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Peer-Reviewed Summary with Critical Appraisal

CADTH

Benzodiazepines in Older Adults: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

January 2011

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CADTH
600-865 Carling Avenue
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Tel.: 613-226-2553
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Canadian Agency for Drugs and Technologies in Health

Benzodiazepines in Older Adults: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Brendan McIntosh, BSc, MSc[1]
Michelle Clark, BSc[1]
Carolyn Spry, BSc[1]

January 2011

[1] Canadian Agency for Drugs and Technologies in Health, Ottawa, ON

Health technology assessment agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision-makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by HTIS is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

Reviewers

These individuals kindly provided comments on this report:

External Reviewers

James L. Silvius, BA (Oxon), MD, FRCPC
Consulting Geriatrician
Alberta Health Services
Calgary, AB

Laurie Mallery, MC, FRCPC
Associate Professor
Dalhousie University
Halifax, NS

Carlo Marra, BSc(Pharm), PharmD, PhD
Associate Professor
University of British Columbia
Vancouver, BC

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Industry: The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Sepracor Pharmaceuticals Inc., Hoffmann-La Roche Ltd., and Pfizer Canada Inc. All comments that were received were considered when preparing the final report.

ACRONYMS AND ABBREVIATIONS

APA	American Psychiatric Association
BZD	benzodiazepine
BPSD	behavioural and psychological symptoms in dementia
CI	confidence interval
CrI	credible interval
IM	intramuscular
OR	odds ratio
RR	relative risk

TABLE OF CONTENTS

TITLE: Benzodiazepines in Older Adults: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

DATE: January 2011

EXECUTIVE SUMMARY

Context and Policy Issues

The use of benzodiazepines has been associated with several adverse effects including, ataxia, dizziness, over-sedation, anterograde amnesia, and dependence. The severity of adverse effects, particularly those associated with the central nervous system, may be greater in older adults. Therefore, close monitoring is typically recommended when benzodiazepines are used by older adults. In addition, several reviews and guidelines recommend that the use of long-acting benzodiazepines by older adults be avoided. High utilization by older adults and documented safety concerns indicate that a review of the evidence on the use of benzodiazepines by older adults is warranted.

Research Questions

1. What is the evidence on the safety of using benzodiazepines in older adults to manage disruptive behaviour or treat anxiety?
2. What is the effectiveness of benzodiazepines compared with that of antidepressants in older adults to manage disruptive behaviour or treat anxiety?
3. What is the cost-effectiveness of using benzodiazepines in older adults to manage disruptive behaviour or treat anxiety?
4. What are the clinical practice guidelines on the use of benzodiazepines in older adults?

Methods

Bibliographic databases were searched through the Ovid interface (MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews) with parallel searches in PubMed and The Cochrane Library (Issue 8, 2010). The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, s, economic studies, and guidelines. Grey literature was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases.

Two independent reviewers screened the titles and abstracts of the retrieved publications and independently evaluated the full-text publications for final article selection. Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials were eligible for inclusion in this report if they involved older adults (60 years or older), compared benzodiazepine use with non-benzodiazepine use (with or without a placebo) or with the use of antidepressants, and reported outcomes that were related to patient safety or clinical effectiveness. Evidence-based recommendations and clinical practice guidelines were included if they provided recommendations or guidance about the use of benzodiazepines by older adults. This report was peer-reviewed by clinical experts.

Summary of Findings

Six systematic reviews and meta-analyses addressed benzodiazepine use by older adults. No studies addressed the safety, comparative efficacy, and cost-effectiveness of using benzodiazepines in older adults to manage behaviour or treat anxiety. Nine evidence-based guidelines and recommendations addressed the use of benzodiazepines by older adults for dementia, mood and behavioural disorders, panic disorder, and sleep disorders.

The included systematic reviews and meta-analyses report that the use of benzodiazepines by older adults is associated with an increase in falls and fractures. However, the impact of using these drugs on cognitive decline and mortality is unclear. This increased risk of falls was similar to the risk observed with other drugs commonly used by older adults, including antidepressants, antihypertensives, diuretics, beta-blockers, sedatives, hypnotics, antipsychotics, and non-

steroidal antiinflammatory drugs. The evidence base for the reviews consisted of observational studies that were subject to a range of confounding factors, the exception being a review of insomnia treatments, which was derived from randomized controlled trials. No studies compared the safety and effectiveness of using benzodiazepines against the use of antidepressants in older adults treated for anxiety. The use of benzodiazepines and antidepressants was shown to be associated with an increased risk of falls and fractures that was similar in magnitude to that observed with other psychotropic medications, such as antipsychotics and sedatives or hypnotics. There were no analyses on the cost-effectiveness of using benzodiazepines in older adults.

