, American aged 65 years or older living in the community	6171 people	Cross-sectional survey, Community dwelling 65 years or older	Beers criteria	18.7 % received at least one PIM while 4.8% received two or more PIM	Diazepam-2.8 %, Chlordiazepoxide-1.95, Flurazepam-1.25%	No
Chin et al. 1999	United States, 65 years or older admitted to an urban hospital ED	898 Patients aged 65 and older	Prospective cohort study, All eligible patients (65 years or older) presented to the ED	Revised Beers criteria (1997)	10.6 % taking PIM, 3.6%were given in the ED while 5.6% received upon discharge	9% prescription for benzodiazepines received as a PIM	Yes, Adverse drug-disease interactions
Golden et al. 1999	United States, Nursing home eligible, home bound older population	2193 aged 60 and over	Retrospective cross-sectional, Nursing-home eligible home bound elderly	Revised Beers criteria (1997)	39.7% taking at least one while 10.4% had two or more	41.6% overall benzodiazepine prevalence while 7.6 % prescribed more than one	No
Hanlon et al. 2000	United States, Community dwelling elderly in North Carolina	3314 patients in wave 2; 2551 patients in wave 3	Retrospective cross-sectional/2nd and 3rd wave Duke established population	Revised Beers criteria (1997)	27% of all participants in wave 2; 22.6% in wave 3	NA	No
Mort et al. 2000	United States, Ambulatory visit and hospital OPD (Psychotropic medications only)	1,373 patients	Retrospective cross-sectional /Office based and out-patient setting	Revised Beers criteria (1997)	27.2 % had at least one PIM	Flurazepam 1.2%, Diazepam 7.43%, Chlordiazepoxide 2.51%	No
Mott et al. 2000	United States, Elderly with Rx. Filled at community pharmacies	1530 new Rx. For 1185 aged 65 and older	Retrospective cross-sectional/Community pharmacies	Beers Criteria	14.3 % had at least one PIM	NA	No
Zhan et al. 2001	United States, Community dwelling elderly	2455 aged 65 and older	Retrospective cross-sectional/ community dwelling elderly	Explicit Criteria	21.3 % had at least one PIM	NA	No
Hanlon et al. 2002	United States, Community dwelling elderly in North Carolina	3234 patients at 4th interview; 2451 patients at 7	Retrospective cross-sectional/Duke established population	Beers modified criteria	28% of all the patients	NA	Yes, mortality and functional status

Author, year	*Country, setting*	*Sample size*	*Study design, population*	*PIM Criteria*	*Prévalence/incidence of PIM*	*% of BZP (overall/*	*Outcome, Yes/No*
Moride et al.[*] 2002	Canada, Community dwelling elderly persons	3400 persons aged 65 and older	Cross-sectional self-reported survey	Beers criteria, implicit by Quebec drug insurance plan	6.5 % used more than one PIM	8.5 % Reported using 2 concomitant BZP while 4.2 % reported using more than 1 long acting BZP.	Yes, drug-drug interactions
Pitkala et al. 2002	Finland, Elderly urban residents aged 75,80,85,90 and 95 years	3921 persons	Cross-sectional study, home-dwelling older persons	Revised Beers criteria (1997)	12.5% at least 1, 1.3% taking 2, while 0.3% 3 PIM	Long-acting BZP 2.6%	No
Stuart et al. 2003	United States, Community dwelling elder person	7628 persons from the 1995 MCBS and 8902 from 1999 MCBS	Retrospective cross-sectional study / Medicare current beneficiary from the year 1995 and 1999.	Revised Beers criteria (1997)	24. 8% taking >1 PIM in 1995 while 21.3 % in the year 1999.	Diazepam 1.9% - 1.5%, Chlordiazepoxide 0.6% - 0.5%, Flurazepam 0.6% - 0.2%	No
Howard et al. 2004	Canada, Senior patients selected from randomly selected family practices	777 patients	Randomized trials, Community dwelling patients	Beers modified criteria	16.3% had at least one PIM	6.4% (Short-acting BZP), most common category of PIM	No
Cornelis et al. 2004	Netherland, all patients 65 and over from 150 general practitioners	18030, 20947, 29605, 26378 and 25258 persons from 1997-2001.	Prospective cohort study, Ambulatory older adults	Beers criteria and Beers modified criteria	16.8% to 18.5% for at least one PIM (1997), 19.1% to 20 % (Modified Criteria)	Diazepam 2.8%, Flurazepam 0.5%, temazepam 2% (Highest Rx. Supratherapeutic dose) and chlordiazepoxide (0.2%) in 2001.	Yes, relation of PIM to co-morbidity
Michel et al. 2004	France, Three-city study, a French longitudinal study	9294 patients	Observational Longitudinal Study, Community dwelling 65 year and older population	Beers criteria modified by a panel of French experts	Nearly 40 % used at least 1 PIM	9.2 % long acting BZP (3rd highest) Bromazepam (4.9%) was the most often reported	No
Azoulat et al. 2005	Iran, Out-patient visits	3000 patients	Cross-sectional study, community dwelling patient 65 years or older	Revised Beers criteria (1997)	27.6% had at least one PIM	BZP overall (16%), Chlordiazepoxide 7.2% while diazepam 5.3%	No
Moral et al. 2006	Spain, 14 rural primary care centers	143 patients	Cross-sectional descriptive study, Immobile	Beers modified criteria	Nearly 35 % used at least 1 PIM	Not given	No

Author, year	*Country, setting*	*Sample size*	*Study design, population*	*PIM Criteria*	*Prévalence/incidence of PIM*	*% of BZP (overall/*	*Outcome, Yes/No*
Maio et al. 2006	Italy, Outpatient Rx. Claim data base	849 425 patients	Retrospective cohort study, outpatient aged 65 years or older	Beers modified criteria	18% used at least 1 PIM, while 11.5% received in 2 and 1.7% for 3 and more PIM	Not given (Bcz not studied as BZP are not reimbursed by INF)	No
Gallagher et al. 2008	Ireland, Old Patients admitted to a university teaching hospital	597 consecutive acute admissions	Prospective observational studies, non-selected community dwelling population requiring hospitalization	Beers modified criteria	24% taking 1, 6% taking 2 and 2% taking more than 2 PIM	Over 50% of all PIM were for psychotropic medications, with over 80% of this subgroup being for BZP.	No
Wessell et al. 2008	United states, 99 primary care practices	124,802 active patients	Prospective demonstrative project, primary care patients 65 years or older	Beers modified criteria	Decreased from always inappropriate 0.41% to 0.33 %, Rarely appropriate 1.48 to 1.30%	Always inappropriate-Flurazepam while Rarely appropriate diazepam and chlordiazepoxide	No
Stafford et al. 2009	Australia, Care home residents	2345 residents	Retrospective cohort study, Patient residing in care homes 65 years or older	Beers modified and Mc leod Criteria	43.8% at least 1 PIM, Beers criteria (35.3%) identified more PIM than McLeod (18.7%)	Beers (Temazepam 13.9%, Oxazepam 7.2%, Diazepam 5. %, alprazolam 2.2%) McLeod (Diazepam 7.1% in dementia and 6.4 % in anxiety)	No
Berdot et al.	France, Three-city study, a French longitudinal study	6343 participants	Prospective cohort study, Community dwelling 65 years or older	Beers modified criteria	32 %	7.8% Long-term BZP while 12.2% short or intermediate acting BZP	Yes, Association with falls
Zaveri et al. 2010	India, Medicine OPD at a tertiary care hospital	407 geriatric patients	Prospective cross-sectional study, Ambulatory patients 65 years or older	Beers modified criteria	23.58%	Diazepam 2.8%, Higher dose of Lorazepam and alprazolam	No
Ruggiero et al. 2010	Italy, ULLISE Project	1716 long term resident	Prospective cross-sectional, nursing home residents 65 years or older	Beers modified criteria	48% at least 1, 11.7% two while 6.1 % had 3 or more PIM	Long acting BZP 3.7 %, short acting BZP 0.8%	Yes, Risk of hospitalization
Barnett et al. 2010	Scotland, Residence of Tayside, Scotland	70299 patients	Cohort study stratified by residence All people between 65 and 99 years	Beers modified criteria	At home, 23.2% at least 1, 6% 2 while 1.7% received 3 or more PIM, at care, 27.1%, 1, 8% ,2 and 2% received 3 or more PIM	Long acting BZP, at home, 6.36% while at care 11.13 % were the third most commonly Rx. PIM	Yes, Increased risk of death

Author, year	*Country, setting*	*Sample size*	*Study design, population*	*PIM Criteria*	*Prévalence/incidence of PIM*	*% of BZP (overall/*	*Outcome, Yes/No*
Sakuma et al. 2011	Japan, Three acute care hospitals	2155 elderly patients	Prospective cohort study, Patients aged 65 years or older	Beers modified criteria	56.1% received at least one PIM	Diazepam 9.5%	Yes, drug related adverse events
Bongue et al. 2011	France, EGB data bases	35,259 patients	Retrospective cross-sectional study, patients aged 75 and older	Explicit criteria/ French PIM List	53.6 % received at least 1 PIM	Long acting BZP 17.8 %	

More recent data indicate that the prevalence of potentially inappropriate medications in community dwelling older adults ranges from 12.5% (29) to 43.8% (30) receiving at least one potentially inappropriate drug, and in nursing home residents from 16.8% (31) to 56.1% (32). The criteria that are used to assess potentially inappropriate medications have an effect on the prevalence of use of these drugs. Differences in prevalence can therefore be partially explained by the criteria used. For example a study conducted in 2009 (30) (Australia) compared the modified beers criteria with McLeod's criteria for assessing prescribing appropriateness in patients residing in care homes and found a prevalence of inappropriate medications in 35.3% of patients using the modified beers criteria compared to half the rate (18.7%) using McLeod's criteria. Similar results have been reported in Ireland where a higher prevalence of inappropriate prescribing was obtained using the STOPP criteria than by using Beers criteria in both the community (21% vs. 18%) and the hospital setting (35% vs. 25%) (33).

Chapter 2. Benzodiazepines as a prototype of inappropriate prescribing in older adults

2.1. Introduction

Long acting benzodiazepines are among the most frequently reported inappropriate prescriptions in older adults (Table 2). These medications are considered inappropriate by all eight existing explicit criteria (Table 1). The tricyclic antidepressants are the only other potentially inappropriate medication reported by all criteria. Benzodiazepines are psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring, which enhances the effect of the neurotransmitter gamma-amino butyric acid (GABA), resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant and amnesic action (34). These properties make benzodiazepines useful for treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures in older adults.

2.2. Classifications of benzodiazepines

Benzodiazepines are classified as short acting, intermediate acting or long acting, depending on their elimination half-life (35). (Table 3)

Table 3 **Classification of benzodiazepines**

Short acting	**Common Brand Name**	**Elimination Half-Life**
Alprazolam	Xanax	6-12 hours
Bromazepam	Lexotan, Lexomil	10-20 Hours
Brotizolam	Dormex	4-5 hours
Chlordiazepoxide	Librium	5-30 hours
Cinolazepam	Gerodorm	9 hours
Estazolam	Prosom	10-24 hours
Etizolam	Etilaam	6 hours

Loprazolam	Dormonoct	6-12 hours
Lorazepam	Ativan	10-20 hours
Lormetazepam	Loramet	10-12 hours
Midazolam	Dormicum	3 hours
Oxazepam	Serax	4-15 hours
Temazepam	Restoril	8-22 hours
Tetrazepam	Mylostan	3-26 hours
Triazolam	Rilamir	2 hours
Intermediate acting	**Common Brand Name**	**Elimination Half-Life**
Clonzepam	Rivotril	18-50 hours
Cloxazolam	Sepazon	18-50 hours
Chlorazepate	Tranxene	36-100 hours
Diazepam	Valium	20-100 hours
Flunitrazepam	Flunipam	18-26 hours
Halazepam	Paxipam	30-100 hours
Ketazoalm	Anxon	30-100 hours
Nimetazepam	Erimin	14-30 hours
Nitrazepam	Mogadon	15-38 hours
Long acting	**Common Brand Name**	**Elimination Half-Life**
Phenazepam	Phenazepam	60 hours
Pinazepam	Domar	40-100 hours
Prazepam	Centrax	36-200 hours
Quzepam	Doral	39-120 hours

Nordazepam	Madar	50-120 hours
Medazepam	Nobrium	36-200 hours
Flutoprazepam	Restas	60-90 hours
Flurazepam	Dalmane	40-250 hours

1. Short-acting compounds have a median half-life of 1–12 hours. They have few residual effects if taken before bedtime. Rebound insomnia may occur upon discontinuation, and they might cause daytime withdrawal symptoms such as next day rebound anxiety with prolonged usage.
2. Intermediate-acting compounds have a median half-life of 12–40 hours. They may have some residual effects in the first half of the day if used as a hypnotic. Rebound insomnia, however, is more common upon discontinuation of intermediate-acting benzodiazepines than longer-acting benzodiazepines.
3. Long-acting compounds have a half-life of 40–250 hours. They have a risk of accumulation in the elderly and in individuals with severely impaired liver function, but they have a reduced severity of rebound effects and withdrawal.

2.3. Indications and adverse events due to benzodiazepine use

Clinicians in general tend to use long half-life benzodiazepines in patients, who have difficulties maintaining sleep and short half-life benzodiazepines for treating sleep onset insomnia. Short and long half- life benzodiazepines are used for both indications and most clinicians feel that the choice of hypnotic should not only be influenced by elimination half-life or the dosage used, but by individual patient preference (36). The most frequent indications for benzodiazepine, according to an analysis of patterns of use in 2262 persons were anxiety (1/3), insomnia (1/3), or crisis (1/4) (37).

In general, benzodiazepines may be safe and effective in the short term, although cognitive impairments and paradoxical effects such as aggression or behavioural disinhibition occasionally occur ((38). Long-term use is controversial due to concerns

about adverse psychological and physical effects, diminished effectiveness and because benzodiazepines are prone to cause tolerance, physical dependence, and, upon cessation of use, a withdrawal syndrome (39). Due to adverse effects associated with the long-term use of benzodiazepines, withdrawal from benzodiazepines, in general, leads to improved physical and mental health (40). A list of adverse events associated with the use of benzodiazepines is provided in Table 4.

Table 4 **List of adverse events related to use of benzodiazepines**

Adverse Events	**References**	**Type of study**	**ODDs Ratio (OR) in 18-65 years adults**	**ODDs Ratio (OR) in 65+ years older adults**
Falls	Bloch et al. 2011	Systematic literature review and meta-analysis	Not reported	1.39 (1.24-1.54) For Institutional 1.61(1.35-1.93) For Ambulatory 1.27(1.11-1.46)
	Woolcott et al. 2009	Cohort, case-control cross-sectional studies	Not reported	1.57 (1.43-1.72)
	Lavasa et al. 2010	Case-control	Not reported	2.49 (1.98-3.14)
	Francesco et al. 2005	Observational Study	Not-reported	1.45 (1.00-2.11) for long half life 1.32 (1.02-1.72) for short half life
	Stenbacka et al. 2002	Cohort	Not-reported	For women's 1.34 (1.09-1.63) once 1.51-(1.14-2.01) Frequent falls
	Frels et al. 2002	Case control	Not reported	2.3 (1.4-3.7)
	Ray et al.2000	Cohort	Not reported	1.44 (1.33-1.56) RR
	Leipzig et al. 1999	Systematic review and meta-analysis	Not reported	1.48 (1.23-1.77) for all 1.44 (1.09-1.90) short 1.32 (.98-1.77) long
	Berdot et al. 2009	Prospective cohort	Not reported	1.58 (1.26-1.98) long acting, occasional user 1.65 (1.33-204)regular 1.34(1.10-1.63) short acting, occasional 1.32(1.08-1.60)regular
	Chang et al. 2010	Case-control	Not reported	2.26 (1.21-4.23)
Fractures	Takkouche et al. 2007	Meta-analysis	Not reported	RR 1.60 (1.38-1.86)

	Ensrud et al. 2003	Cohort	Not reported	1.28(1.05-1.57) HRatio, nonspine frac. 1.54(1.04-2.28) hip farcture
	Sebastian et al 2005	Cross-sectional	Not reported	1.38(1.14-1.66) After correcting confounding Potential cost saving analysis in data claims
	Chang et al. 2007	Nested case-control	Not reported	1.7 (1.2-2.5) 1.8(1.1-3.1) >3mg/day of diazepam equivalent 1.8(1.3-2.7) short-acting
	Bolton et al 2008	population based analysis	50+ 1.10(1.04-1.16)	Not reported
	Finkle et al. 2011	Cohort study	Not reported	1.14(0.80-1.64) Alprazolam 1.53(1.23-1.91) lorazepam
Motor-vehicle accidents	Hemmalgarn et al. 1997	Nested case-control	Not-reported	RR 1.45(1.04-2.03) 1ST Week 1.04(0.81-1.34) after treatment initiation with short acting
	Orriols et al. 2011	Cohort study	1.39 (1.08-1.79)	0.47 %
Cognitive impairment	Paterniti et al. 2002	Longitudinal study	Not-reported	1.9 (1.0–3.6)
	Cazou et al. 2011	Cohort study	(β=−2.13±0.67, $p<0.01$) in delayed free recall	Not reported

Benzodiazepines produce instantaneous effects, and thus may be prescribed for short-term, intermittent, or "as-needed" use. Because many anxiety disorders wax and wane over time, patients with these disorders prefer benzodiazepines because these agents can be taken intermittently, when patients feel the need to take them (41). Older adults are avid consumers of benzodiazepine medication.

In Canada, the use of long half-life benzodiazepines in 2001 was 20.0% in those aged 65 and over (42). The proportion of benzodiazepine prescriptions was the highest among all psychotropic medications in 2002 (43). According to the national population health survey; clonazepam (14.8%) and lorazepam (38.3%) were the highest prescribed benzodiazepines in 2002 (42).

Overall prescriptions of benzodiazepine have decreased consistently over time (25.1% in 1993 to 22.5% in 1998; $P < .001$). However, the prevalence of benzodiazepine

dispensing increases with increasing age (approximately 20% of those age 65 to 69 to approximately 30% of those ages > or =85; P < .001) (44). Benzodiazepines have been associated with several adverse effects, including ataxia, dizziness, over-sedation, anterograde amnesia, and dependence (45). Recently a prospective cohort study conducted by Gillian Bartlett et.al concluded that benzodiazepines are commonly used medicinally among elderly persons, even among those with pre-existing conditions that strongly increase their risk of injuries from falls (46).

The elderly are at an increased risk of suffering from both short- and long-term adverse effects of benzodiazepines (47). The severity of adverse effects, particularly those associated with the central nervous system, may be greater in older adults (8, 48). The association between benzodiazepine use and relatively infrequent but clinically important side effects such as falls, fractures, cognitive impairment and motor vehicle accidents is well established.

A number of observational studies have demonstrated an association between benzodiazepines and adverse events in the elderly, such as falls, hip fracture, cognitive impairment, and auto accidents (49-58). A recent critical systematic review on medications as a risk factor for falls includes 29 studies out of which twenty-seven studies reported results using CNS drugs, and all of them included at least one psychotropic drug or drug group. Benzodiazepines as a group or by certain preparations were associated with falls or fall-related fractures in 17 studies.

The risk of falling increases after a new prescription, in long-term use and regardless of the preparation's half-life. Concomitant use of two or more benzodiazepines increased the risk of hip fracture 2-fold. In contrast, three studies found no association between the use of benzodiazepines and falls (59). A recent cohort study conducted in Quebec showed that patients with pre-existing conditions that increase the risk of injurious falls are significantly more likely to receive a new prescription for a benzodiazepine, further increasing the chances of injurious falls (45).

Two meta-analyses conducted on the association between benzodiazepine use and risk of falling in older adults (60, 61) using different studies showed an odds ratio of 1.57 (95% CI, 1.43-1.72) and 1.39 (95% CI, 1.24-1.54) for benzodiazepine use and risk of falls. Woolcott et al (60) used Bayesian methodology by incorporating the results of previous meta-analysis conducted by Leipzig et al. (62) while Bloch F et al. (61) included all studies apart from studies included by Woolcott et al. (60). They defined their methodological quality criteria to reduce heterogeneity, publication and selection bias to increase the reliability of the meta- analysis.

Cornellis et al. (63) conducted a nested case–control study in a population-based cohort of 7983 older adults and demonstrated that the association between inappropriate benzodiazepine use and risk of fractures was also statistically significant (OR 1.80, 95% CI 1.16, 2.78). Cornellis et al. compared the effect of use of long vs. short-acting benzodiazepines, and found no statistically significant difference in the risk of fracture (OR 1.23, 95% CI 0.73, 2.08). However, when assessing the duration of use, people using between 14 and 90 days had a significantly higher risk of fracture than those using ≤14 days (OR 2.15, 95% CI 1.14, 4.08).

A recent meta-analysis conducted by Takkouche B et al. (64) included 23 cohort and case-control studies published between 1987 and 2005, and revealed a random effects relative risk of 1.34 (95% CI 1.24-1.45) for fractures in benzodiazepine users. There was no evidence of a substantial difference in pooled relative risk according to study design (case-control vs. cohort), type of control (population-based vs. hospital-based) or duration of action (long-term vs. short-term benzodiazepine therapy). In a systematic literature review conducted by Thomas (65) using case control studies from five provinces in Canada and the United States showed an odds ratio range from 0.90 to 6.5 for the association between benzodiazepines and fracture. Three studies conducted in Quebec, Seattle and Tennessee included participants aged 65 and older while others were for 18 and older.

In police and emergency ward studies, BZD use was a factor in 1% to 65% of accidents (65). In another study, where subjects had blood alcohol concentrations less than the legal limit, benzodiazepines were found in 43% and 65% of subjects (66). In a recent systematic review and meta-analysis(67) of 21 epidemiological studies (13 case control and 8 cohort studies), benzodiazepines were associated with a 60% (for case-control studies: pooled odds ratio 1.59; 95% CI 1.10, 2.31) to 80% (for cohort studies: pooled incidence rate ratio 1.81; 95% CI 1.35, 2.43) increase in the risk of traffic accidents and a 40% (pooled OR 1.41; 95% CI 1.03, 1.94) increase in 'accident responsibility'.

Co-ingestion of benzodiazepines and alcohol was associated with a 7.7-fold increase in the accident risk (pooled OR 7.69; 95% CI 4.33, 13.65). In a literature review for 6 studies, two studies reported a lower risk of cognitive decline in former or ever users, two found no association whatever the category of user, and three found an increased risk of cognitive decline in benzodiazepine users (68). A meta- analysis conducted by Melinda J et al. (69) conducted on 10 studies with the age range of 21-75, showed a mean weighted effect size of 0.41 (median=0.37) with a standard deviation of 0.22 for persistence of cognitive effects after withdrawing benzodiazepines.

2.4. A focus on falls

Falls are the second leading cause, after motor vehicle collisions, of injury-related hospitalizations for all ages, accounting for 29% of injury admissions (70). Falls are the leading cause of injury hospitalizations for seniors across the country, contributing to 9% of all emergency department visits by seniors and almost 62% of injury-related hospitalizations for seniors are the result of falls (71). Falls can lead to serious injuries, reduced mobility, nursing home admission and death (72).

The fall-related injury rate is nine times greater among seniors than among those less than 65 years of age (73). Almost half of seniors who fall experience a minor injury, and 5% to 25% sustain a serious injury such as a fracture or a sprain (74, 75). It is

estimated that about 0.2 to 1.5 per cent of falls result in a hip fracture, which in terms of morbidity and mortality is one of the most serious consequences of a fall (76).

Falls are also the most common cause of traumatic brain injuries, accounting for 46 per cent of fatal falls among older adults (77). A systematic review of international studies (78) showed that fall-related costs ranged between 0.85 per cent to 1.5 per cent of the total health care expenditure of countries such as North America, Australia, Europe, and the United Kingdom, equating to 0.07 per cent to 0.20 per cent of the Gross Domestic Product. For comparison purposes, costs were expressed in terms of U.S. dollar (USD) purchasing power parities (PPPs).

In a recent study conducted in Ontario (Canada), average costs for seriously injured fallers and non-faller controls were CAD$ 44,203 and CAD$ 13,507, while length of stay was 45 and 11 days respectively. Hospital costs for a seriously injured faller were $30,696 (95% CI: $25,158 - $36,781) greater than the cost for a non-faller (79). In a study conducted in the United States, the authors reported that falls cause more than 90% of all hip fractures in seniors and 20% die within a year of the fracture in the United States (80).

Families are often unable to provide care, and 40% of all nursing home admissions occur as a result of falls by older people (81). Even without an injury, a fall can cause a loss in confidence and a curtailment of activities, which can lead to a decline in health and function and contribute to future falls with more serious outcomes (82). The magnitude of the problem of falls among older adults is reflected in the 300% increase in publications on the issue between 1985 and 2005 (83). A 20% reduction in falls would translate to an estimated 7,500 fewer hospitalizations and 1,800 fewer permanently disabled seniors. The overall national savings could amount to $138 million annually (84).

2.5. Prevalence of benzodiazepine use in Canada

According to the Canadian Institute for Health Information, 2008 (National prescription drug utilization information system databases), temazepam was the one of the top five medications used by seniors on a chronic basis (85). Benzodiazepines are widely prescribed, with two of them, ativan and apo-lorazepam, listed among the top 13th and 18th most commonly prescribed medications to the general population. Clonazepam was among the top 10 prescribed medications by psychiatry specialists in Canada in 2010. The prevalence of benzodiazepine use among Canadian seniors (those aged 65 years and older) varies. The overall prevalence of benzodiazepine usage in geriatric population is provided in Table 5.

Table 5 **Prevalence of benzodiazepine**

Author, year	*Country, setting*	*Sample size*	*Study Design, population*	*% of BZP (overall/ specific)*	*Outcome, Yes/No*
Ineke N. C et al. 2012	Norway, Norwegian Prescription Database	200,000	Retrospective Cohort study, patients 70 years of age and older	Anxiolytics 15.6% while hypnotics it was 3.6%	No
Fortin et al*. 2011	Canada, Quebec Health survey	1,701 persons	Cross-sectional study, adults 66 years and older	26.2 % women reported using BZP while the men were 16 %	No
Beland et al.* 2011	Canada, Quebec survey on seniors health	2,798 persons	Cross-sectional study, adults 65 years and older	25.2 % reported using BZP	Yes, quality of sleep
Voyer et al.* 2010	Canada, Quebec survey on the health of older persons	2,785 persons	Descriptive Study, adults 65 years of age and older	25.4 % reported using BZP, Lorazepam (42.3 %) and Oxazepam (21.3%) were the highest	Yes, Dependence

Author, year	*Country, setting*	*Sample size*	*Study Design, population*	*% of BZP (overall/ specific)*	*Outcome, Yes/No*
Smith et al. 2008	Canada, Nova Scotia administrative and Australian Pharmaceutical Benefit databases	169, 000 in 2000 and 155, 000 in 2003 in Nova Scotia, 4, 800, 000 in 2000 and 5, 000, 000 in 2003 in Australia	Retrospective cohort study? 62 % in Nova Scotian aged 65 and older while 68 % Australian are aged 65 and older	In 2003 15.5 % in Nova Scotia and 9.2 % in Australia, Lorazepam (25 %) most common in Nova Scotia while Diazepam (33 %) in Australia	No
Kassam et al. 2006	Canada, Longitudinal National Population Health Survey (NPHS)	9,949 in 94/95, 10,238 for 96/97, 10532 for 98/99 and 10,828 for 2000/01	Prospective cohort study, all residents aged 18 and older	7.4 % in 1994/95 and 8.2 % in 2000/01 for the 65 and over age group,	No
Tamblyn et al. [*] 2005	Canada, Medical services claims databases in Quebec	253,244 persons	Prospective cohort study, Community dwelling adults 65 years of age and older	Overall 27.6 % received at one Rx. For BZP, Lorazepam (43.7 5) and Oxazepam (20.2 %) were the highest Rx.	Yes, Injury occurrence
Hagen et al. 2005	Canada, 24 western Canadian LTC facilities in Alberta	2,443 residents	Interrupted time series study, Long-term care residents with mean age of 84.51 years	Urban residents 15.7 % while rural residents it was 7.6 % , Lorazepam 72.7 %) and oxazepam (10.6 %) were the highest Rx.	No
Mamdani et al. 2004	Canada, administrative databases of Ontario	1.4 million residents of Ontario	Retrospective cross-sectional study, adults 65 years of age and older	17 % in 1993 to 15 % in 2002 Increase in proportion of Rx. Of short and medium acting increased while long and ultra-short acting decreased.	No
Hogan et al. 2003	Canada, Canadian study of health and aging (CSHA) from 36 Canadian cities	1,081 community dwelling and institutionalized persons	Prospective cohort study, adults 65 years of age and older	Proportion of subjects using BZP at time 1 and time 2 was similar (26.4% versus 25.2%)	No
Tamblyn et al. [*] 1994	Canada, Medicare registrants made at least one visit to a physician	63,268 Medicare registrants	Retrospective Cohort study, patients 65 years of age and older	Over all BZP- 30.8 % while long –acting BZP it was 12.9 %	No

Author, year	*Country, setting*	*Sample size*	*Study Design, population*	*% of BZP (overall/ specific)*	*Outcome, Yes/No*
Morgan Et al 1998	United Kingdom, Activity and aging survey, Nottingham	1,020 participants	Prospective Cohort study, Community dwelling persons aged 65 and older	16 % reported using BZP	No
Schjott et al. 1999	Norway, Drug administration records of 31 institutions	1,062 patients	Cross-sectional study, Nursing and old age home residents aged 65 and older	25% patients were on hypnotics out of which 50% were long-acting BZP, flunitrazepam (32%) and nitrazepam (16.9%) were the highest Rx.	No
Egan et al. * 2000	Canada, Canadian study of health and aging (CSHAI) from 36 Canadian cities	1,423 community dwelling older	Retrospective Cohort study, adults 65 years of age and older	Over all BZP- 19.8 %	No
Mamdani et al. 2001	Canada, administrative databases of Ontario provincial universal drug benefit program	Over 1 million residents	Retrospective cross-sectional study, adults 65 years of age and older	25.1 % in 1993 and 22.5 % in 1998, Approximately 20 % in those aged 65 to 69 while 30 % in those aged 85 or older	No
Egan et al. * 2001	Canada, Canadian study of health and aging (CSHA) from 36 Canadian cities	1,423 community dwelling older	Retrospective Cohort study, adults 65 years of age and older	Use of high daily doses of BZP was 7.9% (standard one year prevalence), Lorazepam and oxazepam were the highest Rx.	No

Hogan et al. (86) reported that 21.6% and 4% of seniors from the Canadian study of health and aging (CSHA) were using a short or long half-life benzodiazepines, respectively, in 2003, while Tamblyn et al. (87) showed a prevalence of 27.6% of at least one prescription of benzodiazepine in Quebec residents. Dailly et al. (88) reported a 21% prevalence of chronic use of benzodiazepines and an anti-anxiolytic agent, and a 17% prevalence of hypnotic use in the epidemiology of vascular aging (EVA) study in a sample of 1,265 elderly persons. Bastien et al. (89) in Quebec find that nearly 32.6% of elderly (aged 55 and older) chronic users of benzodiazepines used them for insomnia treatment.

In the latter study there were only 46 participants, making the results difficult to generalize. Mellinger et al. (90) reported that despite their high risk, 33 % of older adults (65 years and older) were using benzodiazepines for the long-term (> 1 year). Gleason et al. (91) reported in a cross-sectional community based study, that 22.5% of community

dwelling elderly (65 years and more) were using benzodiazepines as hypnotics using a sample size of 5,181 elderly.

Tamblyn et al. (92) also observed that in 1994, 13% of Quebec seniors were using long half-life benzodiazepines and 31% were using benzodiazepines for periods exceeding 30 days and also observed that Quebec had the highest rate of sedative-hypnotic drug use in three consecutive national health surveys. The highest prevalence of benzodiazepine use as reported by Tamblyn et al. (87) (27.6%), is concordant with other reports from Quebec on the prevalence of benzodiazepine use as per Voyer et al. (93) (25.4%), Béland et al. (94) (25.2%) and Fortin et al. (95) (26.2%). When comparing the results provincially across the Canada; the lowest prevalence of use in Alberta was reported by Hagen et al. (96) (urban 15.7% and rural 7.6%), while the highest prevalence of benzodiazepines was reported from Quebec by Tamblyn et al. (87). Mamdani et al. (43), (41) reported a lower prevalence of benzodiazepines in Ontario than in Québec (17% in 1993 and 15% in 2002). The prevalence of benzodiazepines is higher in Canada compared to reports from the United Kingdom by Morgan et al. (97) (16%) and by Schjott et al. (98) from Norway showing an overall prevalence of 12.5% in these countries. Lorazepam and oxazepam are the most commonly prescribed benzodiazepines in Canada (Table 5).

Chapter 3. Insomnia as a prototype disease in older adults

3.1. Definition

The nature of insomnia probably contributes to the difficulties associated with its treatment. Polysomnographic studies of patients with insomnia generally show abnormalities such as prolonged latency to sleep onset, frequent arousals, and reduced amounts of total sleep. However, objective measures of sleep do not always correlate well with the patient's experience of insomnia, which may be partially due to the fact that the function of sleep itself is still unknown; making it difficult to pinpoint which objective sleep abnormalities contribute to the clinical entity of insomnia (99).

The *DSM-IV* and *ICD* classification systems categorize insomnia as primary when the disorder is characterized as not being related to or caused by another sleep, mental, medical disorder or effects of a medication (100). Breathing-related sleep disorder is a separate diagnosis, often presenting with insomnia complaints (101). There is no formal category for secondary insomnia. Instead, diagnoses reside within the broad dyssomnia section for categories such as Insomnia Related to Another Mental Disorder, Sleep Disorders Due to a General Medical Condition, Insomnia Type, and Substance-Induced Sleep Disorder, Insomnia Type.

3.2. Classification of insomnia

Based on the duration of the symptom, insomnia can be classified as transient, acute, or chronic (100, 101).

A) **Transient insomnia** is characterized as sleepiness and impaired psychomotor performance lasting for less than a week. This type of insomnia can be caused by another disorder, by changes in the sleep environment, by the timing of sleep, severe depression, or by stress.
B) **Acute insomnia** is the inability to consistently sleep well for a period of less than 4 weeks. Acute insomnia is usually related to identifiable factors caused by an emotional or physical discomfort. Examples include acute medical illness; changes in the sleeping environment such as noise, light and temperature; self-

medication; and acute or recurring stress such as work problems, concerns about health and marital strife. There is difficulty in initiating or maintaining sleep and the sleep that is obtained are non-refreshing or of poor quality.

C) **Chronic insomnia** lasts for longer than 4 weeks. It can be caused by high levels of stress hormones or shifts in the levels of cytokines. It includes muscular fatigue, hallucinations, and/or mental fatigue. Chronic insomnia implies that insomnia is either persistent or recurrent. Chronic insomnia is complex requiring a wide range of disorders to be considered in the search for an underlying cause. After establishing the chronicity of the complaint, a differential assessment of chronic insomnia can be made on the basis of whether the patient has difficulty in falling asleep or difficulty in maintaining or staying asleep.

3.3. Prevalence of insomnia

Insomnia is one of the most prevalent health complaints and the most common of all sleep disorders in the geriatric population. A survey in United States reported a prevalence of 45% in people aged 65 and older when only one sleep difficulty criteria is considered (90). A cross-sectional study conducted by Voyer et al. (102) in the province of Quebec (n = 2,332) among seniors living in long-term care facilities found that 144 (6.2%) participants had an insomnia disorder according to DSM-IV criteria.

According to DSM-IV criteria, Ohayon et al. (103) found the prevalence of insomnia in only 4.1–6.7% of community dwelling elderly people. Another prospective cohort study conducted in United States for people aged > 65 years found that between 23% and 34% had insomnia and between 7% and 15% had chronic insomnia (104). More than one half of community dwelling older adults aged 65 years or older report chronic sleep difficulties (10). In a review article, Ohayon et al. described estimates of prevalence for chronic insomnia ranging from 4.4%-48% in the general population depending on the definition used to describe the chronic insomnia, the study type and the instruments used to evaluate the insomnia (103).

Morin et al. (105) conducted a cross sectional study for 2,000 participants (mean age 48.6) for 5 different Canadian regions using a random digit dialing technique to interview the participants. Insomnia disorder was defined according to DSM IV and ICD 10 criteria. They reported a prevalence rate of 10.3% for insomnia disorder for the province of Quebec. In the absence of polysomnographic measures, these results may be overestimated as sampling techniques used by the authors may possibly include people with other sleep problems, like sleep apnea. We used these estimates for estimating the Potential cost saving as this was the only available study for the province of Quebec.

3.4. Economic burden of insomnia

Chronic insomnia incurs negative health consequences on quality of life as well as a significant economic burden for the individual and for society (106, 107). One study (108), analyzed the economic costs of insomnia for participants in the province of Quebec (Canada) differentiating insomnia syndrome (meeting DSM-IV criteria for insomnia diagnosis), insomnia symptoms and good sleepers. The study showed that individuals with insomnia syndrome incur significantly enhanced costs due to utilization of the health care system.

Furthermore, loss of productivity over the last 3 months was almost 5 times higher for persons with insomnia syndrome than in good sleepers. The total direct and indirect annual costs of insomnia for the province of Quebec were estimated at 6.6 billion CAD$, (108). Although studies have been conducted on the overall economic burden of insomnia in Canada, the cost specifically for the elderly population has not yet been assessed.

A few studies conducted in United States (109, 110) have provided data on segmented direct and indirect costs and on adverse effects on quality-of-life parameters in the elderly. In addition to the economic burden of insomnia in the population, insomnia has also been associated with an increased risk of falls, and aggravates existing health conditions (111). Falls are a common and costly problem in older people. Although most

falls are not directly fatal and costly, they are leading cause of injuries and trauma-related hospital admissions and increase the economic burden of the patient (112).

In a survey conducted on 1,526 community-dwelling older adults, various insomnia symptoms were significantly related to the number of reported falls and hospital admissions (112). A separate assessment of health care service costs found that nursing home care related to insomnia in the elderly amounted to $10.9 billion (91% of all health care services related to insomnia, across all age groups) (113). Sleep disturbances in the elderly, and the subsequent disruption of caregivers' sleep exact a toll on family support. Insomnia has been cited as a primary factor in caregivers' decisions to institutionalize an elder, with 20.4% (113) and 52% (114) of admissions to long-term care directly attributable to sleep disturbances.

A survey of 1,855 elderly urban residents found that insomnia was a strong predictor among males for both mortality and nursing home placement (115). Insomnia may also contribute to cognitive decline (116) and insomnia-induced cognitive impairments can confound accurate dementia diagnoses and lead to suboptimal and delayed treatment (111). In a recent study in the United States, after matching and regression-based adjustments were made, the direct medical expenditures were $924 higher for younger patients eventually diagnosed with or treated for insomnia, compared with those who were not (117).

Direct medical expenditures were also $1,143 higher for elderly patients eventually diagnosed with or treated for insomnia, compared with elderly patients who were not. There were also differences in indirect costs, specifically, absenteeism costs were $ 405 higher for those eventually diagnosed with or treated for insomnia (117). It is more difficult to estimate the true burden of insomnia in the geriatric population because the majority of older adults are retired, suffer from co-morbidities (118), and may be socially isolated (119)

3.5. Treatment options for insomnia

3.5.1. Pharmacological treatment

3.5.1.1. Non-prescription medication

Commonly used non-prescription medications include antihistamines, melatonin and valerian (120, 121). Many people who suffer from insomnia self-medicate with over-the-counter products prior to seeking medical advice, usually because they are widely available and relatively inexpensive (122, 123). Among adults aged 60 years and older, the most common self-prescribed therapies include alcohol (13%), antihistamines (36%), and dietary supplements (11%) (121, 123, 124).

There is no official indication for the use of over-the-counter medications for the treatment of insomnia, and none are approved by Food and Drug Administration (FDA) for treating insomnia. Valerian, also known as nature's valium, is an herbal preparation derived from the root of a plant, *Valeriana*. Its sedative effect is attributed to the possible gamma amino butyric acid (GABA) like properties but scientific data regarding its safety are lacking (125).

3.5.1.2. Prescription medication

There are various classes of medication available for the treatment of insomnia. Lists of drug classes with their mechanism of action are provided in

Table 6. Apart from benzodiazepines newer short-acting non-benzodiazepines such as the Z-drugs may be able to induce sleep with fewer side effects than benzodiazepines (126), although this remains controversial.

Table 6 **Prescription medications**

Drug Class	**Mechanism of action & example**
BZD(127)	BZD receptor agonist, lorazepam
Non-BZD (Z-drugs)(127)	BZD receptor agonist, zolpidem

Melatonin (120)	Melatonin receptor agonist, ramelteon
Antipsychotics(128)	Atypical antipsychotic, olanzapine
Antidepressant (124)	SSRI, trazodone

Both benzodiazepine and non-benzodiazepine sedative hypnotics act on GABA-A receptor sites in the brain, but non-benzodiazepines are more specific in the subunits they target. Developed in the late 1980s, these drugs are now the preferred sedative hypnotic drugs for the treatment of insomnia. In general, these drugs are recommended for short-term use (7 - 10 days), and treatment should not exceed 4 weeks. Antidepressants are sometimes used to treat insomnia that may be caused by depression (secondary insomnia). In addition to above; melatonin, 5-hydroxytryptamine antagonist and some antidepressants with sedating properties are prescribed for the treatment of primary insomnia.

3.5.1.2.1 Use of benzodiazepines: Efficacy

The clinical efficacy of benzodiazepines is provided in

Table 7. Three meta-analyses have analyzed the efficacy of benzodiazepines for the treatment of insomnia (129-131). The first meta-analysis pooled twenty-two randomised controlled trials and found that benzodiazepines were superior to placebo in all 4 outcome measures studied (sleep-onset-latency, total sleep time, sleep efficiency and wake after sleep onset) (129).

Table 7 **Clinical efficacy of benzodiazepines**

Ref. (Type)	Population	Outcome, Interventions	Statistical significance	Favours
Sleep quality				
(132) Systematic review	277 people aged 60 years or over with insomnia 7 RCTs in this analysis	Mean subjective sleep-quality score (measured on a 5-point scale) , at least 5 nights 3.1 with benzodiazepines 2.7 with placebo	Mean effect size 0.37 95% CI 0.01 to 0.73 P = 0.04	benzodiazepines

(133) RCT Crossover design 3-armed trial	25 people aged 70 to 89 years with primary insomnia 20 people completed at least 1 treatment arm	Subjective sleep quality (scale 1–5) , 14 days 3.3 with temazepam 15 mg for 14 nights 2.9 with placebo	P <0.05	temazepam
Total sleep time				
(132) Systematic review	277 people aged 60 years or over with insomnia 7 RCTs in this analysis	Total sleep time , at least 5 Nights With benzodiazepines With placebo	Mean difference in increased total sleep time: 34.2 minutes 95% CI 16.2 minutes to 52.8 minutes P <0.01	benzodiazepines
(133) RCT Crossover design 3-armed trial	25 people aged 70 to 89 years 20 people completed at least 1 treatment arm	Subjective total sleep time, 14 days 6.9 hours with temazepam 15 mg for 14 nights 6.3 hours with placebo	P <0.05	temazepam
Number of awakenings				
(132) Systematic review	296 people aged 60 years or over with insomnia 6 RCTs in this analysis	Number of awakenings , at least 5 nights With benzodiazepines With placebo	Mean difference in reduced number of awakenings: –0.60 95% CI –0.41 to –0.78 P <0.0001	benzodiazepines
(133) RCT Crossover design 3-armed trial	25 people aged 70 to 89 years with primary insomnia 20 people completed at least 1 treatment arm	Number of awakenings (subjective measure) , 14 days 1.5 with temazepam 15 mg for 14 Nights 2.0 with placebo	P <0.05	temazepam
Sleep onset latency				
(133) RCT Crossover design 3-armed trial	25 people aged 70 to 89 years with primary insomnia 20 people completed at least 1 treatment arm	Subjective sleep onset latency , 14 days 25.4 minutes with temazepam 15 mg for 14 nights 36.8 minutes with placebo	P <0.05	temazepam
Sleep efficiency				
(134) RCT 4-armed trial	78 people aged at least 55 years (mean age 65 years) with primary insomnia The remaining arms assessed CBT and CBT plus temazepam	Change from baseline in sleep efficiency , 8 weeks From 72.37% to 82.68% with temazepam (variable dose) From 69.11% to 73.39% with placebo	P <0.01	Temazepam
Wake after sleep onset (WASO)				

(134) RCT 4-armed trial	78 people aged at least 55 years (mean age 65 years) with primary insomnia The remaining arms assessed CBT and CBT plus temazepam	With pharmacotherapy (post treatment) = 55 minutes With placebo (post treatment) = 62 minutes	P <0.05	Pharmacotherapy

The second meta-analysis included one hundred and five studies and found a combined weighted mean difference showing that benzodiazepines and non-benzodiazepines (Z-drugs) had significantly shorter sleep onset latency times compared to placebo when measured by polysomnography (WMD: −10.0 minutes; 95% CI: −16.6, −3.4; WMD: −12.8 minutes; 95% CI: −16.9,−8.8) or by sleep diary (WMD: −19.6 minutes; 95% CI: −23.9, −15.3;WMD −17.0 minutes; 95% CI: −20.0, −14.0). The improvements measured by sleep diary were more prominent for both drug groups compared to polysomnography method (130). The third meta-analysis confirmed that sleep time latency for patients receiving a benzodiazepine was 4.2 minutes shorter than for those receiving placebo.

The total sleep duration (using sleep records) for benzodiazepine groups indicated that participants slept for an average of 61.8 minutes (95% CI 37.4 to 86.2) longer than those in the placebo groups. Patients' estimates of sleep latency were examined and the summary estimate of the superiority of benzodiazepines over placebo was 14.3 minutes (95% CI 10.6 to 18.0) (131). There are conflicting recommendations regarding the use of benzodiazepines and non-benzodiazepines for the treatment of insomnia.

For instance, the National Institute of Mental Health Consensus Conference on drugs and insomnia suggests that transient and short-term insomnia be treated with p.r.n or short term (1-2 weeks) use of benzodiazepines respectively, and that treatment of chronic insomnia be limited to benzodiazepine use in minimal effective doses, intermittently, or in short courses (135). The United Kingdom committee on safety of medicines (136) and the Royal College of Psychiatrists (137) both recommend that

benzodiazepines be prescribed for insomnia "only when it is severe, disabling, or subjecting the individual to extreme distress". The Drug and Therapeutics Bulletin (138) states that benzodiazepines "should only be used when sleep disturbance markedly affects the life of an individual or his family, and when other approaches have failed." The 2012 Beers criteria explicitly state that both benzodiazepines and non-benzodiazepines (Z-drugs) should be avoided at all costs for the treatment of chronic insomnia in the elderly (139).

3.5.2. Non-pharmacological treatment

Cognitive–behavioural therapy (CBT) is the evidence-based treatment of choice for several psychiatric disorders, including insomnia (140, 141). Cognitive-behavioural therapy refers to any treatment based on the idea that psychological problems arise as a result of the way in which people interpret or evaluate situations, thoughts, and feelings, as well the behaviors that stem from these evaluations (141). Cognitive behavioural therapy for insomnia (CBT-I) is a multi-component therapy, based on targeting factors that interfere with initiating and maintaining sleep.

The therapy specifically addresses the multiple putative causes and perpetuators of insomnia (142). The underpinnings of CBT-I flow from (a) the application of both operant and classical conditioning paradigms in the form of stimulus control instructions (143); (b) the focus on sleep-interfering behaviors in the form of sleep hygiene (144); (c) the recognition of and focus on reducing the hyper arousal features of insomnia (145); (d) the improvement of circadian and sleep homeostasis regulation of sleep with sleep scheduling and limited, partial sleep deprivation (146); and (e) the adaptation of cognitive therapy to insomnia (147). A stepped care model known as brief behavioural therapy for insomnia (BBTI) is a shorter version of the psychological interventions and can be delivered by primary care nurses and general practitioners. The efficacy of brief behavioural treatment is statistically and clinically significant and sustainable for six months compared to information controls (148).

3.5.2.1. Cognitive behavioural therapy: Efficacy

A growing body of evidence confirms the efficacy of behavioural interventions for persons with insomnia (149-153). Different measures of efficacy are presented in

Table 8. Montgomery et al. (150) conducted a systematic review and reported that there was an improvement in all sleep variables for both post treatment and long term effect.