All the clinical practice guidelines recommended that health care professionals be cautious when considering the use of a benzodiazepine in older patients. However, there was inconsistency in the messaging and recommendations about the place in therapy for these agents in the treatment of anxiety and behavioural symptoms associated with dementia. One guideline stated that benzodiazepines are not recommended because of their high potential for adverse effects. Another guideline stated that there was insufficient evidence to formulate a recommendation. The remaining guidelines recommended a limited role for benzodiazepines. A guideline on the treatment of panic disorder recommends that an antidepressant be used as first-line pharmacotherapy in geriatric patients and that benzodiazepine use be avoided whenever possible. The remaining recommendations in each guideline focused on issues that were related to safety in older adults, with most of the recommendations emphasizing that the adverse effects of using benzodiazepines generally seem to be worse in older adults.

Conclusions and Implications for Decision- or Policy-Making

The available evidence suggests that the use of benzodiazepines is associated with an increase in clinically important adverse events, such as falls and fractures in older adults. Large, well-designed trials that address the treatment of anxiety or behavioural problems in older adults would be needed to accurately assess the safety, clinical effectiveness, and cost-effectiveness of using benzodiazepines for those issues. However, given the potential risk that is associated with benzodiazepine use by older adults, the feasibility of such a study is questionable.

1 CONTEXT AND POLICY ISSUES

Benzodiazepines are compounds that enhance the activity of gamma-aminobutyric acid (GABA)-A receptors by increasing the affinity of the receptors for GABA.[1] Benzodiazepines are typically grouped, based on their pharmacokinetic properties, into three categories: short-acting, intermediate-acting, and long-acting (Table 1).[2] The basis for these groups is the differences in the half-life of parent compounds and active metabolites, which can range from one to four hours for short-acting to 100 hours for long-acting.[2] These differences are a key consideration when health care professionals select a benzodiazepine for use by patients. For example, short-acting agents are preferable for the treatment of insomnia, and intermediate-acting or long-acting agents are preferable for the treatment of anxiety disorders.[2] Overall, the labelled indications include, the treatment of anxiety disorders, panic disorder, insomnia, seizure disorders, skeletal muscle spasticity, and alcohol withdrawal.[2]

Benzodiazepines have been associated with several adverse effects, including ataxia, dizziness, over-sedation, anterograde amnesia, and dependence.[2] The severity of adverse effects, particularly those associated with the central nervous system, may be greater in older adults. Therefore, close monitoring is typically recommended when benzodiazepines are used by older adults.[2] In addition, several reviews and guidelines recommend that long-acting benzodiazepines be avoided by older adults.[3-5]

In 2005, Mamdani et al. estimated that in Ontario, the prevalence of benzodiazepine use by adults older than 65 years was 15%.[6] Despite a downward trend in use, benzodiazepines remained the most highly prescribed mental-health related drug in this population from 1996 to 2002.[6] Based on the high use of the drug and the documented safety concerns for older adults, a review of the evidence is warranted.

2 RESEARCH QUESTIONS

1. What is the evidence on the safety of using benzodiazepines in older adults to manage disruptive behaviour or treat anxiety?
2. What is the effectiveness of benzodiazepines compared with that of antidepressants in older adults to manage disruptive behaviour or treat anxiety?
3. What is the cost-effectiveness of using benzodiazepines in older adults to manage disruptive behaviour or treat anxiety?
4. What are the clinical practice guidelines on the use of benzodiazepines by older adults?