Table 8 **Clinical efficacy of cognitive behavioural therapy**

Ref. (Type)	Population	Outcome, Interventions	Statistical significance	Favours
Sleep quality				
(154) RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years	Mean subjective sleep-quality score (measured on a 5-point scale) , at least 5 nights 3.60 with CBT 3.30 with placebo	Not reported	Not applicable
Total sleep time				
(154) RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years	With CBT = 408 minutes With placebo = 404 minutes	Not reported	Not applicable
Number of awakening				
(154) RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years	Number of awakenings , at least 5 nights With CBT = 1.80 With placebo = 1.77	Not reported	Not applicable
Sleep onset latency				
(154) RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years	Change from baseline in sleep onset latency , 8 weeks From 44.61 minutes to 19.85 minutes with CBT From 41.42 minutes to 30.50 minutes with control	P <0.05	CBT
(155) RCT	35 people aged >60 years with DSM-IV criteria for primary insomnia	Change in self-reported mean time to fall asleep , 4 weeks From 38.32 minutes to 16.80 minutes with brief behavioural treatment for insomnia (BBTI) From 29.67 minutes to 26.85	P <0.05	BBTI

		minutes with information-only control		
Sleep efficiency				
(153) Systematic review	Participants aged at least 55 years 6 RCTs in this analysis	Ratio of time asleep to time in Bed with CBT with no treatment	Mean effect size 0.38 95% CI 0.12 to 0.65 P <0.005	CBT
(154) RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years	Change from baseline in sleep efficiency , 8 weeks From 72.87% to 86.80% with CBT From 72.36% to 79.32% with control	P <0.05	CBT
Wake after sleep onset (WASO)				
(154) RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years	Change from baseline in sleep efficiency , 8 weeks From 71.55 minutes to 26.92 minutes with CBT From 58.07 minutes to 37.56 minutes with control (sham biofeedback)	P <0.05	CBT
(155) RCT	35 people aged >60 years with DSM-IV criteria for primary insomnia	Change in self-reported WASO , 4 weeks From 61.21 minutes to 27.72 minutes with brief behavioural treatment for insomnia (BBTI) From 47.91 minutes to 35.5 minutes with information-only control	P <0.05	BBTI

Wake after sleep onset with diaries improved from 22 minutes to 13 minutes while with polysomnography it improved from 24 to 10 minutes. Total wake time improvement with diaries was 62 minutes and 38 minutes with polysomnography. Sleep duration was improved by 32 minutes with diaries and by 19 minutes with polysomnography. Sleep efficiency was improved by 7.5% according to sleep diaries and by 6.3% by polysomnography.

Erwin et al. (153) conducted a meta-analysis including twenty-three randomised controlled trials. Overall statistically significant effects were observed for sleep quality (7 studies; fixed-effect ES 0.76, 95% CI: 0.48, 1.03), sleep latency (21 studies; random-effects ES -0.50, 95% CI: -0.82, -0.19, p<0.001), sleep efficiency (8 studies; random-effects ES 0.74, 95% CI: 0.11, 1.38, p<0.001) and wake after sleep onset (15 studies;

fixed-effect ES -0.64, 95% CI: -0.82, -0.47, p=0.86), but not for total sleep time. In a systematic literature review including 6 randomised controlled trials with participants aged at least 55 years, the authors reported mean effect size of 0.38 95% CI 0.12 to 0.65 (P <0.005) for sleep efficiency with cognitive behavioural therapy compared to no treatment.

3.6. Efficacy and clinical effectiveness of pharmacological versus non-pharmacological treatments for insomnia

Wu et al. (156) conducted a randomised clinical trial in 2006 comparing cognitive-behavioural and pharmacological therapy for chronic insomnia. Seventy-one patients with chronic insomnia were randomly divided into 4 groups and either received cognitive-behavior therapy (CBT, n = 19), pharmacological therapy (PCT, n = 17), CBT plus medication (Combined, n = 18) or placebo (n = 17). The treatments lasted for 8 weeks with follow-ups conducted at 3 and 8 months. On the day after treatment ended, all patients were assessed using a polysomnography (PSG), a sleep diary and a psychological assessment.

Patients who received combined treatments did not have as good a long-term outcome as those who receive behavioural therapy alone (157), although the reasons for this finding have not been clearly elucidated (46). Cognitive behavioural therapy patients showed the greatest improvements in sleep parameters at 3-month follow-up. The subjective and objective sleep-onset latency in the CBT group was less than 30 minutes, while sleep efficiency and total sleep time exceeded 85% and 382 minutes respectively.

For patients on benzodiazepines, the average sleep-onset latency was 47.2 minutes, sleep efficiency was lower than 80% and total sleep time was 368 minutes (156). There was a statistically significant difference between the two groups for sleep latency, total sleep time and sleep efficiency using both outcome measures (polysomnography and sleep diaries). However Mitchell et al. (158) reported that the quality of the evidence comparing benzodiazepines to cognitive behavioural therapy for insomnia in the short term is of very low grade, meeting 3 of 9 quality points in the

GRADE system, making it difficult to draw firm conclusions about the superiority of CBT over benzodiazepines.

Erwin et al. conducted a meta-analysis on the short-term efficacy of pharmacotherapy (benzodiazepines or benzodiazepine receptor agonists) compared with behavioural therapy (stimulus control and sleep restriction) for primary insomnia in 21 studies using prospective measures and within-subject designs (159). Comparable short-term outcomes were seen for both pharmacotherapy and behavioural therapy except in sleep latency where behavioural therapy revealed a greater reduction in sleep latency. Post-treatment weighted-effect sizes included sleep latency (pharmacotherapy Cohen's d = 0.45, behavioural therapy Cohen's d = 1.05), sleep quality (pharmacotherapy Cohen's d = 1.20, behavioural therapy Cohen's d = 1.44), wakefulness after sleep onset (pharmacotherapy Cohen's d = 0.89, behavioural therapy Cohen's d = 1.03), and total sleep time (pharmacotherapy Cohen's d = 0.84, behavioural therapy Cohen's d = 0.46) (159).

A different meta-analysis of 59 studies assessing non pharmacologic treatment of chronic insomnia found that stimulus control and sleep restriction techniques were most helpful in producing improvements over an average six-month follow-up period, but sleep hygiene treatment alone was not deemed effective (160). The American Academy of Sleep Medicine published two systematic reviews and concluded that CBTI leads to significant improvements in the primary presenting sleep complaint (sleep initiation and/or maintenance) with sustained improvement seen for 6–24 months post-treatment (161). Clearly, efficacy coupled with minimal side effects makes behavioural techniques highly recommended for treating insomnia; however, factors such as cost, lack of availability, and potential problems with patient motivation and compliance make the use of behavioural techniques difficult as first line treatment (46).

3.7. Cost-effectiveness of treatment options for insomnia

Although emerging studies have compared the clinical effectiveness of various interventions for the treatment of chronic insomnia in older adults (134, 151, 157, 162), data on the cost-effectiveness of treatment options in chronic insomnia are scarce. Some health technology reports exist showing the cost effectiveness of various non-benzodiazepine drugs (163) in the treatment of chronic insomnia. For instance, studies have been conducted on Eszopiclone, a z-drug hypnotic (164), psychological treatment in combination with benzodiazepine use (165), and newer hypnotic drugs (Zopiclone, Zolpidem, Zaleplon) versus benzodiazepines (166). To our knowledge, no economic evaluation exist comparing cognitive behavioural therapy alone versus benzodiazepines in the treatment of chronic insomnia in geriatric populations.

3.8. Current scenario in Canada

Despite the evidence of clinically equivalent benefit with less adverse events (167, 168), and maintained clinical benefits over a longer period of time (134), cognitive behavioural therapy is under-used in Canada (169). Health care policy likely contributes to the underuse of cognitive behavioural therapy in Canada. Medical visits, medications, and "medically necessary" expenses are covered by the Canada Health Act (24), whereas psychological services are not (170). Provinces fund psychotherapy administered by physicians, or in the case of non-physician therapists, those employed by public institutions (170). Psychotherapy may be covered by private insurance, but most fees are paid for by the individual (171).

3.9. Rationale for the study

Non-pharmacological interventions such as cognitive behavioural therapy are as effective as pharmacological treatments in the management of chronic insomnia in older adults over the short term (172-174), and in some cases are reported as superior over the long term (134). Consensus statements in Canada, as well as other treatment guidelines (175) (176) that examine the diagnosis and treatment of insomnia in the elderly

recommend the initial use of non-pharmacological interventions. Unfortunately, use of cognitive behavior therapy remains limited.

Perlis and colleagues (174) discuss reasons for this gap, including a lack of trained providers, cost, lack of third party reimbursement and lack of understanding of the treatment methods. Despite their short-comings, and strong associations with falls, benzodiazepines continue to rank among the top five medications consumed by the geriatric population (85). Furthermore, studies suggest that new benzodiazepine prescriptions are dispensed at a rate of 6% per year to the elderly, and that primary care practitioners are responsible for 87% of these new prescriptions (177).

The use of benzodiazepine drugs for the treatment of chronic insomnia is known to increase the risk of falls by 57% in older adults and also incurs a greater risk of cognitive impairment. The Canadian Agency for Drugs and Technologies in Health (CADTH) has suggested that, although benzodiazepines are inexpensive, they may carry an additional hidden cost in the increased health care resources that are used to treat adverse events in the elderly. To date, no such economic evaluation has been conducted to investigate this hypothesis.

As of March 2012, even the short-acting formulations of benzodiazepines appear on the updated Beers list of drugs to avoid in the elderly for treatment of insomnia. Despite these warnings, prevalence rates of benzodiazepine use among Canadian seniors persistently hover between 17-33% depending on the province and geographic location. Studies suggest that new benzodiazepine prescriptions are dispensed at a rate of 6% per year to the elderly, and that primary care practitioners are responsible for 87% of these new prescriptions. As a result, benzodiazepines continue to rank among the top five medications consumed by the geriatric population, according to a report published by the Canadian Institute for Health Information (CIHI).

The most common indication for benzodiazepine therapy in the elderly is chronic insomnia. This disease is characterized by difficulty initiating or maintaining sleep over

a period of at least 30 days. Insomnia leads to daytime fatigue, impairs cognitive and physical performance, diminishes quality of life, and contributes to motor vehicle accidents and falls. A recent Canadian population-based survey estimated a 10% prevalence of chronic insomnia among community-dwelling older adults, though the prevalence may range from 4-48% depending on the population studied and the definition used.

Of the different therapeutic options that exist, drug treatment with benzodiazepine-receptor agonists and cognitive-behavioural therapies are equally efficacious for treating insomnia in the elderly. The problem is that access to cognitive-behavioural therapy is not supported by provincial insurance coverage for seniors. Thus benzodiazepines continue to be prescribed as first-line therapy despite their higher risk of falls.

In Canada, fall prevention figures prominently among public health priorities to reduce disability among a growing aged population. One-in-three older adults are expected to fall per year, with 20% of falls resulting in an emergency room visit. In 2009, there were 53,545 fall-related hospitalizations among Canadian seniors, costing approximately $30,000 each (178).

Most recommended fall prevention programs include a medication review component. Gradual withdrawal of psychotropic medication yields an anticipated 66% reduction in the rate of falls. The prescription of benzodiazepine drugs for the treatment of chronic insomnia therefore runs counter to the general goal of fall prevention. We therefore intend to conduct a cost consequence and cost-utility analysis taking into account the predicted incidence and costs of falls associated with both treatments. A potential cost savings analysis was also conducted to examine the financial repercussions of a new government reimbursement strategy for cognitive behavioural therapy for treating geriatric insomnia.

Chapter 4. Objective of the study

4.1. Overall objective of the study

To examine the cost-effectiveness of benzodiazepines versus cognitive behavioural therapy for the long term management of insomnia in older adults

4.2. Specific research question

To what extent is the treatment cost of cognitive behavioural therapy offset by fewer drug-induced falls compared to treatment with benzodiazepines in older adults with insomnia over a one-year period?

4.3. Hypotheses to be tested

1. When the costs of falls are accounted for, the average per person cost of cognitive behavioural therapy will be less than benzodiazepine therapy.

2. When the quality of life impact of falls is accounted for, the average cost per quality adjusted life year resulting from treatment with cognitive behavioural therapy will be less than the average cost of a quality adjusted life year for older persons treated with benzodiazepines to treat chronic insomnia.

Chapter 5. Methods: Cost consequence analysis

5.1. Study Question

To evaluate the potential cost saving by the utilization of cognitive behavioral therapy over benzodiazepines use in older adults aged 70 years and over for treating insomnia.

5.2. Economic Evaluations chosen

We conducted a cost consequence analysis as an intermediate step in reporting the cost utility analysis, with the outcomes and costs presented in a disaggregate form to improve the reporting transparency.

5.3. Target Population

Target population of interest was older adult's aged 70 years and older suffering from insomnia in Canada as of March, 2012 (179).

5.4. Comparators

A 6-week course of cognitive behavioural therapy (CBT) were compared to single dose of 0.5 mg. lorazepam (benzodiazepine) per day over a period of 1 year, as an equally effective treatment alternative for adults aged > 70 with chronic insomnia.

5.5. Perspective

This study was conducted from a Canadian health payer's perspective with only the cost of health service resources being considered.

5.6. Time Horizon

The time horizon chosen for the model was a period of 1-year.

5.7. Discounting

As the time horizon was one year, we did not discount costs associated with the competing interventions.

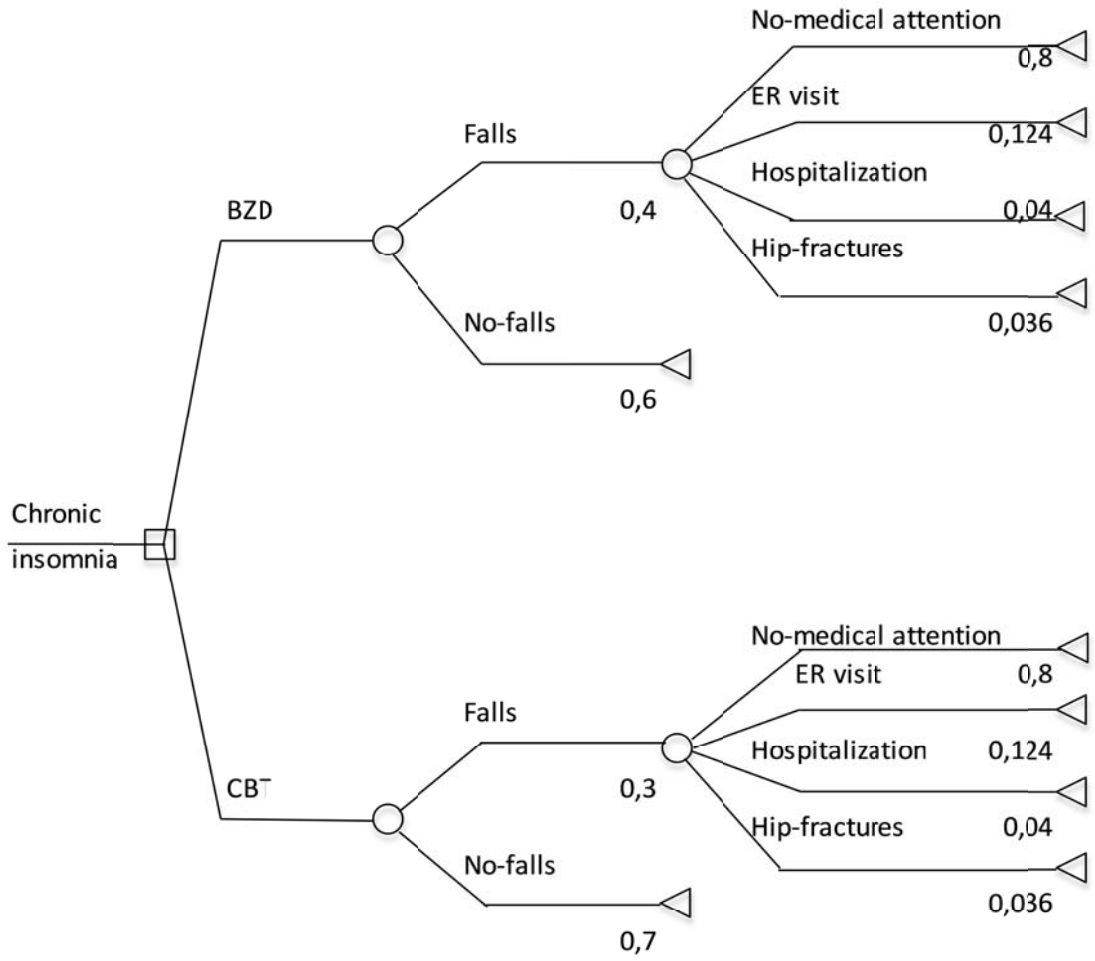
5.8. Study design

Cost consequence analysis (CCA) compares alternative interventions in which the components of incremental costs and consequences are listed without aggregation. A cost consequence analysis was conducted to model the costs of benzodiazepine treatment versus a 6-week course of cognitive behavioural therapy (CBT), as benzodiazepines increases the risk of falls in adults aged > 70 with chronic insomnia (180). The main outcome was cost per year for the two competing interventions, including the cost of falls related to treatment.

5.9. Modelling

A hypothetical analytic decision tree was constructed for two different treatment scenarios for insomnia: pharmacologic treatment with benzodiazepines, and non-pharmacologic treatment with CBT. Figure 1depicts how a cohort of seniors might travel through the decision tree. The experience of chronic insomnia may lead the patient to consult their general practitioner and obtain a prescription for a benzodiazepine. Alternatively, after consultation, the patient may elect a trial of cognitive behavioural therapy instead of pharmacologic management. Of course, in many instances professional consultation is not sought, or treatment is not adhered to, resulting in symptom persistence (untreated insomnia). Our model assumes that all seniors with chronic insomnia seek and adhere to treatment.

Figure 1 **Decision tree model**



As a senior enters the model, he/she may either fall or not fall. When a clinically important or injurious fall is experienced, the individual may visit the emergency room or possibly be admitted to hospital, with or without a hip fracture. The decision tree was constructed using Tree Age Pro 2012.

Health states of the analytic model are based on how seniors would transition between healthcare settings once they experienced a fall that would result in either an emergency room visit or hospitalization. The transition between the various medical settings is based on transition probabilities. These are used to quantify the likelihood of the occurrence of an event over a particular period that is captured by the model. The time period chosen for the model is 1-year.

5.10. Model input parameters

5.10.1. Probability of falls in older adults

5.10.1.1. Base case

The estimation of transition probabilities for falls and fractures was estimated from the odd ratios (60, 181). First, we determined the proportion of seniors falling in the general population. For this base-case, we estimated a 30% incidence of falls in adults 70+ over a 1 year-period, based on data from the Public Health Agency of Canada (178).

Data from the Public Health Agency of Canada report come from the Discharge Abstract Database. The analyses use an episode-based methodology, which has an advantage over separation-based methodology, as the rates associated with hospital separations tend to be higher than the rates associated with episodes of care. This can lead to an overestimate of the demand for care, and an underestimate of the resource utilization involved in treating falls in acute care hospitals (i.e., length of stay). Thus, shifting from separations to episodes of care provides a more comprehensive view of the extent of acute care involved in treating fall-related hospitalizations.

The 30% 1-year estimate of falls in the older population that we used for the model has been confirmed in other countries such as the United States with large population-based studies such as the Women's Health Initiative (n=22,774 participants aged 70-79) (182). The Women's Health Initiative was a longitudinal study that recruited volunteers and thus cannot be fully representative of the population from which it is

drawn. Because of the selection process for both the dietary and hormone trials, this study would be expected to have more women with healthy life styles thus having a disadvantage of selection Potential cost saving analysis. Also data from this study is limited to women only. We did not find any population-based studies of the prevalence of falls in older Canadian men, so have assumed that the estimate is similar to women based on data from the Public Health Agency of Canada.

5.10.1.2. Prevalence of falls with benzodiazepine treatment

The estimate for the increased risk of falls from benzodiazepine use was derived from the most recent meta-analysis indicating that the use of BZD increases the risk of falls by 1.57 (95% confidence interval, 1.23-1.77) (183). A primary strength of this study was the use of Bayesian methodology, which allowed incorporation of information from previous meta-analyses with more recently completed studies to evaluate the level of association between drug classes and experiencing a fall. Although the number of new studies included was small for every drug class assessed, the total number of additional participants included in the meta-analysis was greater than that in the previous meta-analyses by Leipzig et al. (62). We used the Bayesian pooled estimate for the increased risk of falls from benzodiazepine use from the Woolcott et al. meta-analysis (OR 1.57), but in order to account for uncertainty, we enlarged the bounds of confidence interval (1.23 -1.77) from the Bloch F et al. study (61). Odd ratios were converted to probabilities using the equation from Rothman's Textbook of Modern Epidemiology (184).

$$\text{Equation 1 Odds ratio} = \frac{p1/(1-p1)}{p2/(1-p2)}$$

Where p1 is the probability for the first group, and p2 is the probability for the second.

For example, if an increased risk of falls associated with benzodiazepines is reported as an odds ratio of 1.57, then the probability of falls due to benzodiazepines, assuming a base case probability of falls (p2) of 0.30, will be:

$$1.57 = \frac{p1/(1-p1)}{(0.3/0.7)} \qquad \text{i.e. } 0.42\ 46^{*}\ 1.57 = (p1 / 1\text{-}p1)$$

That is $0.6848 = 1.6846p$

$$\text{Or } p = \frac{0.6848}{1.6848} \qquad \text{i.e. } p = 0.40$$

5.10.1.3. Prevalence of falls with cognitive behavioural therapy

Since CBT is not associated with adverse events, we assumed that the proportion of seniors falling following the use of CBT would be the same as that of seniors not suffering from insomnia (base case).

5.10.2. Probability of visiting the emergency room or being hospitalized

The Ontario injury prevention resource center reports that 55% of the emergency room visits by seniors aged 65 years and above are due to falls and of these, 23% require hospitalization (185). In a recent longitudinal cohort study of elder fallers presenting to the emergency room conducted in British Columbia, the authors reported that from November 2007 to November 2008, there were 70,251 visits to the Vancouver general hospital emergency department. Among all visits by persons ≥70 years of age

($n = 7,764$), 1,484 (19%) were fall-related. The difference between these 2 studies may be due to the fact that exclusion criteria were stricter in the British Columbia study (186).

The findings from the British Columbia cost saving study are concordant with a review article from Finland, which concluded that approximately 20% of falls in the elderly require medical attention. Among the 20% of falls resulting in emergency room care for injury (187) 8% require hospital admission. Review articles are often written by one or two "experts" in a field. This leads to potential bias, including the influence of the authors' personal viewpoints, gaps in literature searching practices that may further lead to the omission of relevant research, errors in the translation of data from the primary literature to summarization in the review, misrepresentation or misinterpretation of original source data. We therefore used data from the British Columbia cost saving study for the purposes of our analyses for two main reasons: first it was a recent study and second, it was a prospective study.

5.10.3. Probability of hip-fracture after falls

The prevalence of hip-fractures varies and increases as a function of age. A large prospective cohort study conducted in the United States reported a prevalence rate of hip fractures as .022 (2.2%) among community dwelling elderly with a mean age of 79 years (181). This is one of the largest prospective studies to describe the risk of hip fracture in a diverse cohort (12 sites in United States) of older nursing-home-eligible persons living in the community (number = 5,187 and follow up for 7 years).

Another study using self-report data from 5,630 community-dwelling elderly people 70 years or older conducted in the United States reported a baseline prevalence of 0.042 (188). This study has several primary strengths. First, because they used a large, nationally representative cohort of community-dwelling elderly people (n = 5,630), their results are more likely than the results of hospital-based studies to be generalizable to the overall community-dwelling elderly population.

Second, they assessed risk factors before the occurrence of hip fractures; this eliminated recall Potential cost saving analysis, which can be problematic in case–control studies. Third, they included a number of socioeconomic factors. A limitation of this study is that they used self-reported information on hip fracture and comorbid conditions.

In addition, their exclusion of individuals with proxy respondents may have resulted in underestimations of the magnitude of some risk factors. Another recent longitudinal cohort study of elder fallers presenting to the emergency room in British Columbia cost saving reported that among the 20% of falls resulting in emergency room care, 5% incurred treatment for hip fractures (189). For the purposes of our study, we took an average of the hip fracture rate reported from the above studies and used an estimate of 0.036.

5.10.4. Direct health-care costs

Health system cost data included the costs of medication/therapy, consultations with physician/psychologists, and health care costs related to emergency room visits and hospitalizations due to fall injuries. Unit costs were based on 2012 data from the Government of British Columbia cost saving (190, 191). We took cost data from British Columbia cost saving in accordance with the prospective micro-costing study on the cost of fall-related presentations to the emergency department in British Columbia cost saving.

The average cost of benzodiazepines was based on a report published by Brogan International on Canadian Pharmaceutical Trends stating that lorazepam was the most commonly prescribed benzodiazepine in 2011 in Canada (192). The cost of lorazepam 0.5 mg qhs was used to represent the average cost of a benzodiazepine prescription. The average dispensing fee of $10 Canadian per month were taken from Patented Medicine Prices Review Board (193). The reimbursement rate of generic lorazepam for a daily prescription for 30 days were calculated and a dispensing cost of CAD$ 10 per month was added to drive the total yearly medication cost.

Cognitive behavioural therapy costs were derived from the British Columbia cost saving hourly reimbursement rate for psychologists, which is CAD$ 160 per hour (Table 9). Hourly wages were multiplied by 6 for the usual number of sessions for CBT and divided by 4 as CBT is generally delivered to groups of 4 individuals. The total cost of cognitive behavioural therapy was calculated by adding the cost of the general physician visit and the cost of the group sessions with the psychologist.

5.10.5. Costs of falls and hip-fracture

Health system costs including emergency room visits, hospitalization, and the cost of surgery and rehabilitation for hip fractures were derived from Woolcott et al.'s 1-year micro-economic cohort study of elder fallers presenting to the emergency room in British Columbia cost saving (186). This was a 1-year longitudinal cohort study of elder fallers presenting to the emergency room in British Columbia cost saving. Data were collected prospectively on seniors (>70 years) with injurious falls.

The population sample of 101 patients was representative of the general older population as the authors compared them with three other samples of 'senior emergency department fallers'. The data for the study sample fell within one confidence interval of the data for the three comparison groups. Specifically, the authors compared the sample against (a) all senior fallers who presented to the Vancouver general hospital emergency department in 2008, (b) a sample of 58 consecutive fallers recruited at the Vancouver general hospital emergency department in 2003, and (c) a highly cited large randomised controlled trial that recruited senior fallers in the United Kingdom (194).

There were no statistical differences between the recruited population and the global population of elderly fallers to the Vancouver general hospital. The British Columbia cost saving study has several strengths including accurate capture of costs prospectively and in real-time for each participant (micro costing). The costing approach used in this study has an advantage over administrative data that has been shown to underestimate the incidence of falls (195). As a result, rather than extrapolating the care and costs of care from Case Mix Group data or Resource Intensity Weight data, they

estimated micro cost according to the care received by each participant and were not relying on coding/chart review.

This study also has some limitations, the most important of which is an underestimation of the costs associated with falls. Participants were followed until discharge from the emergency department, hospital, or rehabilitation facility and no subsequent costs incurred were included in their estimates. If post hospital costs had been included, the cost estimates may have been larger. Also, the British Columbia cost saving study did not recruit non-English speaking or cognitively impaired individuals who may have different fall-related health resource utilization and costs compared to the sample population. All cost estimates and parameters including estimates of uncertainty are provided in the Table 9.

Table 9 **Parameters used in the decision tree model, including estimates of uncertainty**

Variable	**Base-case value**	**Range of uncertainty used for 1-way deterministic sensitivity analysis**	**Probability distribution (standard deviation) used for multi-way probabilistic sensitivity analysis**	**Reference**
Probability parameters				
Baseline probability of falls for an older adult	0.30	0.28 - 0.32	0.05, Beta	(178)
Probability of emergency department visit without hospitalization after a fall*	0.124	0.10 – 0.30	0.02, Beta	(186, 196, 197)
Probability of a hospitalization without hip fracture post-fall*	0.04	0.02 – 0.06	0.005, Normal	(186, 198)

Probability of a hospitalization for a hip fracture post- fall*	0.036	0.022 -0.042	0.005, Normal	(181, 186, 188)
Incremental risk of falls due to benzodiazepine	1.57	1.23 -1.77	0.1, Beta	(60, 61)
Probability of falls with benzodiazepine	0.40	0.34 -0.43	0.05, Beta	(60, 61, 199)
Costs (CAD $)				
Benzodiazepine acquisition^{+}/year	14.16 $ (0.0388/pill)	-	-	(200)
Dispensing cost/year	10.18 $	-	-	(201)
Total drug cost/year	136.32 $	134.54 -150.13	0.5, Gamma	(201-203)
GP single consultation for insomnia	94.67 $	68.00 -200.00	10, Gamma	(204-206)
Single psychologist session	160.00 $			(191)
Total cost for a 6-week group cognitive behavioral therapy program^{++}/person	240.00 $	120.00 – 270.00	20, Normal	(191, 207, 208)
Emergency room visit for a fall	708.00 $	636.00 – 779.00	65, Gamma	(186, 209, 210)
Fall-related hospitalization	30,851.00 $	27,765.00 - 33,936.00	2,900, Gamma	(186, 209, 210)
Hospitalization for hip fracture	41,509.00 $	37,358.00 – 45,659.00	3,900, Gamma	(186, 209, 210)

5.10.6. Sensitivity analysis for the cost consequence analysis

Sensitivity analysis isolates study variables or parameters, changes their values, and recalculates the study results. This process identifies the parameters with the most

influence over the summary measure (or result) while assessing the impact the intervention can have by using varied parameters. Sensitivity analyses are conducted to test the overall robustness of the results of the model. Testing the robustness of the results enhances the credibility of the study. In seeking to address parameter uncertainty, both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were conducted as per recent NICE recommendations (211).

Sensitivity analyses were conducted for both probability and cost parameters. Upper and lower bounds for the base case probability of falls (0.28- 0.32), the probability of an emergency room visit due to falls (0.10 – 0.30), the probability of a hospitalization due to falls (0.02 – 0.06) and the probability of hip fractures due to falls (0.022 – 0.042) were derived from values in our literature review. The cost of medications including dispensing cost (CAD$ 108.92 – CAD$ 162.50), general physician visits (CAD$ 68.00 – CAD$ 200.00), psychologist visits and overall cost of cognitive behavioural therapy (CAD$ 120.00 - CAD$ 270.00) were calculated for each province of Canada and upper and lower bounds were used for the sensitivity analysis (Table 9).

Differences in provinces' per diem costs were used to calculate the upper and lower bound costs for an emergency visit (CAD$ 606.60 - CAD$ 741.40), cost of hospitalization (CAD$ 26,426.70 – CAD$ 32,299.30) and cost of hip fracture (CAD$ 35,556.30 - CAD$ 43,457.19). Cost of hospitalization and hip fracture was highest in Yukon and Northwest Territories while least in Prince Edwards's islands across Canada. Aggregate, Ward and ICU Per Diem costs per province were taken from Canadian institute for health information (CIHI) Table 10.

Data for the distribution in probabilities and cost variations for conducting sensitivity analysis are shown in Table 10 and Table 11. We took the average per diem cost for hospitals across the Canada to see the uncertainty around the cost parameters. Aggregate data (ICU plus hospital bed) were the highest (+11.7% higher for Newfoundland than British Columbia cost saving), (but if we include Yukon and the

Northwest Territories it would be 67% higher) while the lowest bracket of change in health resource costs across Canada was for PEI (-23% in Prince Edward Island).

Table 10 **Aggregate, ward and ICU per diems, by number of beds, by province/territory and Canada, 2009-10**

Aggregate (Ward & ICU Combined) Hospital Per Diems, by Number of Beds, by Province/Territory and Canada, 2009-10 (CAD $)

Province	0-50 Beds	51-150 Beds	Greater than 150 Beds	Provincial Average
Newfoundland	1,095	1,398	1,272	1,273
Prince Edward Island				873
Nova Scotia	575	811	1,219	977
New Brunswick	701	1,043	1,109	1,047
Ontario	791	924	1,129	1,086
Manitoba	730	821	1,308	1,118
Saskatchewan	687	1068	1,306	1,187
Alberta	869	1167	1,273	1,138
British Columbia cost saving	995	1028	1,224	1,139
Northwest Territories				1,905
Yukon	1,492			1,492
Canada	**827**	**973**	**1,178**	**1,105**

CIHI 2012.

Table 11 **Provincial variations in cost parameters**

Province	Total medication cost (in CAD $)			Primary care visit / visit (in CAD $)	Psychologist fee / hour (in CAD $)	Total cost of a 6 week course of CBT* (in CAD $)
	Drug acquisition cost/ tablet	Dispensing cost / Rx.	Total cost/ year			
Quebec	0.035	8.00	109.00	75.66	125.00	187.50
Ontario	0.035	10.12	134.00	77.20	140.00	210.00
British Columbia	0.037	10.18	136.00	94.67	160.00	240.00
Nova Scotia	0.035	10.62	140.00	123.40	150.00	225.00
Alberta	0.035	11.00	145.00	84.67	180.00	270.00
Manitoba	0.039	11.31	150.00	74.15	155.00	232.50
Prince Edward Island	0.038	7.94	109.00	68.00	100.00	150.00
Saskatchewan	0.035	9.61	128.00	65.10	95.00	142.50
NWT and Nunavut	Not reported	Not reported	Not reported	114.28	Not reported	Not reported
New Brunswick	Not reported	8.59	Not reported	120.00	80.00	120.00
Newfoundland & Labrador	0.036	7.94	108.00	115.21	150.00	225.00
Yukon	Not reported	Not reported	Not reported	200.00	100.00	150.00

*** Psychologist fee/hr. X 6 / 4 = $ / person**

Each parameter was studied to estimate the type of distribution and a corresponding type of distribution was assigned to each parameter. For example if the parameter was normally distributed then the normal distribution was assigned and; if the parameter was positively skewed then the gamma distribution was assigned to conduct

probabilistic sensitivity analysis. Benzodiazepine- like drugs (Z-drugs) are commonly prescribed drugs for the treatment of insomnia in the elderly, and are gradually replacing benzodiazepines in many provinces as the most frequently prescribed medication for insomnia. Although not formally studied in meta-analysis, research suggests that the hypnotic effect of z-drugs incurs a similar risk of falls (212). Z-drugs are typically more expensive than benzodiazepines. We examined changes in the model for the prescription of z-drugs instead of benzodiazepines (estimated at CAN$ 487.00/year vs. $133.67/year using 2012 Pharma-care cost data from British Columbia cost saving).

5.11. Uncertainty

Both deterministic and probabilistic sensitivity analysis was conducted to handle the uncertainty around probability of falls and fractures, probabilities of emergency room visit or hospitalization and cost data associated with use and consequences of use with the competing interventions.

5.12. Reporting

The results for the cost consequence analysis were reported as absolute cost saved per person per year.

Chapter 6. Methods: Cost utility analysis

6.1. Study Question

To conduct the cost utility analysis for cognitive behavioral therapy over benzodiazepines use in older adults aged 70 years and over for treating insomnia

6.2. Economic Evaluations chosen

We conducted a cost utility analysis for the two competing interventions for the treatment of insomnia in older adults aged 70 years and over. Cost–utility analysis was developed to help decision-makers compare the value of alternative interventions that have very different health benefits, and it facilitates these comparisons without recourse to placing monetary values on different health states. Cost–utility analysis specifies what value is attached to specific health states, and thus increasingly facilitates the transparency of resource allocation processes.

6.3. Target Population

Target population of interest was older adult's aged 70 years and older suffering from insomnia in Canada as of March, 2012.

6.4. Comparators

A 6-week course of cognitive behavioural therapy (CBT) were compared to single dose of 0.5 mg. lorazepam (benzodiazepine) per day over a period of 1 year, as an equally effective treatment alternative for adults aged > 70 with chronic insomnia.

6.5. Perspective

This study was conducted from a Canadian health payer's perspective with only the cost of health service resources being considered.

6.6. Effectiveness

Wu et al. (156) conducted a randomised clinical trial in 2006 comparing cognitive-behavioural and pharmacological therapy for chronic insomnia. Seventy-one

patients with chronic insomnia were randomly divided into 4 groups and either received cognitive-behavior therapy (CBT, n = 19), pharmacological therapy (PCT, n = 17), CBT plus medication (Combined, n = 18) or placebo (n = 17). The treatments lasted for 8 weeks with follow-ups conducted at 3 and 8 months. On the day after treatment ended, all patients were assessed using a polysomnography (PSG), a sleep diary and a psychological assessment.

For patients on benzodiazepines, the average sleep-onset latency was 47.2 minutes, sleep efficiency was lower than 80% and total sleep time was 368 minutes. There was a statistically significant difference between the two groups for sleep latency, total sleep time and sleep efficiency using both outcome measures (polysomnography and sleep diaries). However Mitchell et al. (158) reported that the quality of the evidence comparing benzodiazepines to cognitive behavioural therapy for insomnia in the short term is of very low grade, meeting 3 of 9 quality points in the GRADE system, making it difficult to draw firm conclusions about the superiority of CBT over benzodiazepines. Some meta-analysis conducted for the effectiveness of cognitive behavioral therapy and benzodiazepines for treating insomnia are discussed in much more details in section 3.6.

6.7. Time Horizon

The time horizon chosen for the model was a period of 1-year.

6.8. Discounting

As the time horizon was one year, we did not discount costs associated with the competing interventions.

6.9. Valuing Outcomes

Health utilities associated with chronic insomnia vs. no insomnia and falls vs. no falls were derived from a comprehensive literature review and abstracted from population surveys or randomized controlled trials using SF-36 or EQ-5D derived algorithms for different sleep states, falls, fractures and fear of falling (213, 214). Utility weights are shown in Table 12.

Table 12 **Utilities associated with different health states in the cost-utility model**

1. **Utility weights associated with different health states in the cost-utility model**

Health state	Utility weight	Variation lower bound (ref)	Variation upper bound (ref)	Standard deviation	Probabilistic analysis distribution
Insomnia treated with benzodiazepines	0.66	0.60 (213)	0.72 (213)	0.06	Gamma
Insomnia treated with CBT	0.66	0.60 (213)	0.72 (213)	0.06	Gamma
Untreated insomnia	0.63	0.58	0.66	0.06	Gamma

2. **Utility weights lost due to falls and fear-of-falling used in the cost-utility model**

Health state	Utility weight lost	Variation lower bound (ref)	Variation upper bound (ref)	Standard deviation	Probabilistic analysis distribution
Fear of falling	0.06	0.05 (214)	0.10 (214)	0.005	Gamma
Fall	0.03	0.02 (214)	0.04 (214)	0.005	Normal
Fracture	0.17	0.14 (215)	0.20 (215)	0.01	Normal

6.10. Study design

A cost-utility analysis was conducted to model the quality of life outcomes and costs of benzodiazepine treatment for adults aged > 70 with chronic insomnia. The model also determined the cost-utility of a 6-week course of cognitive behavioural therapy (CBT), as an equally effective treatment alternative (216). The analysis was conducted from a Canadian health payer's perspective, over a 1-year time horizon. The results of this cost-utility analysis are reported as incremental cost per Quality Adjusted Life Years (QALYs) gained. As the time horizon is one year, we did not discount costs and QALYs associated with the competing interventions.

6.11. Modeling

The decision tree used for the Cost Consequence Analysis was expanded to add the utility values for the cost utility analysis.

6.12. Model input parameters

6.12.1. Probability and cost data

These are the same as described in section 5.3 for the Cost Consequence Analysis.

6.12.1.1. Health utilities associated with chronic insomnia vs. no insomnia

Health utilities associated with chronic insomnia vs. no insomnia were taken from a cross-sectional survey (SLEEPI-i) from 3 countries including 4067 persons in the US (n = 1,298; 478 good sleepers and 820 patients with insomnia), France (n = 1858; 998 good sleepers and 860 patients with insomnia) and Japan (n = 911; 506 good sleepers and 405 patients with insomnia). Web and paper-based SF-36 questionnaires were used to measure health related quality of life in chronic patients with insomnia and good sleepers. The SF-36 data were transformed into the preference-based 6-dimensional health state classification, the SF-6D utility scores using a well-validated algorithm.

The SF-36 questionnaire was validated in French and Japanese but the different interviewing techniques used in the three countries (i.e., internet, telephone, or postal questionnaire) may have impacted on the responses of subjects and be associated with recall bias, explaining the slightly different results obtained from each country. There was also a sampling bias in the selection of participants as participants were recruited from an online panel. This may have affected the estimates towards the null as more healthy participants were likely to take part in the survey and underestimation of the utility values lost due to insomnia may have occurred.

6.12.1.2. Health utilities lost due to falls vs. no falls

Health utilities lost due to falls vs. no falls were taken a study (214) that used individual patient-level data from two randomised controlled trials (Hip protector study (217), Calcium and vitamin D study (218)) and one prospective, comprehensive, cohort study (219) to explore the impact of falls and fractures on HRQoL, as measured by the EuroQol-5D (EQ-5D). The authors measured quality of life with a measure of utility (the EuroQol-5D), which allowed the burden of fear of falling to be converted to a single measure of HRQoL. For the quantification of falls and fractures, the authors relied on self-report via postal questionnaire.

We acknowledge that this may be a less accurate form of outcome assessment, subject to under or over reporting. Participation rates were also very low in these studies, suggesting the possibility of volunteer Potential cost saving analysis. Finally, the results only apply to women.

6.12.1.3. Health utilities lost due to hip fracture

Utilities lost due to hip fracture were derived from EQ-5D data from a prospective cohort of 278 older adults (mean age 77) suffering hip fractures in Sweden (220). In this cohort, a mean utility value of 0.17 (95% CI 0.14-0.20) was lost at four months post-hip fracture compared to pre-fracture status (Table 12). The five health dimensions of the EQ-5D divide health status into 243 possible health states.

Social tariff values for these health states, estimated as time trade off (TTO) utility values, were applied to the observed health states in this study. A potential caveat with regard to the calculated loss of quality of life in this study was that the patients' health status before fracture was retrospectively collected. This could probably lead to some potential recollection bias in the respect that patients might perceive their quality of life to be better than it actually was which could lead to an overestimation of the loss in quality of life related to fracture.

6.13. Sensitivity analysis for the cost utility study

Both probabilistic and deterministic sensitivity analysis were conducted to estimate the effect of changes in parameters on the outcome of the study. Apart from the probability and cost parameters used in the cost consequence analysis, we also included variation in the utilities values, derived from the literature. We included utility values for treated insomnia either with benzodiazepines or cognitive behavioural therapy (0.60 – 0.66), utilities lost due to fear of falls (0.05 – 0.10), utilities lost due to falls (0.02 – 0.04) and utilities lost due to hip fracture (0.14 – 0.20). All utility values used in the sensitivity analysis along with the references are presented in Table 12.

6.14. Uncertainty

Both deterministic and probabilistic sensitivity analysis was conducted to handle the uncertainty around probability of falls and fractures, probabilities of emergency room visit or hospitalization, utilities associated with insomnia and adverse health consequences with the use of benzodiazepines such as falls and fractures; and cost data associated with use and consequences of use with the competing interventions.

6.15. Reporting

The primary outcome of a cost–utility analysis is the cost per QALY, or incremental cost-effectiveness ratio (ICER), which is calculated as the difference in the expected cost of two interventions, divided by the difference in the expected QALYs produced by the two interventions.

Chapter 7. Methods: Potential cost saving analysis

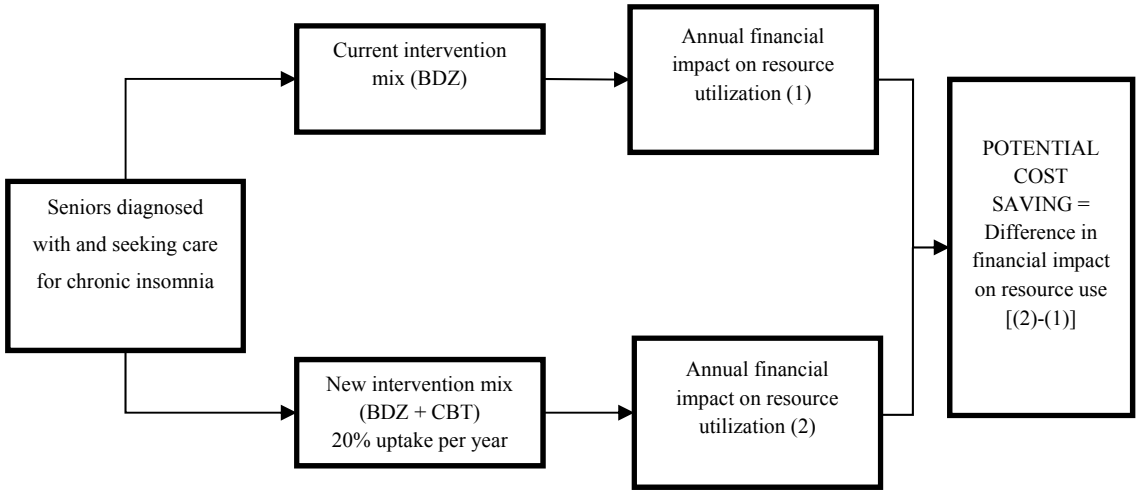
7.1. Study Question

A potential cost saving analysis over a period of 5 years was conducted to estimate the impact of cognitive behavioural therapy compared to BDZ (lorazepam) on the healthcare budget, should cognitive behavioural therapy become universally reimbursed in Canada for seniors diagnosed with and seeking care for chronic insomnia.

7.2. Economic Evaluations chosen

The framework used for this analysis is depicted in Figure 2. According to Figure 2, two scenarios were compared in this analysis. The first scenario was the current intervention mix or reference case, composed of lorazepam only while the second scenario, the new intervention mix, was composed of the possibility of drug treatment (lorazepam) or a 6-week treatment with cognitive behavioural therapy.

Figure 2 **Potential cost saving analysis framework**



Since these patients would be ascribed to either lorazepam or cognitive behavioural therapy, two sub-populations were created. These sub-populations were estimated by the product of the proportion of seniors diagnosed with insomnia, that is the prevalence of insomnia (105), the number of elderly individuals aged 70 years and older (343,000) (221), and the market share of the intervention. As cognitive behavioural therapy is currently not reimbursed in Canada, no data exists on the current use of cognitive behavioural therapy. We postulated that if cognitive behavioural therapy were reimbursed, the uptake would be gradual, at a rate of 20 % per year over a period of five years.

7.3. Target Population

The target population is all older adults aged 70 years and older with chronic insomnia who could have access to cognitive behavioural therapy. No current literature exists on the current use of cognitive behavioural therapy in Canada but in the United States, only 11 % of patients received cognitive behavioural therapy for anxiety, while in Great Britain, only 5 % to 15 % of patients received counseling of any kind (222). The assumption is that coverage will be accessible to all eligible candidates after provincial reimbursement change. The proportion of patients diagnosed with insomnia will be multiplied by the number of elderly individuals aged 70 years and older between 2012 and 2016 and by the rate of patients covered (assumed to be 100%). This calculation will result in the total number of patients eligible for treatment of insomnia

7.4. Perspective

The potential cost saving analysis was performed according to the Canadian health payer's perspective. According to this perspective, all costs included in the Cost consequence analysis were considered in this analysis.

7.5. Time Horizon

The time horizon chosen for the model was a period of 5 years with a base case of 2012.

7.6. Cost Valuation for the potential cost saving analysis

The potential cost saving analysis was performed according to the Canadian health payer's perspective. According to this perspective, all costs included in the Cost consequence analysis were considered in this potential cost saving analysis. The costs considered were: drug acquisition cost, doctor visit costs and the cost of falls associated with the different competing interventions. After adding these costs, the total cost per year for each patient suffering from insomnia was obtained.

For the current intervention mix, the total cost per year for each patient suffering from insomnia (case) was obtained by adding the following costs: drug acquisition costs per case per year, doctor visit cost per case per year and cost of drug-induced falls per case per year. Then, the total costs per year for each patient was multiplied by the size of the sub-population ascribed to lorazepam. The same reasoning was applied to the calculation of the annual financial impact on resource use for the new intervention mix. The budgetary impact of reimbursing cognitive behavioural therapy was ascertained by subtracting the total cost generated by cognitive behavioural therapy from that of lorazepam. The temporal framework was 5 years with 2012 as the base year.

The financial impact on resource use of both scenarios was calculated annually. For every fiscal year, the potential cost saving analysis estimation consisted in deducting the financial impact on resource use of the current intervention mix from that of the new intervention mix. To obtain the 5-year potential cost saving analysis estimate, we summed the 1-year potential cost saving analysis estimates from 2012 to 2016.

Some assumptions made in this potential cost saving analysis must be highlighted. The population modeled was assumed constant over the temporal framework. The rationale underlying this assumption was that entry into the cohort would be counterbalanced by the mortality rate in the same group, over the 5-year period.

It was postulated that the potential cost saving analysis would start the year that cognitive behavioural therapy would be reimbursed and the pre– cognitive behavioural therapy market condition would consist only of lorazepam. The model assumes that increased use of cognitive behavioural therapy would result in a drop in lorazepam use with a gradual cognitive behavioural therapy uptake of 20% per year over 5 years. The model also assumes that a 6-week course of cognitive behavioural therapy would only be delivered once to each individual, with the effects sustained indefinitely.

7.7. Sensitivity analysis for potential cost saving analysis

In univariate sensitivity analysis, we tested four parameters: the base case expected incidence of falls, the impact of an annual increase in insomnia, varying uptake of cognitive behavioural therapy, and the cost of pharmacologic treatment. No studies were identified that provided evidence on the incidence of chronic insomnia in the elderly. For the sensitivity analyses we therefore used a 7.4% annual incidence rate for insomnia syndrome from a population based study with a mean age of 45 years (223).

Data for this study were derived from a large epidemiological study conducted in the province of Quebec, Canada (aged 18 years and over). The authors conducted a telephone and postal survey to document the prevalence of insomnia and determinants of health-seeking behaviors. The one-year incidence rate of 7.4% for insomnia was multiplied by the size of the target population and added to the annual prevalence rate of insomnia in elderly population to obtain the economic impact of the intervention.

Since no data exists in Canada for the utilization of cognitive behavioural therapy for treating insomnia in elderly, we postulated an estimate of 20% utilization of cognitive behavioural therapy for the base case. We tested the impact of an annual increase of 10 to 30% uptake of cognitive behavioural therapy on the provincial budget. We also conducted sensitivity analysis for the variation in the base case probability of falls within a range of 0.20 to 0.40. The cost of pharmacological therapy was also varied from least expensive (generic benzodiazepine agents) to most expensive (brand name Z-drug non-benzodiazepine alternates costing CAD$ 582 per person per year including consultation fees) (203). This was done for the reason that most prescribers are switching to prescription of benzodiazepine-like drugs instead of benzodiazepines, which are more costly than benzodiazepines.

Chapter 8. Results

8.1. Results for the cost consequence analysis

8.1.1. Base case analysis

The results of the cost consequence analysis are shown in Table 13. When health care resources due to falls are not considered in the analysis, benzodiazepine treatment costs 30% less than the price of cognitive behavioural therapy (CAN $231 vs. CAN $335 per individual per year). However, when the cost of falls is considered, the cost of cognitive behavioural therapy becomes 13% less than benzodiazepine treatment. The cost and utilities associated with treatment before and after considering the costs of falls are provided in Table 13 (absolute cost-saving CAN$ 177 per person per year respectively, CAN $1357 vs. $1180).

Table 13 **Cost and utilities associated with the treatment of geriatric insomnia before and after considering the risk of falls**

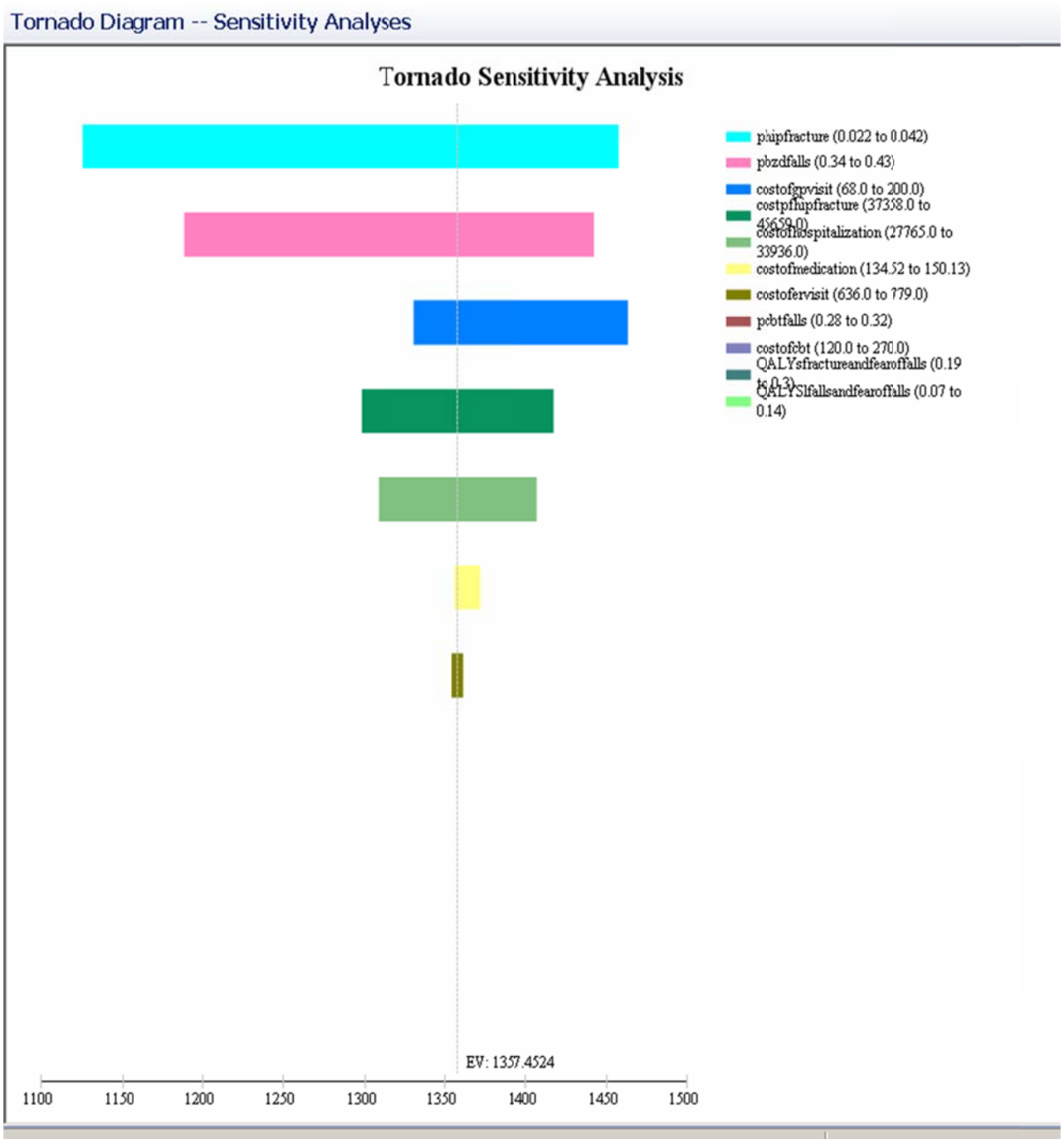
	Without consideration of fall-related adverse events			**Consideration of fall-related adverse events**		
	Cost/person/year	**Utilities**	**Incremental Value (CAD $)**	**Cost/person/year + cost/person/fall-related ADE**	**Average utilities**	
Treatment with BDZ	$ 231	0.66	104 (in favor of BDZ)	$ 1,357	0.63	0
Treatment with CBT	$ 335	0.66	0	$ 1,180	0.64	$177 (in favor of CBT)

8.1.2. Results for sensitivity analysis

We conducted both deterministic and probabilistic sensitivity analyses to observe the effect of varying parameters on the outcome of the analysis. A tornado diagram shows the most influential parameters that have the most impact on the outcome in univariate deterministic sensitivity analyses (Figure 3). In the tornado diagram the horizontal axis is the outcome; along the vertical axis, parameters are arrayed and

horizontal bars represent the outcome range associated with the specified parameter's range.

Figure 3 Deterministic sensitivity analyses for Cost Consequence Analysis

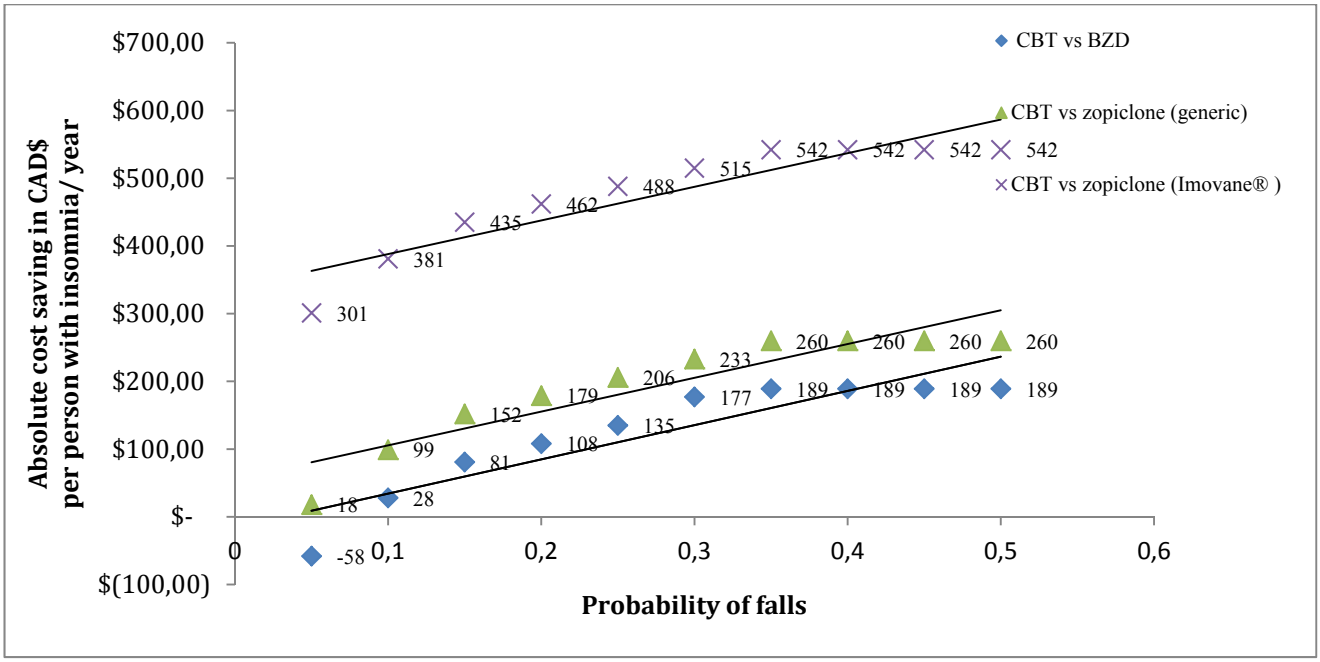


The outcome point estimate corresponding to base-case values is indicated by a vertical line cutting through all horizontal bars. The longest bar (reflecting the parameter generating the widest uncertainty) is placed at the top, and the other bars are arrayed in descending order of length. Thus, the deterministic sensitivity analysis for the Cost Consequence Analysis shows that the variation in the probability of hip fracture has the highest impact on the outcome of the analysis while the probability of falls with benzodiazepines ranks second.

The costs of general practitioner visit ranked third. The results of the probabilistic sensitivity analysis report for the cost consequence analysis are presented in section 12.1.1. The probabilistic sensitivity analysis report shows that even at different varying parameters, benzodiazepines cost CAD$ 1,342, S.D $ 577 (range 252-3,764) on average per person per year vs. CAD$ 1,159, S.D $ 524 (range 349-2,828) on average per person per year for cognitive behavioural therapy; thus saving an average of CAD$ 183 per person per year when the cost of falls are considered across all provinces in Canada.

Results for the changes in the model for the prescription of benzodiazepine-like drugs (Z-drugs) instead of benzodiazepines are presented in Figure 4 . The result shows that benzodiazepines are cost saving compared to cognitive behavior therapy at a minimum 0.08 probability of falls in the elderly. As shown in the figure, the cost savings from cognitive behavioural therapy increase as the cost of the pharmacological intervention increases and cost savings reach their highest level with branded Zopiclone with an estimate of nearly CAD$ 301 saved per person per year in favor of cognitive behavioural therapy in a population with even at a minimum 0.08 risk of falling.

Figure 4 **Graph showing absolute cost saving versus base case probabilities of falls**



Zopiclone (Generic) = CAD$=204.67/year

Zopiclone (Brand) = CAD$=487.00/year

8.2. Results for cost utility analysis

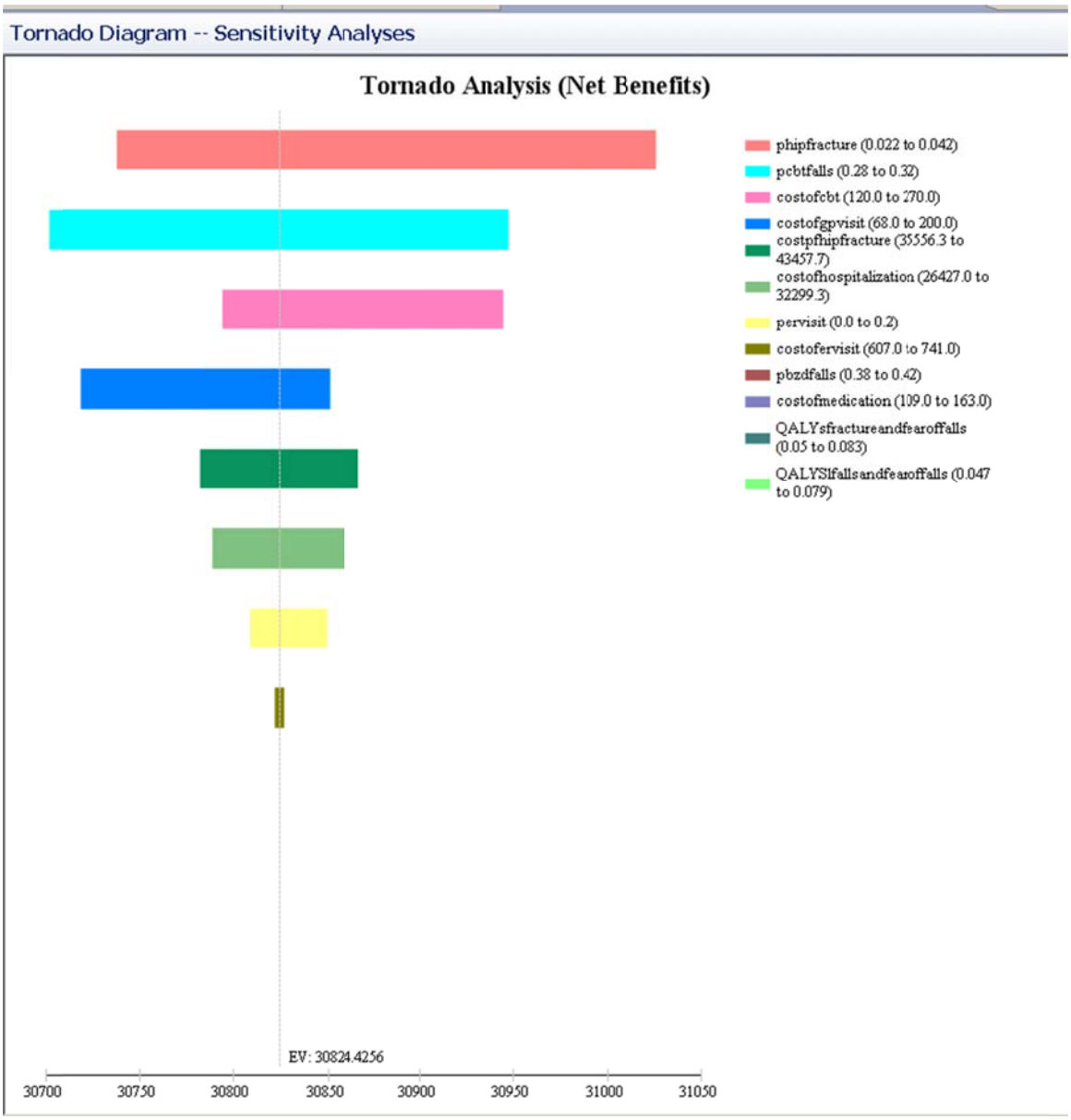
8.2.1. Base case analysis

The results of the cost-utility analysis are shown in section 12.1.2. When cognitive behavioural and benzodiazepine treatment are considered without fall-related consequences, the health utility associated with treated insomnia in both instances is 0.66, which is not surprising since the two therapies appear to be equally efficacious, yielding similar health states. However when falls are considered, the utility associated with benzodiazepines is 0.63, while for CBT it is 0.64. The average cost effectiveness for benzodiazepines becomes CAN $ 2,147 while for cognitive behavioural therapy it becomes CAN $ 1,845, showing that benzodiazepines were dominated. (see page 108)

8.2.2. Results for sensitivity analysis

We conducted both deterministic and probabilistic sensitivity analyses to observe the effect of varying parameters on the outcome of the analysis. Apart from uncertainty in probability and cost parameters used in the Cost Consequence Analysis, we also included variation in utilities values due to falls, fear of falls and fractures in geriatric patients. The deterministic sensitivity analysis in the form of a tornado diagram is presented in Figure 5.

Figure 5 **Deterministic sensitivity analyses for cost utility analysis**

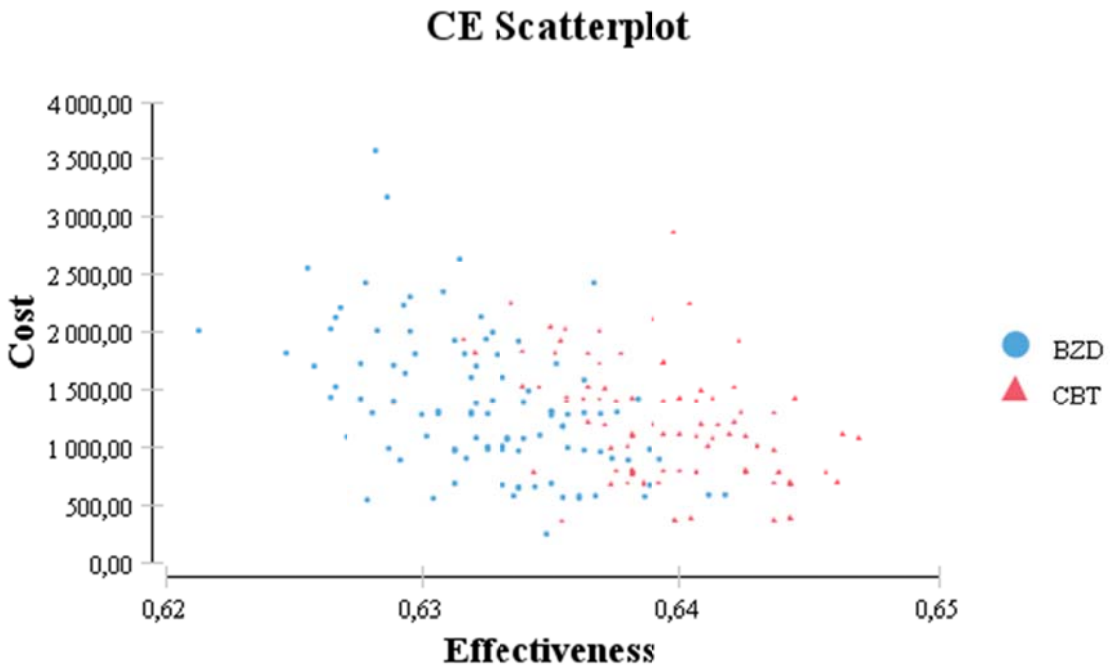


The tornado analysis shows that the variation in the probability of hip fracture has the highest impact on the outcome of the analysis, while the probability of falls due to cognitive behavioural therapy has the second highest impact. The reason behind this may be that health states are most affected by the occurrence of a hip fracture, which is driven

by the probability of hospitalization due to hip fracture. The probabilistic sensitivity analysis report shows that even at different varying parameters cognitive behavioural therapy has a net monetary benefit of CAD$ 30,844 with equivalent utilities. The results for probabilistic sensitivity analyses are presented in section 12.1.2.

The Monte Carlo cost effectiveness acceptability curve and preferred strategy at a particular willingness to pay are shown in section 12.2.1 These results show that cognitive behavioural therapy is 97 % cost effective at 30,000 CAD $ of willingness to pay and 100% cost effective at any value of willingness to pay from CAD$ 60,000 to CAD$ 100,000. Cost effectiveness scatter plots are presented in Figure 6.

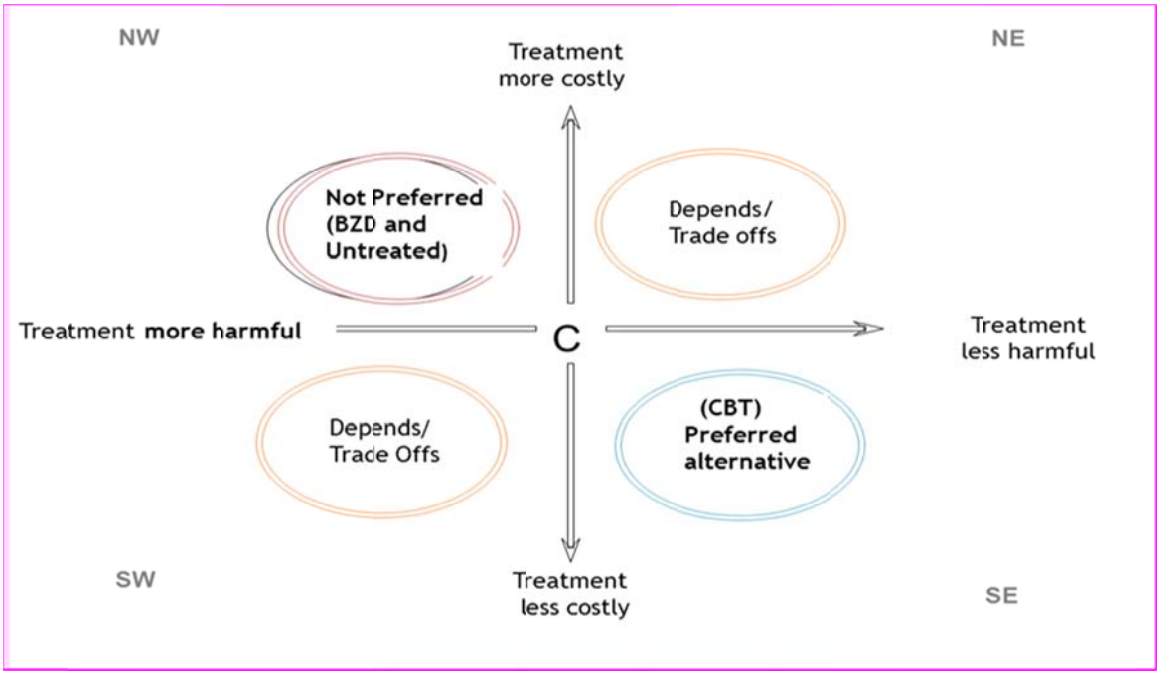
Figure 6 **Cost effectiveness scatter plots**



In the scatter plot cognitive behavioural therapy lies predominantly in the southeast quadrant of the cost effectiveness plane (Figure 7) showing its preference over benzodiazepines in terms of a superior overall health state when falls are considered and

more costs saved. Points in the northeast quadrant indicate that on many occasions cognitive behavioural therapy will cost the same as lorazepam, but will yield a marginally better health state. This is because of the relatively rare probability of injurious falls in the population overall.

Figure 7 **Cost effectiveness plane**



8.3. Results for the potential cost saving analysis

8.3.1. Base case scenario

The results of the potential cost saving analysis (base case scenario) are presented in Table 14 . Based on our results, if reimbursement of cognitive behavioural therapy were to result in a 20% market share of treatment for insomnia during the first year, reimbursement of CBT would result in a cost-savings of approximately 5.1 million Canadian dollars due to fall-related savings, compared to the current scenario where only benzodiazepines are reimbursed. In 2016, if the CBT market share were to increase up to

100% (completely replacing lorazepam therapy), the expected annual direct cost savings for the treatment of insomnia would be $ 441.00 million CAD dollars, with a cumulative cost savings of $112.00 billion CAD dollars over the 5-year potential cost saving analysis temporal framework due to prevention of drug-induced falls and fall-related consequences.

Table 14 **Potential cost saving**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	343,000	343,000	343,000	343,000
CBT uptake	**BDZ**	100%	80%	60%	40%	20%	0
	CBT	0	20%	20%	20%	20%	0,2
Direct medical costs without ADE(in millions CAD$)		79.20	86.40	70.50	54.70	38.80	22.90
Falls related costs (in millions CAD$)		465.40	453.30	360.20	267.10	174.00	80.90
Total direct costs attributable to the management of chronic insomnia (in millions CAD$)		544.70	539.70	431.00	321.80	212.80	103.90
Annual savings due to reimbursement of CBT (in millions CAD$)		-	5.10	113.90	222.80	331.90	441.00

BDZ: Benzodiazepines CBT: Cognitive Behavioural Therapy

8.3.2. Results for the univariate sensitivity analysis

The overall results for the sensitivity analyses for the potential cost saving analysis are presented in Table 14 . The univariate sensitivity analysis shows that the application of a 7.4 % annual incidence in the rate of seniors with chronic insomnia and a change in cognitive behavioural therapy uptake rate have an important impact on the estimated cost-savings (Table 15). As anticipated, the projected total savings per year is positively

correlated with the application of the incidence rate of chronic insomnia and the increase in the uptake of cognitive behavioural therapy, which in turn is associated with the most important cumulative cost savings as shown in Table 16 ($713 million Can dollars).

Table 15 **Sensitivity analysis for the potential cost saving**

		parameter	Budget impact results expressed in Canadian dollars (in millions CAD$)					
			2012	2013	2014	2015	2016	Total
Market share (in percentage)	**Lorazepam**		80%	60%	40%	20%	0	
	CBT		20%	20%	20%	20%	0,2	
Base case results, cost saved (in millions CAD$)		-	5.10	113.90	222.80	331.90	441.00	1,121.00
Incidence rate of chronic insomnia		7.4% increase annually	5.10	113.00	103.00	152.00	340.00	713.00
Uptake of CBT		10%	2.50	5.70	11.10	16.50	28.40	64.20
		30%	7.51	170.90	334.30	492.70	544.60	1,549.91
Base case probability of falls		0.20	0.12	87.00	172.80	258.60	344.50	863.02
		0.40	6.90	137.20	267.40	397.60	527.80	1,336.80
Cost of pharmacotherapy [Zopiclone (branded)] (including G.P consultation)		CAD$ 582	5.80	218.60	378.60	538.50	698.40	1,839.90

CBT: Cognitive Behavioural Therapy

Table 16 **Sensitivity analysis results at the incidence rate of 7.4 % increase annually**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	559,000	598,000	640,000	684,000
CBT uptake	**BDZ**	100%	80%	60%	40%	20%	0
	CBT	0	20%	20%	20%	20%	0.2
Direct medical costs without ADE (in millions CAD$)		79.20	86.30	70.50	89.10	67.70	42.80
Falls related costs (in millions CAD$)		465.40	453.30	587.15	465.80	324.70	161.60
Total direct costs attributable to the management of chronic insomnia (in millions CAD$)		544.60	539.60	657.60	555.00	392.50	204.50
Annual savings due to reimbursement of CBT (in millions CAD$)		-	5.10	112.90	103.30	152.10	340.00

On the contrary, the cumulative cost savings decrease to its lowest value when cognitive behavioural therapy uptake is only 10 % as shown in Table 17 64.2 million Can dollars) and maximum when uptake is 30% as shown in Table 18 (155 billion CAD$). As we can see in Table 19, even at a lesser base case of probability of falls (0.20), cognitive behavioural therapy saves a total of 86 billion dollars over a period of five years. As expected, an increase in the base case probability of falls (0.40) and an increase in the cost of pharmacotherapy (CAD$ 582 per person per year for branded Zopiclone) results in a huge impact on budgetary saving of $134 and $184 billion CAD over a period of five years (Table 20 and Table 21)

Table 17 **Sensitivity analysis results at the CBT uptake rate of 10% annually**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	343,000	343,000	343,000	343,000
CBT uptake	**BDZ**	100%	90%	80%	70%	60%	0
	CBT	0	10%	10%	10%	10%	0,5
Direct medical costs without ADE (in millions CAD$)		79.20	82.80	74.80	66.90	59.00	57.40
Falls related costs (in millions CAD$)		465.40	459.30	412.80	366.20	319.70	202.30
Total direct costs attributable to the management of chronic insomnia (in millions CAD$)		544.60	542.10	487.70	433.20	378.70	259.80
Annual savings due to reimbursement of CBT (in millions CAD$)		-	2.50	5.70	11.10	16.50	28.40

Table 18 **Sensitivity analysis results at the CBT uptake rate of 30% annually**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	343,000	343,000	343,000	343,000
CBT uptake	**BDZ**	100%	70%	40%	10%	0%	0
	CBT	0	30%	30%	30%	10%	0
Direct medical costs without ADE(in millions CAD$)		79.20	89.90	66.10	42.30	11.40	0
Falls related costs (in millions CAD$)		465.40	447.20	307.60	167.90	404.70	0
Total direct costs attributable to the management of chronic insomnia(in millions CAD$)		544.60	537.10	373.70	210.30	519.60	0
Annual savings due to reimbursement of CBT (in millions CAD$)		-	7.51	170.90	334.30	492.70	544.60

Table 19 **Sensitivity analysis results with 0.20 base case probabilities of falls**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	343,000	343,000	343,000	343,000
CBT uptake	**BDZ**	100%	80%	60%	40%	20%	0
	CBT	0	20%	20%	20%	20%	0.2
Direct medical costs without ADE(in millions CAD$)		79.20	86.30	70.50	54.60	38.80	22.90
Falls related costs(in millions CAD$)		349.80	341.40	271.50	201.50	131.50	61.60
Total direct costs attributable to the management of chronic insomnia (in millions CAD$)		429.00	427.80	342.00	256.20	170.40	84.50
Annual savings due to reimbursement of CBT (in millions CAD$)		-	0.12	87.00	172.80	258.60	344.50

Table 20 **Sensitivity analysis results with 0.40 base case probabilities of falls**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	343,000	343,000	343,000	343,000
CBT uptake	**BDZ**	100%	80%	60%	40%	20%	0
	CBT	0	20%	20%	20%	20%	0.2
Direct medical costs without ADE (in millions CAD$)		79.20	86.30	70.50	54.60	38.80	22.90
Falls related costs (in millions CAD$)		571.70	557.60	443.20	328.90	214.50	100.20
Total direct costs attributable to the management of chronic insomnia (in millions CAD$)		651.00	644.00	513.80	383.60	253.40	123.20
Annual savings due to reimbursement of CBT (in millions CAD$)		-	6.90	137.20	267.40	397.60	527.80

Table 21 **Sensitivity analysis results with increased cost of pharmacotherapy**

		Reference	2012	2013	2014	2015	2016
Estimated size of target population (constant)		343,000	343,000	343,000	343,000	343,000	343,000
CBT uptake	**BDZ**	100%	80%	60%	40%	20%	0
	CBT	0	20%	20%	20%	20%	0.2
Direct medical costs without ADE (in millions CAD$)		199.60	182.60	142.70	102.80	62.90	22.90
Falls related costs (in millions CAD$)		599.90	558.00	438.00	318.00	198.10	78.10
Total direct costs attributable to the management of chronic insomnia (in millions CAD$)		799.50	740.70	580.80	420.90	261.00	101.10
Annual savings due to reimbursement of CBT (in millions CAD$)		-	5.80	218.60	378.60	538.50	698.40

Chapter 9. Discussion

The economic analysis presented in this paper indicates that although benzodiazepines are inexpensive, they carry substantial hidden costs in increased health care resources attributable to falls in the elderly. The results of the sensitivity analyses suggest that cognitive behavioural therapy is almost always cost-saving, and variation in the input parameters for the model do not significantly affect this finding; only the magnitude of the savings with cognitive behavioural therapy changes. Falls not only incur monetary loss, but also lead to diminished quality of life. The result with benzodiazepine treatment is increased cost for a net reduction in quality of life for the geriatric population with insomnia.

Findings from the economic analysis revealed that when falls are *not* considered, benzodiazepine therapy costs 13% less per individual than cognitive behavioural therapy and when the cost of falls attributable to benzodiazepine use is considered, cognitive behavioural therapy emerges as a cost-saving strategy, saving the health care system CAN $177 per year per person treated for insomnia (CAN $1,357 for benzodiazepines vs. $1,180 for cognitive behavioural therapy). Probabilistic sensitivity analyses suggest that even at different varying parameters, benzodiazepines cost CAD$ 1,305, S.D $ 598 ($\pm$245-2,625) on average per person per year vs. CAD$ 1,129, S.D $ 514 ($\pm$342-2,526) on average per person per year for cognitive behavioural therapy when the cost of falls are considered in geriatric populations. Cognitive behavioural therapy dominates benzodiazepines in geriatric patients when the cost of falls is considered.

One of the greatest challenges in preparing the economic model for this analysis was selection of the parameters to populate the decision tree. While the 30% baseline prevalence of falls in the elderly is fairly well recognized, and easily subject to modification in sensitivity analyses, the degree to which benzodiazepines increase the risk of falls over baseline was more difficult to establish with certainty. Two recent well-conducted meta-analyses suggest that indeed a strong association between benzodiazepine use and the risk of falling exists for older adults (60, 61). Woolcott et al. reported a pooled OR of 1.57 (95% CI 1.43-1.72) while Bloch et al. reported an OR of

1.39 (1.24-1.54) for benzodiazepines. However, which exact value to choose for the economic analyses required much scrutiny and debate.

Woolcott et al (60) used Bayesian methodology while Bloch F et al. (61) used a frequentist approach for their meta-analysis. There were 11 studies in the Woolcott meta-analysis that included benzodiazepine use and risk of falling in older adults, out of which 6 were conducted among community dwelling older adults. The authors report the OR for the total group of 20,652 participants, of which 8,704 participants resided in long term care or the acute care hospital setting (i.e. 60% community individuals).

The mean age for the sample was 77 years. Unfortunately Woolcott et al. did not report tests of homogeneity for their meta-analysis; however various estimates of association were similar. For instance, the OR using prior evidence was 1.48 (1.23-1.77), for the Bayesian pooled estimate 1.57 (1.43-1.72) and for a random effects model 1.60 (1.46-1.75). Only the smallest of the six studies that included community dwelling adults had a lower limit of the confidence interval that crossed 1. The other five were well above 1. The authors did conducted stratified analyses by setting and stated that there was no significant difference in the OR for the risk of benzodiazepines and falls by setting, but the exact results were not reported.

There were 14 studies included in the Bloch et al. meta-analysis examining the use of benzodiazepines and the risk of falls. The authors report a pooled OR of 1.39 (1.24-1.54) for the entire sample of 20,576 individuals but present a stratified analysis by setting which showed a pooled OR of 1.61 (1.35-1.93) for persons living in institutions (n=9 studies), and an OR of 1.27 (1.11-1.46) for a group of 5 studies that reported "ambulatory or both" settings. No details were provided on how the authors made this distinction. The Bloch et al. group showed that the risk of falls decreased for individuals aged > 80, which runs counter to many other studies. Furthermore the analysis for the "ambulatory or both" group showed an I^2 value of greater than 50%, suggesting that there was marked heterogeneity within this group. This further reduced our confidence in the estimate of the OR of 1.27 (1.11-1.46) for community-dwelling adults.

There were also methodological differences between the two meta-analyses for the ascertainment of falls and medication use. Bloch et al. analyzed psychotropic drugs as a single class and also as individual classes of drugs. Falls were predominantly ascertained by self-report. Woolcott et al. ascertained falls by incident report in hospital or by recall. Medications were ascertained at baseline or by interview. Overall, because our population of interest was community dwelling elderly we used the Bayesian pooled estimate for the increased risk of falls from benzodiazepine use from the Woolcott et al. meta-analysis (OR 1.57), but in order to account for uncertainty, we enlarged the bounds of confidence interval (1.23 -1.77) from the Bloch et al. study.

It could be argued that the resultant health state attributable to treatment of insomnia with benzodiazepines (0.63) compared to the health state attributable to treatment with cognitive behavioural therapy (0.64) is not significantly different. If so, the analysis presented in this thesis could be viewed as a non-inferiority analysis. The conclusion remains the same: although there is no significant gain in overall health state to the elderly by offering cognitive behavioural therapy for the treatment of insomnia, substantial cost savings result in terms of diminished health care resource use due to drug-induced falls.

Cost estimates for adverse events associated with the use of benzodiazepines for the treatment of insomnia were calculated in the year 2009, and these costs were inflated to 2012 CAD$ using the consumer price index (210). Using these manipulations in the potential cost saving analysis, substitution of non-pharmacologic management over drug therapy for geriatric insomnia emerged as a cost-effective fall prevention strategy. The effectiveness of the strategy rose proportionate to increases in expected fall rates, for example in frail older adults living in residential or long-term care, or in high risk previous fallers. The effectiveness of the strategy also rose proportionate to the cost of the type of medication used to treat insomnia.

The probabilistic sensitivity analysis report shows that even at different varying parameters cognitive behavioural therapy has a net monetary benefit of CAD$ 30,844 with equivalent utilities. The cost effectiveness acceptability curve shows that cognitive behavioural therapy is 97 % cost effective at 30,000 CAD $ of willingness to pay and

100% cost effective at any value of willingness to pay from CAD$ 60,000 to CAD$ 100,000. Based on our potential cost saving analysis, if reimbursement of cognitive behavioural therapy were to result in a 20% market share of treatment for insomnia during the first year, reimbursement of CBT would result in a cost-savings of approximately 5.5 million Canadian dollars due to fall-related savings, compared to the current scenario where only benzodiazepines are reimbursed. In 2016, if the CBT market share were to increase up to 100% (completely replacing lorazepam therapy), the expected annual direct cost savings for the treatment of insomnia would be $ 441 million CAD dollars, with a cumulative cost savings of $112 billion CAD dollars over the 5-year potential cost saving temporal framework due to the prevention of drug-induced falls and fall-related consequences.

Practical implications of our findings point to the wisdom of discontinuing benzodiazepines in all chronic users and substituting cognitive behavioural therapy as treatment for insomnia. We recognize this may not be a realistic solution, especially given the current reimbursement scenario. Furthermore, discontinuation of benzodiazepine therapy is known to be difficult among long-term consumers, despite evidence suggesting that chronic use is no longer associated with improved sleep quality in the elderly (224, 225). Physicians also tend to minimize benzodiazepine-associated adverse effects, anticipate withdrawal failure, and wish to avoid patient resistance (225).

Nonetheless, discontinuation of benzodiazepines is certainly possible, as has been documented as a result of physician interventions that highlight the risk of injury in certain patients. Robyn Tamblyn et al. (226) conducted a cluster randomized controlled trial of 81 family physicians and 5628 of their patients aged 65 and older who were prescribed psychotropic medication. The authors concluded that the intervention reduced the risk of injury by 1.7 injuries per 1,000 patients (95% CI 0.2/1000 to 3.2/ 1,000; p= 0.02). Hoebert et al. (227) conducted a retrospective observational database study in Netherland using electronic health records–based Netherlands Information Network of General Practice (LINH) using 13,596 patients. The authors concluded that a

reimbursement restriction on benzodiazepine use in patients with newly diagnosed sleeping disorder was lower in the first 2 to 3 quarters after the policy change.

As Medicare Part D excludes benzodiazepine medications from coverage, and some state Medicaid programs in United States also limit coverage, Briesacher et al. (228) conducted a quasi-experimental study that included 1 068, 104 residents from 48 states. The authors concluded that no supplemental coverage for benzodiazepines reduced the utilization of benzodiazepines. The no-supplemental-coverage policy resulted in an immediate and significant reduction of 10 absolute points in benzodiazepine use (27.0% to 17.0%) after Medicare Part D was implemented (95% confidence interval, -0.11 to -0.09; $P < .001$). Of note, benzodiazepine use remained stable in the partial-supplemental- and complete-supplemental-coverage states. Baillargeon et al. (229) conducted a randomized controlled trials using 344 participants, (mean age 67.4 years) randomly assigned to undergo cognitive-behavioural therapy plus gradual tapering of the drug (combined treatment) or gradual tapering only. The authors concluded that offering a 6-week course of cognitive behavioural therapy has been shown to effectively allow patients to transition to better sleep habits during a gradual tapering protocol.

Formal health economic analyses of cognitive behavioural therapy in Canada are lacking. Even if available, the channels for submission of this evidence are difficult to determine. This situation contrasts with the clearly defined procedures for medications, which are evaluated via the Common Drug Review process (Canadian Agency for Drugs and Technologies 2009). This thesis responds to the demand for further evaluation of the economic benefits of cognitive behavioural therapy in the elderly by health technology assessment organizations in Quebec such as L'Institut national d'excellence en santé et en services sociaux (INESSS) and the Canadian Agency for Drugs and Technologies (CADTH) in Canada.

This is the first Canadian study looking at the economic impact of fall-related consequences in the drug management of chronic insomnia in seniors aged 70+. To our knowledge, this type of "geriatric-oriented" economic analysis has previously never been attempted. It sets the precedent for investigating the economic impact of other drugs

known to incur falls or other non-traditional geriatric syndromes (confusion, incontinence) in the elderly. Hopefully, we will build a growing body of evidence showing that the reimbursement of non-pharmacological therapy is equally, if not more important, for seniors at risk of functional decline in their later years of life.

Chapter 10. Limitations

Decision-tree analysis is the simplest form of modeling technique, quick and easy to generate results, but is considered limited for chronic disease management. We used a decision tree in our economic analysis because various input parameters like cost and utilities associated with insomnia in older adults are scarce and the available studies provided data for a maximum time period of 1 year only. Although a Markov model could have potentially provided more information about insomnia remission and treatment, we did not have valid data to populate such a model and decided it was preferable to restrict the analysis to a 1-year decision tree.

Some of our assumptions also underestimated the complexity of our analysis. We assumed that the risk of falls with cognitive behavioural therapy equaled that of the general population and that there was no incremental risk of falls with cognitive behavioural therapy. We also assumed that there would be complete adherence of patients for cognitive behavioural therapy and BZD treatments. These assumptions may be unrealistic. We also did not look at the possibility of recurrent falls during the one-year time period, nor recurrence of insomnia after cognitive behavioural therapy.

We limited our analysis to the occurrence of falls due to benzodiazepine use, however, there are many other adverse events associated with the use of benzodiazepines in the elderly people such as cognitive impairment and motor vehicle accidents. We only accounted for falls and fractures, thus underestimating the real cost saved by the use of cognitive behavioural therapy for the treatment of insomnia in the elderly. We did not include cognitive impairment as it is difficult to quantify its impact, and we did not include automobile crashes as many older persons no longer drive.

We also did not model the possibility of death in the model, which could have occurred post-surgery for hip fracture or due to head trauma after a fall. Nor did we include the costs of nursing home admission after hip fracture. This lack of data to populate the model increases uncertainty around the cost-utility analysis and the potential cost saving analysis, in the direction of underestimation of the costs due to benzodiazepine-induced falls.

Cost of medication acquisition, dispensing fees and general physician visit were taken from directly from the Ministry of Health website and represent an accurate estimation of medication cost. Cost of Psychologists visit were taken from the psychological association of the British Columbia and thus represent only an estimate but results were generalized for Canada by conducting sensitivity analysis for the lower and highest drug acquisition cost, GP visit and psychologist visit for different provinces in Canada. Cost of adverse consequences resulted from the use of benzodiazepines were taken from a single study and were presented for the year 2009. We inflated that cost for the year 2012 by using consumer price index (ref.). There is a great variation in the health resource cost between the provinces in Canada, so we collected aggregate per diem cost for different provinces for Canada and difference for the highest and lowest province price were inflated to the 2012 cost.

QALYs for the insomnia versus no insomnia were taken using SF-36 validated questionnaire but there was a sampling Potential cost saving analysis in the selection of participants as participants were recruited from an online panel. This may have affected the estimates towards the null as more healthy participants were likely to take part in the survey and underestimation of the utility values lost due to insomnia may have occurred. For the quantification of utilities lost due to falls, the authors relied on self-report via postal questionnaire; we acknowledge that this may be a less accurate form of outcome assessment, subject to under or over reporting.

Participation rates were also very low in these studies, suggesting the possibility of volunteer Potential cost saving analysis. Finally, the results only apply to women. Utilities lost due to fractures were estimated by the time trade off (TTO) method and comparison to a health state before the fracture and these data were retrospectively collected. This could probably lead to some potential recall bias in the respect that patients might perceive their quality of life to be better than it actually was which could lead to an overestimation of the loss in quality of life related to fracture. Probability values for falls. fractures, emergency room visit and hospitalization with two interventions as well as with insomnia itself were taken after a literature search and any uncertainty around the estimates were resolved by using a wide range for input

parameters used in sensitivity analysis. Despite all these limitations, we believe that our model clearly captures the fact that substantial cost-savings could occur if cognitive-behavioural therapy were to replace drug-therapy for the treatment of insomnia.

Chapter 11. Conclusion and future directions

In conclusion, this case example illustrates that the current treatment reimbursement options that fund pharmacologic therapy instead of non-pharmacologic therapy for geriatric insomnia are neither cost-saving nor ethically recommendable from the health system's perspective. Perceived as more expensive and resource intensive, non-pharmacologic therapies are actually cost saving by preventing falls, fractures and hospitalizations. In the future both clinicians and decision-makers need to consider restructuring their decision-making process for prescribing, renewing and reimbursing benzodiazepine therapy for chronic insomnia in the elderly. More studies in this area would be greatly welcome and might help the shift from pharmacologic to non-pharmacological therapies.

Other medications, chronic conditions and geriatric syndromes should be analyzed to add to a growing body of evidence that reimbursement of non-pharmacologic therapies should be considered to treat chronic conditions in the elderly. For benzodiazepines in particular, it would be interesting to find a way to account for all adverse events including falls, fractures, cognitive impairment and motor-vehicle accidents in order to estimate the overall health burden for using benzodiazepines in the elderly for treating insomnia. Longer clinical studies are also needed on the long-term effectiveness of cognitive behavioural therapy in order to account for repeated treatment rates in the Potential cost saving.

Chapter 12. Appendix

12.1. List of supplementary Tables

12.1.1. Probabilistic sensitivity analysis for cost consequence analysis

Monte Carlo Statistics

Statistic	BZD	CBT
Mean	1341.75	1158.70
Std Devation	574.76	524.48
Minimum	252.23	348.83
2.5%	273.47	355.91
10%	681.48	643.18
Median	1284.34	1086.59
90%	2100.36	1895.53
97.5%	2415.95	2125.78
Maximum	3763.65	2828.14
Size (n)	100.00	100.00
Variance	330347.76	275084.04
Variance/Size	3303.48	2750.84
SQRT[Variance/Size]	57.48	52.45

12.1.2. Ranking for cost utility analysis

Cost-Effectiveness Rankings

subset	Strategy	Elf	IncrEff	Cost	IncrCost	IC/IE	Dominance	Avg CE
⊟ abs. dominated								
	BZD	0.63	-0.01	1357.45	177.94	-25743.00	(Dominated)	2146.67
⊟ undominated								
	CBT	0.64	0.00	1179.52	0.00	0.00		1845.12
⊟ all								
	CBT	0.64	0.00	1179.52	0.00	0.00		1845.12
	BZD	0.63	-0.01	1357.45	177.94	-25743.00	(Dominated)	2146.67

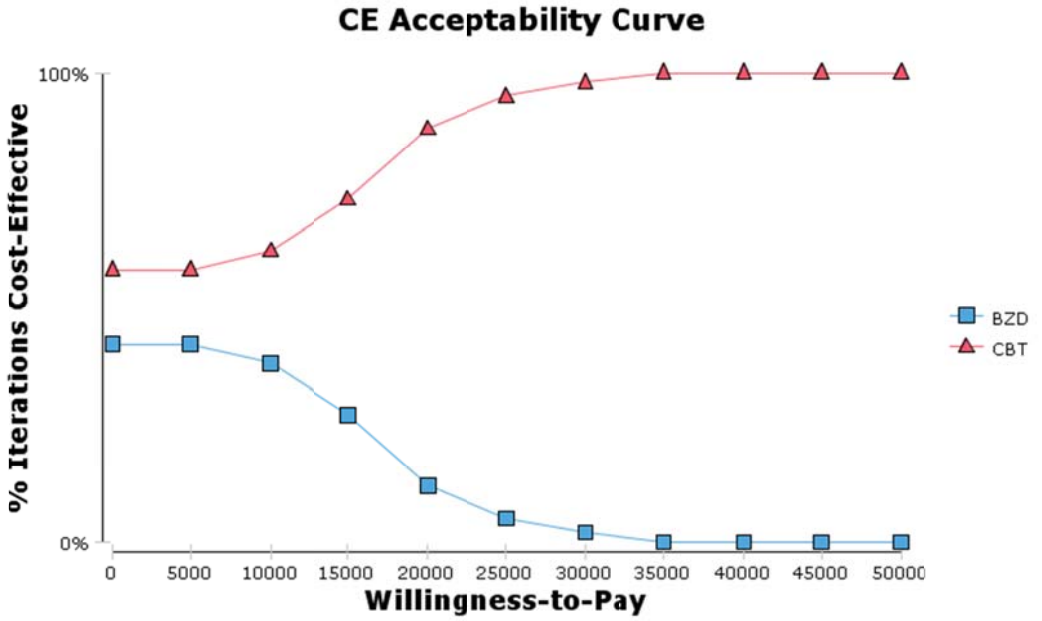
12.1.3. Probabilistic sensitivity analysis for cost utility analysis

Monte Carlo C-E Statistics

Attribute	Statistic	BZD	CBT
◢ Cost			
	Mean	1304.9851000000	1128.9649000000
	Std Deviation	598.4765629538	514.0963219310
	Minimum	245.1500000000	341.7500000000
	2.5%	252.2300000000	348.8300000000
	10%	660.2400000000	377.1500000000
	Median	1184.8400000000	1093.6700000000
	90%	2231.1100000000	1817.2700000000
	97.5%	2529.6100000000	2317.7000000000
	Maximum	2624.9600000000	2526.7100000000
	Size (n)	100.0000000000	100.0000000000
	Variance	358174.1964049889	264295.0282229...
	Variance/Size	3581.7419640499	2642.9502822299
	SQRT[Varianc...	59.8476562954	51.4096321931
◢ Eff			
	Mean	0.6329422000	0.6396923000
	Std Deviation	0.0036364253	0.0035448238
	Minimum	0.6234000000	0.6300800000
	2.5%	0.6250400000	0.6320300000
	10%	0.6274300000	0.6347400000
	Median	0.6331000000	0.6400300000
	90%	0.6379500000	0.6442500000
	97.5%	0.6392100000	0.6461400000
	Maximum	0.6411000000	0.6474000000
	Size (n)	100.0000000000	100.0000000000
	Variance	0.0000132236	0.0000125658
	Variance/Size	0.0000001322	0.0000001257
	SQRT[Varianc...	0.0003636425	0.0003544824
◢ NMB			
	Mean	30342.1248999999	30855.65009999...
	Std Deviation	722.7031944215	639.8296998616
	Minimum	28739.8900000000	29044.32000000...
	2.5%	28845.9700000000	29460.29999999...
	10%	29391.7200000000	30028.55000000...
	Median	30506.9200000000	30911.13999999...
	90%	31106.6000000000	31660.51000000...
	97.5%	31676.7700000000	31933.75000000...
	Maximum	31746.8500000000	32028.24999999...
	Size (n)	100.0000000000	100.0000000000
	Variance	522299.9072269853	409382.0448249...
	Variance/Size	5222.9990722699	4093.8204482499
	SQRT[Varianc...	72.2703194421	63.9829699862

12.2. List of supplementary figures

12.2.1. Cost effectiveness acceptability curve



WEIGHT	STRATEGY	STRATEGYNAME	ACCEPTABILITY
0	0	BZD	0,47
0	1	CBT	0,53
10000	0	BZD	0,45
10000	1	CBT	0,55
20000	0	BZD	0,11
20000	1	CBT	0,89
30000	0	BZD	0,03
30000	1	CBT	0,97
40000	0	BZD	0,02
40000	1	CBT	0,98
50000	0	BZD	0,02
50000	1	CBT	0,98
60000	0	BZD	0
60000	1	CBT	1
70000	0	BZD	0
70000	1	CBT	1
80000	0	BZD	0
80000	1	CBT	1
90000	0	BZD	0
90000	1	CBT	1
100000	0	BZD	0
100000	1	CBT	1

Chapter 13. References

References:

1. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med. 1997 Jul 28;157(14):1531-6. PubMed PMID: 9236554. Epub 1997/07/28. eng.
2. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther. 2007 Apr;32(2):113-21. PubMed PMID: 17381661. Epub 2007/03/27. eng.
3. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007 Jul 14;370(9582):173-84. PubMed PMID: 17630041. Epub 2007/07/17. eng.
4. Organisation WH. Definition of an older or elderly person. Health statistics and health information systems. 2011.
5. Canada S. Estimates of Population by Age and Sex for Canada, Provinces and Territories. Definitions, data sources and methods. 2010;July 1.
6. Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. BMC Geriatr. 2009;9:5. PubMed PMID: 19175914. Pubmed Central PMCID: 2642820. Epub 2009/01/30. eng.
7. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med. 1991 Sep;151(9):1825-32. PubMed PMID: 1888249. Epub 1991/09/01. eng.
8. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003 Dec 8-22;163(22):2716-24. PubMed PMID: 14662625. Epub 2003/12/10. eng.
9. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol. 2007 Aug;63(8):725-31. PubMed PMID: 17554532. Epub 2007/06/08. eng.
10. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008 Feb;46(2):72-83. PubMed PMID: 18218287. Epub 2008/01/26. eng.
11. Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. Scand J Prim Health Care. 2009;27(3):153-9. PubMed PMID: 19462339. Epub 2009/05/23. eng.
12. Holt SS, S; Thürmann, P A. Potentially Inappropriate Medications in the Elderly: The PRISCUS List. aerzteblatt-internationalde. 2010;107(31-32):543-51.
13. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ. 1997 Feb 1;156(3):385-91. PubMed PMID: 9033421. Pubmed Central PMCID: 1226961. Epub 1997/02/01. eng.

14. Rancourt C, Moisan J, Baillargeon L, Verreault R, Laurin D, Gregoire JP. Potentially inappropriate prescriptions for older patients in long-term care. BMC Geriatr. 2004 Oct 15;4:9. PubMed PMID: 15488143. Pubmed Central PMCID: 529256. Epub 2004/10/19. eng.
15. Winit-Watjana W, Sakulrat P, Kespichayawattana J. Criteria for high-risk medication use in Thai older patients. Arch Gerontol Geriatr. 2008 Jul-Aug;47(1):35-51. PubMed PMID: 17675177. Epub 2007/08/07. eng.
16. Stefanacci RG, Cavallaro E, Beers MH, Fick DM. Developing explicit positive beers criteria for preferred central nervous system medications in older adults. Consult Pharm. 2009 Aug;24(8):601-10. PubMed PMID: 19689175. Epub 2009/08/20. eng.
17. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases. JAMA: The Journal of the American Medical Association. 2005 August 10, 2005;294(6):716-24.
18. Campbell SM, Cantrill JA. Consensus methods in prescribing research. J Clin Pharm Ther. 2001 Feb;26(1):5-14. PubMed PMID: 11286603. Epub 2001/04/05. eng.
19. Gurwitz JH, Soumerai SB, Avorn J. Improving medication prescribing and utilization in the nursing home. J Am Geriatr Soc. 1990 May;38(5):542-52. PubMed PMID: 2185295. Epub 1990/05/01. eng.
20. PJ Pronovost TN, S Zeger, M Miller and H Rubin,. How can clinicians measure safety and quality in acute care? Lancet. 2004;363:7.
21. JT Hanlon KSaGSea. A method for assessing drug therapy appropriateness. J Clin Epidemiol 1992;45:6.
22. Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med. 1996 Apr;100(4):428-37. PubMed PMID: 8610730. Epub 1996/04/01. eng.
23. Lipton HL, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. Med Care. 1992 Jul;30(7):646-58. PubMed PMID: 1614233. Epub 1992/07/01. eng.
24. Jeffery S RC, Twersky J et al. Effect of an interdisciplinary team on suboptimal prescribing in a long-term care facility. Consult Pharm. 1999;14:5.
25. Wenger NS, Shekelle PG. Assessing care of vulnerable elders: ACOVE project overview. Ann Intern Med. 2001 Oct 16;135(8 Pt 2):642-6. PubMed PMID: 11601946. Epub 2001/10/17. eng.
26. Mackinnon NJ, Hepler CD. Indicators of preventable drug-related morbidity in older adults 2. Use within a managed care organization. J Manag Care Pharm. 2003 Mar-Apr;9(2):134-41. PubMed PMID: 14613342. Epub 2003/11/14. eng.
27. Gosney M, Tallis R. Prescription of contraindicated and interacting drugs in elderly patients admitted to hospital. Lancet. 1984 Sep 8;2(8402):564-7. PubMed PMID: 6147611. Epub 1984/09/08. eng.
28. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison

with Beers' criteria. Age Ageing. 2008 Nov;37(6):673-9. PubMed PMID: 18829684. Epub 2008/10/03. eng.
29. Pitkala KH, Strandberg TE, Tilvis RS. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. Arch Intern Med. 2002 Aug 12-26;162(15):1707-12. PubMed PMID: 12153373. Epub 2002/08/03. eng.
30. Stafford AC, Alswayan MS, Tenni PC. Inappropriate prescribing in older residents of Australian care homes. J Clin Pharm Ther. 2011 Feb;36(1):33-44. PubMed PMID: 21198718. Epub 2011/01/05. eng.
31. Van Der Hooft CS, Jong GWt, Dieleman JP, Verhamme KMC, Van Der Cammen TJM, Stricker BHCH, et al. Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria – a population-based cohort study.
32. Sakuma M, Morimoto T, Matsui K, Seki S, Kuramoto N, Toshiro J, et al. Epidemiology of potentially inappropriate medication use in elderly patients in Japanese acute care hospitals. Pharmacoepidemiol Drug Saf. 2011 Apr;20(4):386-92. PubMed PMID: 21254304. Epub 2011/01/22. eng.
33. Clive Page MS, Michael Curtis Integarted Pharmacology. Book. 2002;2nd.
34. Addiction Cf, Health aM. Do You Know... Benzodiazepines. About mental health and addiction. 2011.
35. CH A. Benzodiazepines: how they work & how to withdraw. aka The Ashton Manual). 2002.
36. Rickels K. The clinical use of hypnotics: indications for use and the need for a variety of hypnotics. Acta Psychiatr Scand Suppl. 1986;332:132-41. PubMed PMID: 2883820. Epub 1986/01/01. eng.
37. Bjerrum L, Andersen UA. [Benzodiazepine prescriptions in general practice. An analysis of the pattern of use in first time users]. Ugeskr Laeger. 1996 Sep 30;158(40):5616-9. PubMed PMID: 8966790. Epub 1996/09/30. Benzodiazepinordinationer i almen praksis. En analyse of forbrugsmonstret for forstegangsbrugere. dan.
38. Saias T, Gallarda T. [Paradoxical aggressive reactions to benzodiazepine use: a review]. Encephale. 2008 Sep;34(4):330-6. PubMed PMID: 18922233. Epub 2008/10/17. Reactions d'agressivite sous benzodiazepines: une revue de la litterature. fre.
39. Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry. 2005 May;18(3):249-55. PubMed PMID: 16639148. Epub 2006/04/28. eng.
40. Salzman C. The APA Task Force report on benzodiazepine dependence, toxicity, and abuse. Am J Psychiatry. 1991 Feb;148(2):151-2. PubMed PMID: 1987812. Epub 1991/02/01. eng.
41. Mamdani M, Rapoport M, Shulman KI, Herrmann N, Rochon PA. Mental health-related drug utilization among older adults: prevalence, trends, and costs. Am J Geriatr Psychiatry. 2005 Oct;13(10):892-900. PubMed PMID: 16223968. Epub 2005/10/15. eng.
42. Aliya Kassam SBP. CANADIAN TRENDS IN BENZODIAZEPINE & ZOPICLONE USE. Can J Clin Pharmacol. 2006;13(1):6.

43. Tu K, Mamdani MM, Hux JE, Tu JB. Progressive trends in the prevalence of benzodiazepine prescribing in older people in Ontario, Canada. J Am Geriatr Soc. 2001 Oct;49(10):1341-5. PubMed PMID: 11890493. Epub 2002/03/14. eng.
44. Ashton H. Guidelines for the rational use of benzodiazepines. When and what to use. Drugs. 1994 Jul;48(1):25-40. PubMed PMID: 7525193. Epub 1994/07/01. eng.
45. Bartlett G, Abrahamowicz M, Grad R, Sylvestre MP, Tamblyn R. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. BMC Fam Pract. 2009;10:1. PubMed PMID: 19126237. Pubmed Central PMCID: 2627814. Epub 2009/01/08. eng.
46. McIntosh A SD, Smyth R, Burns J, Darjee R Depressants". Oxford Handbook of Psychiatry Oxford University Press. 2005;1:540.
47. Petrovic M, Mariman A, Warie H, Afschrift M, Pevernagie D. Is there a rationale for prescription of benzodiazepines in the elderly? Review of the literature. Acta Clin Belg. 2003 Jan-Feb;58(1):27-36. PubMed PMID: 12723259. Epub 2003/05/02. eng.
48. Grad RM. Benzodiazepines for insomnia in community-dwelling elderly: a review of benefit and risk. J Fam Pract. 1995 Nov;41(5):473-81. PubMed PMID: 7595266. Epub 1995/11/01. eng.
49. Greenblatt DJ, Allen MD, Shader RI. Toxicity of high-dose flurazepam in the elderly. Clin Pharmacol Ther. 1977 Mar;21(3):355-61. PubMed PMID: 13961. Epub 1977/03/01. eng.
50. Cumming RG, Klineberg RJ. Psychotropics, thiazide diuretics and hip fractures in the elderly. Med J Aust. 1993 Mar 15;158(6):414-7. PubMed PMID: 8479356. Epub 1993/03/15. eng.
51. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA. 1989 Dec 15;262(23):3303-7. PubMed PMID: 2573741. Epub 1989/12/15. eng.
52. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ, 3rd. Psychotropic drug use and the risk of hip fracture. N Engl J Med. 1987 Feb 12;316(7):363-9. PubMed PMID: 2880292. Epub 1987/02/12. eng.
53. Sorock GS, Shimkin EE. Benzodiazepine sedatives and the risk of falling in a community-dwelling elderly cohort. Arch Intern Med. 1988 Nov;148(11):2441-4. PubMed PMID: 2903726. Epub 1988/11/01. eng.
54. Taggart HM. Do drugs affect the risk of hip fracture in elderly women? J Am Geriatr Soc. 1988 Nov;36(11):1006-10. PubMed PMID: 3171037. Epub 1988/11/01. eng.
55. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988 Dec 29;319(26):1701-7. PubMed PMID: 3205267. Epub 1988/12/29. eng.
56. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995 Mar 23;332(12):767-73. PubMed PMID: 7862179. Epub 1995/03/23. eng.
57. Larson EB, Kukull WA, Buchner D, Reifler BV. Adverse drug reactions associated with global cognitive impairment in elderly persons. Ann Intern Med. 1987 Aug;107(2):169-73. PubMed PMID: 2886086. Epub 1987/08/01. eng.

58. Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. Am J Epidemiol. 1992 Oct 1;136(7):873-83. PubMed PMID: 1442753. Epub 1992/10/01. eng.
59. Hartikainen S, Lönnroos E, Louhivuori K. Medication as a Risk Factor for Falls: Critical Systematic Review. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2007 October 1, 2007;62(10):1172-81.
60. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009 Nov 23;169(21):1952-60. PubMed PMID: 19933955. Epub 2009/11/26. eng.
61. Bloch F, Thibaud M, Dugue B, Breque C, Rigaud AS, Kemoun G. Psychotropic drugs and falls in the elderly people: updated literature review and meta-analysis. J Aging Health. 2011 Mar;23(2):329-46. PubMed PMID: 20947876. Epub 2010/10/16. eng.
62. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc. 1999 Jan;47(1):30-9. PubMed PMID: 9920227. Epub 1999/01/27. eng.
63. van der Hooft CS, Schoofs MW, Ziere G, Hofman A, Pols HA, Sturkenboom MC, et al. Inappropriate benzodiazepine use in older adults and the risk of fracture. Br J Clin Pharmacol. 2008 Aug;66(2):276-82. PubMed PMID: 18460035. Pubmed Central PMCID: 2492915. Epub 2008/05/08. eng.
64. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf. 2007;30(2):171-84. PubMed PMID: 17253881. Epub 2007/01/27. eng.
65. Thomas RE. Benzodiazepine use and motor vehicle accidents. Systematic review of reported association. Can Fam Physician. 1998 Apr;44:799-808. PubMed PMID: 9585853. Pubmed Central PMCID: 2277821. Epub 1998/05/20. eng.
66. Longo MC, Hunter CE, Lokan RJ, White JM, White MA. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: Part II: The relationship between drug prevalence and drug concentration, and driver culpability. Accident Analysis & Prevention. 2000;32(5):623-32.
67. Dassanayake T, Michie P, Carter G, Jones A. Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review and meta-analysis of epidemiological and experimental evidence. Drug Saf. 2011 Feb 1;34(2):125-56. PubMed PMID: 21247221. Epub 2011/01/21. eng.
68. Verdoux H, Lagnaoui R, Begaud B. Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies. Psychol Med. 2005 Mar;35(3):307-15. PubMed PMID: 15841867. Epub 2005/04/22. eng.
69. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. Arch Clin Neuropsychol. 2004 Apr;19(3):437-54. PubMed PMID: 15033227. Epub 2004/03/23. eng.
70. CIHI. National trauma registry 2004 report. Injury hospitalizations (includes 2002-2003 data). 2004.

71. CIHI. Emergency Department Visits: Volumes and Median Length of Stay by Triage Level, Visit Disposition, and Main Problem. 2011.
72. PHAC. Report on Seniors' Falls in Canada Minister of Public Works and Government Services Canada, 2005. 2005.
73. Health M. Preventing falls and fall-related injuries in Manitoba. A review of best practicesImpact, 2005. 2005.
74. Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. American journal of public health. 1992 Jul;82(7):1020-3. PubMed PMID: 1609903. Pubmed Central PMCID: 1694056. Epub 1992/07/01. eng.
75. Kelsey JL, Procter-Gray E, Hannan MT, Li W. Heterogeneity of Falls Among Older Adults: Implications for Public Health Prevention. American journal of public health. 2012 Sep 20. PubMed PMID: 22994167. Epub 2012/09/22. Eng.
76. Care ACoSaQiH. Preventing falls and harm from falls in older people - best practice guidelines for Australian community care. 2009.
77. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention. 2006 Oct;12(5):290-5. PubMed PMID: 17018668. Pubmed Central PMCID: 2563445. Epub 2006/10/05. eng.
78. Heinrich S, Rapp K, Rissmann U, Becker C, Konig HH. Cost of falls in old age: a systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2010 Jun;21(6):891-902. PubMed PMID: 19924496. Epub 2009/11/20. eng.
79. Zecevic AA, Chesworth BM, Zaric GS, Huang Q, Salmon A, McAuslan D, et al. Estimating the cost of serious injurious falls in a Canadian acute care hospital. Can J Aging. 2012 Jun;31(2):139-47. PubMed PMID: 22621825. Epub 2012/05/25. eng.
80. Zuckerman JD. Hip fracture. N Engl J Med. 1996 Jun 6;334(23):1519-25. PubMed PMID: 8618608. Epub 1996/06/06. eng.
81. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med. 1997 Oct 30;337(18):1279-84. PubMed PMID: 9345078. Epub 1997/11/05. eng.
82. Cumming RG, Salkeld G, Thomas M, Szonyi G. Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. J Gerontol A Biol Sci Med Sci. 2000 May;55(5):M299-305. PubMed PMID: 10819321. Epub 2000/05/20. eng.
83. Close JC. Prevention of falls--a time to translate evidence into practice. Age Ageing. 2005 Mar;34(2):98-100. PubMed PMID: 15713852. Epub 2005/02/17. eng.
84. http://www.smartrisk.ca/downloads/burden/Canada1998/EBI-Can-Summary.pdf. The economic burden of unintentional injury in Canada. 1998.
85. CIHI. Drug use among seniors on public drug program. Canadain Institute of health and informatics. 2010.
86. Hogan DB, Maxwell CJ, Fung TS, Ebly EM. Prevalence and potential consequences of benzodiazepine use in senior citizens: results from the Canadian Study

of Health and Aging. Can J Clin Pharmacol. 2003 Summer;10(2):72-7. PubMed PMID: 12879145. Epub 2003/07/25. eng.
87. Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. J Am Geriatr Soc. 2005 Feb;53(2):233-41. PubMed PMID: 15673346. Epub 2005/01/28. eng.
88. Dailly E, Bourin M. The use of benzodiazepines in the aged patient: clinical and pharmacological considerations. Pakistan journal of pharmaceutical sciences. 2008 Apr;21(2):144-50. PubMed PMID: 18390445. Epub 2008/04/09. eng.
89. Bastien CH, LeBlanc M, Carrier J, Morin CM. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. Sleep. 2003 May 1;26(3):313-7. PubMed PMID: 12749551. Epub 2003/05/17. eng.
90. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. Arch Gen Psychiatry. 1985 Mar;42(3):225-32. PubMed PMID: 2858188. Epub 1985/03/01. eng.
91. Gleason PP, Schulz R, Smith NL, Newsom JT, Kroboth PD, Kroboth FJ, et al. Correlates and prevalence of benzodiazepine use in community-dwelling elderly. Journal of general internal medicine. 1998 Apr;13(4):243-50. PubMed PMID: 9565387. Pubmed Central PMCID: 1496936. Epub 1998/06/13. eng.
92. Tamblyn RM, McLeod PJ, Abrahamowicz M, Monette J, Gayton DC, Berkson L, et al. Questionable prescribing for elderly patients in Quebec. CMAJ. 1994 Jun 1;150(11):1801-9. PubMed PMID: 8199957. Pubmed Central PMCID: 1337055. Epub 1994/06/01. eng.
93. Voyer P, Roussel ME, Berbiche D, Preville M. Effectively detect dependence on benzodiazepines among community-dwelling seniors by asking only two questions. J Psychiatr Ment Health Nurs. 2010 May;17(4):328-34. PubMed PMID: 20529183. Epub 2010/06/10. eng.
94. Beland SG, Preville M, Dubois MF, Lorrain D, Grenier S, Voyer P, et al. Benzodiazepine use and quality of sleep in the community-dwelling elderly population. Aging Ment Health. 2010 Sep;14(7):843-50. PubMed PMID: 20658372. Epub 2010/07/27. eng.
95. Fortin D, Preville M, Ducharme C, Hebert R, Trottier L, Gregoire JP, et al. Factors associated with long-term benzodiazepine use among elderly women and men in Quebec. J Women Aging. 2007;19(3-4):37-52. PubMed PMID: 18032252. Epub 2007/11/23. eng.
96. Hagen BF, Armstrong-Esther C, Quail P, Williams RJ, Norton P, Le Navenec CL, et al. Neuroleptic and benzodiazepine use in long-term care in urban and rural Alberta: characteristics and results of an education intervention to ensure appropriate use. Int Psychogeriatr. 2005 Dec;17(4):631-52. PubMed PMID: 16246262. Epub 2005/10/26. eng.
97. Morgan K, Dallosso H, Ebrahim S, Arie T, Fentem PH. Prevalence, frequency, and duration of hypnotic drug use among the elderly living at home. Br Med J (Clin Res Ed). 1988 Feb 27;296(6622):601-2. PubMed PMID: 3126921. Pubmed Central PMCID: 2545235. Epub 1988/02/27. eng.

98. Schjott J, Opedal K, Rutledal JE. A survey of hypnotic use in geriatric institutions in Sogn og Fjordane, Norway. Aging (Milano). 1999 Feb;11(1):50-5. PubMed PMID: 10337443. Epub 1999/05/25. eng.
99. Erman MK. Sleep architecture and its relationship to insomnia. J Clin Psychiatry. 2001;62 Suppl 10:9-17. PubMed PMID: 11388592. Epub 2001/06/05. eng.
100. Association AP. Diagnostic and Statistical Manual of Mental Disorders 2000 (4th).
101. Organisation WH. International Statistical Classification of Diseases and Related Health Problems 2007;10th revision.
102. Voyer P, Verreault R, Mengue PN, Morin CM. Prevalence of insomnia and its associated factors in elderly long-term care residents. Arch Gerontol Geriatr. 2006 Jan-Feb;42(1):1-20. PubMed PMID: 16125810. Epub 2005/08/30. eng.
103. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev. 2002 Apr;6(2):97-111. PubMed PMID: 12531146. Epub 2003/01/18. eng.
104. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep. 1995 Jul;18(6):425-32. PubMed PMID: 7481413. Epub 1995/07/01. eng.
105. Morin CM, LeBlanc M, Belanger L, Ivers H, Merette C, Savard J. Prevalence of insomnia and its treatment in Canada. Can J Psychiatry. 2011 Sep;56(9):540-8. PubMed PMID: 21959029. Epub 2011/10/01. eng.
106. Daley M, Morin CM, LeBlanc M, Gregoire JP, Savard J. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. Sleep. 2009 Jan;32(1):55-64. PubMed PMID: 19189779. Pubmed Central PMCID: 2625324. Epub 2009/02/05. eng.
107. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. Am J Psychiatry. 1997 Oct;154(10):1417-23. PubMed PMID: 9326825. Epub 1997/10/27. eng.
108. Daley M, Morin CM, LeBlanc M, Gregoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. Sleep Med. 2009 Apr;10(4):427-38. PubMed PMID: 18753000. Epub 2008/08/30. eng.
109. Stoller MK. Economic effects of insomnia. Clin Ther. 1994 Sep-Oct;16(5):873-97; discussion 54. PubMed PMID: 7859246. Epub 1994/09/01. eng.
110. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep. 1999 May 1;22 Suppl 2:S379-85. PubMed PMID: 10394611. Epub 1999/07/08. eng.
111. Ancoli-Israel S. Insomnia in the elderly: a review for the primary care practitioner. Sleep. 2000 Feb 1;23 Suppl 1:S23-30; discussion S6-8. PubMed PMID: 10755805. Epub 2001/02/07. eng.
112. Brassington GS, King AC, Bliwise DL. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64-99 years. J Am Geriatr Soc. 2000 Oct;48(10):1234-40. PubMed PMID: 11037010. Epub 2000/10/19. eng.

113. Walsh JK, Engelhardt CL. The direct economic costs of insomnia in the United States for 1995. Sleep. 1999 May 1;22 Suppl 2:S386-93. PubMed PMID: 10394612. Epub 1999/07/08. eng.
114. Sanford JR. Tolerance of debility in elderly dependants by supporters at home: its significance for hospital practice. British medical journal. 1975 Aug 23;3(5981):471-3. PubMed PMID: 1156826. Pubmed Central PMCID: 1674274. Epub 1975/08/23. eng.
115. Pollak CP, Perlick D, Linsner JP, Wenston J, Hsieh F. Sleep problems in the community elderly as predictors of death and nursing home placement. Journal of community health. 1990 Apr;15(2):123-35. PubMed PMID: 2355110. Epub 1990/04/01. eng.
116. Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. J Am Geriatr Soc. 2001 Sep;49(9):1185-9. PubMed PMID: 11559377. Epub 2001/09/18. eng.
117. Ozminkowski RJ, Wang S, Walsh JK. The direct and indirect costs of untreated insomnia in adults in the United States. Sleep. 2007 Mar;30(3):263-73. PubMed PMID: 17425222. Epub 2007/04/12. eng.
118. Silva Pereira YD, Estibeiro A, Dhume R, Fernandes J. Geriatric patients attending tertiary care psychiatric hospital. Indian J Psychiatry. 2002 Oct;44(4):326-31. PubMed PMID: 21206594. Pubmed Central PMCID: 2955301. Epub 2002/10/01. eng.
119. Kobayashi E, Fujiwara Y, Fukaya T, Nishi M, Saito M, Shinkai S. [Social support availability and psychological well-being among the socially isolated elderly. Differences by living arrangement and gender]. [Nihon koshu eisei zasshi] Japanese journal of public health. 2011 Jun;58(6):446-56. PubMed PMID: 21970078. Epub 2011/10/06. jpn.
120. Holcomb SS. Recommendations for assessing insomnia. Nurse Pract. 2006 Feb;31(2):55-60. PubMed PMID: 16452903. Epub 2006/02/03. eng.
121. Kamel NS, Gammack JK. Insomnia in the elderly: cause, approach, and treatment. Am J Med. 2006 Jun;119(6):463-9. PubMed PMID: 16750956. Epub 2006/06/06. eng.
122. Bain KT. Management of chronic insomnia in elderly persons. Am J Geriatr Pharmacother. 2006 Jun;4(2):168-92. PubMed PMID: 16860264. Epub 2006/07/25. eng.
123. Ancoli-Israel S, Cooke JR. Prevalence and Comorbidity of Insomnia and Effect on Functioning in Elderly Populations.
124. Turkoski BB. Managing insomnia. Orthop Nurs. 2006 Sep-Oct;25(5):339-45; quiz 46-7. PubMed PMID: 17035922. Epub 2006/10/13. eng.
125. Ringdahl EN, Pereira SL, Delzell JE, Jr. Treatment of primary insomnia. J Am Board Fam Pract. 2004 May-Jun;17(3):212-9. PubMed PMID: 15226287. Epub 2004/07/01. eng.
126. Review: benzodiazepines and zolpidem are effective for chronic insomnia. Evidence Based Mental Health. 1998 November 1, 1998;1(4):117.
127. Tariq SH, Pulisetty S. Pharmacotherapy for insomnia. Clin Geriatr Med. 2008 Feb;24(1):93-105, vii. PubMed PMID: 18035234. Epub 2007/11/24. eng.
128. Salzman C. Pharmacologic treatment of disturbed sleep in the elderly. Harv Rev Psychiatry. 2008;16(5):271-8. PubMed PMID: 18803102. Epub 2008/09/23. eng.

129. Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF, 3rd, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. JAMA. 1997 Dec 24-31;278(24):2170-7. PubMed PMID: 9417012. Epub 1998/01/07. eng.
130. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. Journal of general internal medicine. 2007 Sep;22(9):1335-50. PubMed PMID: 17619935. Pubmed Central PMCID: 2219774. Epub 2007/07/11. eng.
131. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000 Jan 25;162(2):225-33. PubMed PMID: 10674059. Pubmed Central PMCID: 1232276. Epub 2000/02/16. eng.
132. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169. PubMed PMID: 16284208. Pubmed Central PMCID: 1285093. Epub 2005/11/15. eng.
133. Glass JR, Sproule BA, Herrmann N, Busto UE. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. Journal of clinical psychopharmacology. 2008 Apr;28(2):182-8. PubMed PMID: 18344728. Epub 2008/03/18. eng.
134. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA. 1999 Mar 17;281(11):991-9. PubMed PMID: 10086433. Epub 1999/03/23. eng.
135. Marks J NA. Drugs and insomnia. BMJ. 1984;288(161).
136. Medicines CoSo. Benzodiazepines, dependence and withdrawal symptoms. Curr Probl. 1988;28.
137. Psychiatrists RCo. Benzodiazepine, and dependence: a college statement. Bull Royal College Psychiatrists 1988;12:2.
138. Editorial. The treatment of insomnia. Drug Ther Bull 1990;28:3.
139. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 Apr;60(4):616-31. PubMed PMID: 22376048. Epub 2012/03/02. eng.
140. Evans C. Cognitive-behavioural therapy with older people. Journal of continuing professional development. 2007;13:111-8.
141. Evans C. Cognitive–behavioural therapy with older people. Advances in Psychiatric Treatment. 2007 March 1, 2007;13(2):111-8.
142. Pigeon WR. Treatment of adult insomnia with cognitive-behavioral therapy. Journal of clinical psychology. 2010 Nov;66(11):1148-60. PubMed PMID: 20853442. Epub 2010/09/21. eng.
143. Bootzin RR, & Nicassio, P. Behavioral treatments for insomnia. Progress in behavior modification (pp 1–47) New York: Academic Press. 1978.
144. Hauri PJ. Sleep disorders: Current concepts (2nd ed.). Kalamazoo, MI,Upjohn Company. 1982;2nd.

145. Leshner A. NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. Clinical relaxation strategies New York: Wiley. 2005; In K.L.Lichstein (Ed.).
146. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. The Psychiatric clinics of North America. 1987 Dec;10(4):541-53. PubMed PMID: 3332317. Epub 1987/12/01. eng.
147. Morin CM, Azrin NH. Behavioral and cognitive treatments of geriatric insomnia. J Consult Clin Psychol. 1988 Oct;56(5):748-53. PubMed PMID: 3192792. Epub 1988/10/01. eng.
148. Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. Arch Intern Med. 2011 May 23;171(10):887-95. PubMed PMID: 21263078. Pubmed Central PMCID: 3101289. Epub 2011/01/26. eng.
149. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. Cochrane Database Syst Rev. 2003 (1):CD003161. PubMed PMID: 12535460. Epub 2003/01/22. eng.
150. Montgomery P, Dennis J. A systematic review of non-pharmacological therapies for sleep problems in later life. Sleep Med Rev. 2004 Feb;8(1):47-62. PubMed PMID: 15062210. Epub 2004/04/06. eng.
151. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry. 1994 Aug;151(8):1172-80. PubMed PMID: 8037252. Epub 1994/08/01. eng.
152. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. J Consult Clin Psychol. 1995 Feb;63(1):79-89. PubMed PMID: 7896994. Epub 1995/02/01. eng.
153. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2006 Jan;25(1):3-14. PubMed PMID: 16448292. Epub 2006/02/02. eng.
154. Soeffing JP, Lichstein KL, Nau SD, McCrae CS, Wilson NM, Aguillard RN, et al. Psychological treatment of insomnia in hypnotic-dependant older adults. Sleep Med. 2008 Jan;9(2):165-71. PubMed PMID: 17644419. Pubmed Central PMCID: 2330271. Epub 2007/07/24. eng.
155. Germain A, Moul DE, Franzen PL, Miewald JM, Reynolds CF, 3rd, Monk TH, et al. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2006 Oct 15;2(4):403-6. PubMed PMID: 17557467. Epub 2007/06/15. eng.
156. Wu R, Bao J, Zhang C, Deng J, Long C. Comparison of sleep condition and sleep-related psychological activity after cognitive-behavior and pharmacological therapy for chronic insomnia. Psychotherapy and psychosomatics. 2006;75(4):220-8. PubMed PMID: 16785771. Epub 2006/06/21. eng.

157. Jacobs GD, Pace-Schott EF, Stickgold R, Otto MW. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. Arch Intern Med. 2004 Sep 27;164(17):1888-96. PubMed PMID: 15451764. Epub 2004/09/29. eng.
158. Mitchell M, Gehrman P, Perlis M, Umscheid C. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Family Practice. 2012;13(1):40. PubMed PMID: doi:10.1186/1471-2296-13-40.
159. Allison T Siebern RM. New developments in cognitive behavioral therapy as the first-line treatment of insomnia. Dove press. 2011;2:21-8.
160. Bastien CH, Morin CM, Ouellet MC, Blais FC, Bouchard S. Cognitive-behavioral therapy for insomnia: comparison of individual therapy, group therapy, and telephone consultations. J Consult Clin Psychol. 2004 Aug;72(4):653-9. PubMed PMID: 15301650. Epub 2004/08/11. eng.
161. Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep. 2006 Nov;29(11):1398-414. PubMed PMID: 17162986. Epub 2006/12/14. eng.
162. Taylor SR, Weiss JS. Review of insomnia pharmacotherapy options for the elderly: implications for managed care. Population health management. 2009 Dec;12(6):317-23. PubMed PMID: 20038257. Epub 2009/12/30. eng.
163. McIntosh B CM, Spry C. Benzodiazepines in Older Adults: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Canadian Agency for Drugs and Technologies in Health. 2011;1.
164. Botteman MF, Ozminkowski RJ, Wang S, Pashos CL, Schaefer K, Foley DJ. Cost effectiveness of long-term treatment with eszopiclone for primary insomnia in adults: a decision analytical model. CNS drugs. 2007;21(4):319-34. PubMed PMID: 17381185. Epub 2007/03/27. eng.
165. Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M. Psychological treatment for insomnia in the regulation of long-term hypnotic drug use. Health technology assessment (Winchester, England). 2004 Feb;8(8):iii-iv, 1-68. PubMed PMID: 14960254. Epub 2004/02/13. eng.
166. Dundar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, et al. Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2004 Jun;8(24):iii-x, 1-125. PubMed PMID: 15193209. Epub 2004/06/15. eng.
167. McClusky HY, Milby JB, Switzer PK, Williams V, Wooten V. Efficacy of behavioral versus triazolam treatment in persistent sleep-onset insomnia. Am J Psychiatry. 1991 Jan;148(1):121-6. PubMed PMID: 1888345. Epub 1991/01/01. eng.
168. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. Sleep. 2000 Mar 15;23(2):243-308. PubMed PMID: 10737342. Epub 2000/03/29. eng.
169. Canada. S. Canadian Community Health Survey: Mental Health and Well-Being. Statistics Canada. 2002.

170. Romanow RJ, & Marchildon, G. P. Psychological services and the future of health care in Canada. Canadian Psychology/Psychologie canadienne. 2003;44(4):15.
171. J. H. The cost-effectiveness of psychological interventions. Canadian Psychological Association;. 2002.
172. Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry. 2002 Jan;159(1):5-11. PubMed PMID: 11772681. Epub 2002/01/05. eng.
173. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. Cochrane Database Syst Rev. 2002 (2):CD003161. PubMed PMID: 12076472. Epub 2002/06/22. eng.
174. Perlis ML, Smith MT, Cacialli DO, Nowakowski S, Orff H. On the comparability of pharmacotherapy and behavior therapy for chronic insomnia. Commentary and implications. J Psychosom Res. 2003 Jan;54(1):51-9. PubMed PMID: 12505555. Epub 2002/12/31. eng.
175. Petit L, Azad N, Byszewski A, Sarazan FF, Power B. Non-pharmacological management of primary and secondary insomnia among older people: review of assessment tools and treatments. Age Ageing. 2003 Jan;32(1):19-25. PubMed PMID: 12540343. Epub 2003/01/24. eng.
176. Montplaisir J, Hawa R, Moller H, Morin C, Fortin M, Matte J, et al. Zopiclone and zaleplon vs benzodiazepines in the treatment of insomnia: Canadian consensus statement. Hum Psychopharmacol. 2003 Jan;18(1):29-38. PubMed PMID: 12532313. Epub 2003/01/18. eng.
177. Halme AS, Beland SG, Preville M, Tannenbaum C. Uncovering the source of new benzodiazepine prescriptions in community-dwelling older adults'. International journal of geriatric psychiatry. 2012 May 8. PubMed PMID: 22565497. Epub 2012/05/09. Eng.
178. Scott V, Wagar, L., & Elliott, S. Falls & Related Injuries among Older Canadians: Falls related Hospitalizations & Intervention Initiatives. Prepared on behalf of the Public Health Agency of Canada, Division of Aging and Seniors. 2010;Victoria BC: Victoria Scott Consulting.
179. http://www.statcan.gc.ca/start-debut-eng.html. Older adults aged 70 years and older, accessed on Dec. 15, 2012.
180. Morin CM, Benca R. Chronic insomnia. The Lancet. 2012;379(9821):1129-41.
181. Walter LC, Lui LY, Eng C, Covinsky KE. Risk of hip fracture in disabled community-living older adults. J Am Geriatr Soc. 2003 Jan;51(1):50-5. PubMed PMID: 12534845. Epub 2003/01/22. eng.
182. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Annals of epidemiology. 2003 Oct;13(9 Suppl):S107-21. PubMed PMID: 14575943. Epub 2003/10/25. eng.
183. McIntosh B CM, Spry C. Benzodiazepines in older adults: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). 2011.

184. Rothman K. Modern epidemiology. Wolters Kluwer Health/Lippincott Williams & Wilkins. 2008.
185. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. Lancet. 1999 Jan 9;353(9147):93-7. PubMed PMID: 10023893. Epub 1999/02/19. eng.
186. Woolcott JC, Khan KM, Mitrovic S, Anis AH, Marra CA. The cost of fall related presentations to the ED: a prospective, in-person, patient-tracking analysis of health resource utilization. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2012 May;23(5):1513-9. PubMed PMID: 21892675. Epub 2011/09/06. eng.
187. Kannus P, Sievanen H, Palvanen M, Jarvinen T, Parkkari J. Prevention of falls and consequent injuries in elderly people. Lancet. 2005 Nov 26;366(9500):1885-93. PubMed PMID: 16310556. Epub 2005/11/29. eng.
188. Wilson RT, Chase GA, Chrischilles EA, Wallace RB. Hip fracture risk among community-dwelling elderly people in the United States: a prospective study of physical, cognitive, and socioeconomic indicators. American journal of public health. 2006 Jul;96(7):1210-8. PubMed PMID: 16735617. Pubmed Central PMCID: 1483878. Epub 2006/06/01. eng.
189. Woolcott JC, Khan KM, Mitrovic S, Anis AH, Marra CA. The cost of fall related presentations to the ED: A prospective, in-person, patient-tracking analysis of health resource utilization. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011 Sep 3. PubMed PMID: 21892675. Epub 2011/09/06. Eng.
190. http://www.health.gov.bc.ca/pharmacare. Medication cost. Pharmacare. 2012.
191. http://www.psychologists.bc.ca/drupal/users. Psychologist cost, British Columbia. Accessed on Dec, 15, 2012. 2012.
192. Brogan I. Canadian Pharmaceutical Trends. 2010.
193. Board PMPR. Public Drug Plan Dispensing Fees: A Cost-Driver Analysis,. National Prescription Drug Utilization Information System. 2011.
194. Kannus P, Parkkari J, Koskinen S, Niemi S, Palvanen M, Jarvinen M, et al. Fall-induced injuries and deaths among older adults. JAMA. 1999 May 26;281(20):1895-9. PubMed PMID: 10349892. Epub 1999/06/01. eng.
195. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet. 1996 Jul 20;348(9021):145-9. PubMed PMID: 8684153. Epub 1996/07/20. eng.
196. Owens PL, Russo CA, Spector W, Mutter R. Emergency Department Visits for Injurious Falls among the Elderly, 2006: Statistical Brief #80. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville MD2006.
197. Samaras N, Chevalley T, Samaras D, Gold G. Older patients in the emergency department: a review. Annals of emergency medicine. 2010 Sep;56(3):261-9. PubMed PMID: 20619500. Epub 2010/07/14. eng.

198. Sanders AB. Changing clinical practice in geriatric emergency medicine. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 1999 Dec;6(12):1189-93. PubMed PMID: 10609919. Epub 1999/12/28. eng.
199. Rothman KS, G ; Lash, T. L. Modern Epidemiology. 3rd edn., Lippincott-Raven, U.S.A., 2008: Chapter 14, Page No. 248.
200. www.health.gov.bc.ca/pharmacare/lca/lca-price-r3.xls. Medication cost. Pharmacare, accessed on December 15, 2012. 2012.
201. http://canadianemployeebenefitplans.ca/wp-content/uploads/Average-Dispensing-Fees-June-Dec-2012.pdf. Dispensing fees for different provinces in Canada. Telus Health Care, accessed on Feb 18, 2013. 2012.
202. https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_2012_04_20_en.pdf. RAMQ - Liste des médicaments. Accessed on Dec,15 2012. 2012.
203. http://www.gov.mb.ca/health/mdbif/schedule.pdf. Mannitoba Health, Drug reimbursement cost. Accessed on Dec,15 2012. 2012.
204. http://www.health.gov.bc.ca/msp/infoprac/physbilling/payschedule/pdf/7-general-practice.pdf. Physcian reimbursement Accessed on Dec,15 2012. 2012.
205. http://www.gov.pe.ca/photos/original/doh_masteragree.pdf. Prince Edward Island Goverment, Master agreement between the medical society of PEI and the Government Accessed on Dec,18 2012. 2010.
206. http://www.hss.gov.yk.ca/pdf/physicianfeeguide.pdf. Physician reimbursement fees, Payment Schedule For Yukon - Health and Social Services ... Accessed on Dec18, 2012. 2011.
207. http://therapists.psychologytoday.com/rms/prof_detail.php. Psychologist association of New Brunswick, Psychologist fees per hour. Accessed on Dec,15 2012. 2012.
208. http://www.psychologistsassociation.ab.ca/. Psychologists' Association of Alberta, Fees per hour. Accessed on Dec,15 2012. 2012.
209. CIHI. Aggregate, Ward and ICU Per Diems cost by Number of Beds, by Province/Territory and Canada, 2009-10. 2010.
210. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161k-eng.htm. Consumer Price Index, 2012. Accessed on Feb, 15, 2013.
211. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making. Health technology assessment (Winchester, England). 2009 Jun;13(29):iii, ix-xi, 1-61. PubMed PMID: 19500484. Epub 2009/06/09. eng.
212. Frey DJ, Ortega JD, Wiseman C, Farley CT, Wright KP, Jr. Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial. J Am Geriatr Soc. 2011 Jan;59(1):73-81. PubMed PMID: 21226678. Epub 2011/01/14. eng.
213. Leger D, Morin CM, Uchiyama M, Hakimi Z, Cure S, Walsh JK. Chronic insomnia, quality-of-life, and utility scores: comparison with good sleepers in a cross-

sectional international survey. Sleep Med. 2012 Jan;13(1):43-51. PubMed PMID: 22093806. Epub 2011/11/19. eng.
214. Iglesias CP, Manca A, Torgerson DJ. The health-related quality of life and cost implications of falls in elderly women. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2009 Jun;20(6):869-78. PubMed PMID: 18846400. Epub 2008/10/11. eng.
215. Borgström F, Sobocki P, Ström O, Jönsson B. The societal burden of osteoporosis in Sweden. Bone. 2007;40(6):1602-9.
216. Morin CM, Benca R. Chronic insomnia. The Lancet. 2012.
217. Birks YF, Porthouse J, Addie C, Loughney K, Saxon L, Baverstock M, et al. Randomized controlled trial of hip protectors among women living in the community. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2004 Sep;15(9):701-6. PubMed PMID: 14997286. Epub 2004/03/05. eng.
218. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005 Apr 30;330(7498):1003. PubMed PMID: 15860827. Pubmed Central PMCID: 557150. Epub 2005/04/30. eng.
219. Porthouse J, Birks YF, Torgerson DJ, Cockayne S, Puffer S, Watt I. Risk factors for fracture in a UK population: a prospective cohort study. QJM : monthly journal of the Association of Physicians. 2004 Sep;97(9):569-74. PubMed PMID: 15317925. Epub 2004/08/20. eng.
220. Borgstrom F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2006;17(5):637-50. PubMed PMID: 16283064. Epub 2005/11/12. eng.
221. Canada S. The Canadian Population in 2011: Age and Sex. 2011.
222. Myhr G, Payne K. Cost-effectiveness of cognitive-behavioural therapy for mental disorders: implications for public health care funding policy in Canada. Can J Psychiatry. 2006 Sep;51(10):662-70. PubMed PMID: 17052034. Epub 2006/10/21. eng.
223. LeBlanc M, Merette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. Sleep. 2009 Aug;32(8):1027-37. PubMed PMID: 19725254. Pubmed Central PMCID: 2717193. Epub 2009/09/04. eng.
224. Beland SG, Preville M, Dubois MF, Lorrain D, Voyer P, Bosse C, et al. The association between length of benzodiazepine use and sleep quality in older population. International journal of geriatric psychiatry. 2011 Sep;26(9):908-15. PubMed PMID: 20963787. Epub 2010/10/22. eng.
225. Cook JM, Marshall R, Masci C, Coyne JC. Physicians' perspectives on prescribing benzodiazepines for older adults: a qualitative study. Journal of general internal medicine. 2007 Mar;22(3):303-7. PubMed PMID: 17356959. Pubmed Central PMCID: 1824720. Epub 2007/03/16. eng.

226. Tamblyn R, Eguale T, Buckeridge DL, Huang A, Hanley J, Reidel K, et al. The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from drug side effects: a cluster randomized trial. Journal of the American Medical Informatics Association : JAMIA. 2012 Jan 12. PubMed PMID: 22246963. Epub 2012/01/17. Eng.
227. Hoebert JM, Souverein PC, Mantel-Teeuwisse AK, Leufkens HG, van Dijk L. Reimbursement restriction and moderate decrease in benzodiazepine use in general practice. Annals of family medicine. 2012 Jan-Feb;10(1):42-9. PubMed PMID: 22230829. Pubmed Central PMCID: 3262472. Epub 2012/01/11. eng.
228. Briesacher BA, Soumerai SB, Field TS, Fouayzi H, Gurwitz JH. Medicare part D's exclusion of benzodiazepines and fracture risk in nursing homes. Arch Intern Med. 2010 Apr 26;170(8):693-8. PubMed PMID: 20421554. Pubmed Central PMCID: 2907144. Epub 2010/04/28. eng.
229. Baillargeon L, Landreville P, Verreault R, Beauchemin JP, Gregoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. CMAJ. 2003 Nov 11;169(10):1015-20. PubMed PMID: 14609970. Pubmed Central PMCID: 236226. Epub 2003/11/12. eng.