Table 1: Pharmacokinetic Classification of Benzodiazepines Available in Canada[2]

Long-acting	Intermediate-acting	Short-acting
Chlordiazepoxide	Alprazolam	Midazolam
Clorazepate	Bromazepam	Triazolam
Diazepam	Clobazam	
Flurazepam	Clonazepam	
	Lorazepam	
	Nitrazepam	
	Oxazepam	
	Temazepam	

3 METHODS

3.1 Literature search

Peer-reviewed literature searches were conducted to obtain published literature for this review. All search strategies were developed by an Information Specialist with input from the project team. The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, and BIOSIS Previews. Parallel searches were run in PubMed and The Cochrane Library (Issue 8, 2010). The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic studies, and guidelines. See Appendix 1 for detailed search strategies.

The search was restricted to English language clinical articles that were published between January 1, 2005 and August 24, 2010. Regular alerts were established on MEDLINE, Embase, and BIOSIS, and the information that was retrieved through alerts was current to October 4, 2010.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional information. These searches were supplemented by handsearching the bibliographies and abstracts of key papers, and through contacts with appropriate experts and agencies.

Rapid reviews are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, economic evaluations, and evidence-based guidelines.

3.2 Article selection

Two independent reviewers (BM and MC) screened the titles and abstracts of the retrieved publications and independently evaluated the full-text publications for final article selection. Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials were eligible for inclusion if they involved adults who were 60 years or older, compared benzodiazepine use with non-benzodiazepine use (with or without a placebo) or with antidepressants, and reported outcomes related to patient safety or clinical effectiveness. Studies involving healthy volunteers were excluded. Evidence-based recommendations and clinical practice guidelines were included if they provided recommendations or guidance about the use of benzodiazepines by older adults. Appendix 2 details the eligibility criteria.

This report was peer-reviewed by clinical experts.

4 SUMMARY OF FINDINGS

No studies directly addressed any of the research questions on the safety, comparative efficacy, and cost-effectiveness of using benzodiazepines in older adults to manage disruptive behaviour or treat anxiety. The literature search identified a total of 596 citations, and 15 publications were included in this report (Appendix 3). Six relevant systematic reviews addressed the association between benzodiazepine use in older adults and falls,[7,8] cognitive decline,[9] fractures,[10] cognitive and psychomotor adverse events,[11] and mortality.[12] Nine evidence-based guidelines and recommendations addressed the use of benzodiazepines by older adults for dementia,[13-16] mood and behavioural disorders,[17] panic disorder,[18] and sleep disorders.[19-21]

4.1 Systematic reviews and meta-analyses

4.1.1 Risk of falls

In 2009, Woolcott et al.[7] conducted a systematic review and meta-analysis to evaluate the impact of nine classes of medication on the risk of falls in older adults. The drugs that were investigated included benzodiazepines, antidepressants, antihypertensives, diuretics, beta-blockers, sedatives/hypnotics, neuroleptics/antipsychotics, narcotic analgesics, and non-steroidal antiinflammatory agents. The report was an update of three previously published reviews: two meta-analyses by Leipzig et al. (1999)[22,23] and a systematic review by Hartikainen et al. (2007).[8] References were obtained from the three reviews and a literature update was done to obtain additional studies. The updated search involved multiple databases. Many of the studies that were identified by Hartikainen et al.[8] could not be included in the meta-analysis because the data were presented in a format that did not allow for pooling. Patient and trial characteristics were documented in the report. A risk of bias assessment was done in duplicate using an appropriate method for randomized and non-randomized studies (Downs and Black checklist[24]). The results of the risk of bias assessment were not presented, and it was not stated to what extent these results were considered in the review's analysis and conclusions. Additional limitations with this review were the exclusion of non-English language publications, uncertainty about the use of duplicate reviewers for study selection and data extraction, and a lack of formal assessment of statistical heterogeneity. The population of interest for this review was patients older than 60 years. The authors did not report the inclusion criteria that were used in each primary study. However, the mean age of participants was older than 65 years in all studies.

The meta-analysis included 11 non-randomized studies reporting the effects of benzodiazepines (four cross-sectional, two case-control, and five cohort). The pooled estimate of effect for these studies showed a statistically significant increase in the risk of falls among patients taking benzodiazepines (odds ratio [OR] 1.57; 95% credible interval [CrI] 1.43 to 1.72). The review included nine non-randomized studies reporting the effects of antidepressants (four cross-sectional, three case-control, and two cohort) and the pooled estimate of effect was statistically significant (OR 1.68; 95% CrI 1.47 to 1.91). The risk of falls after the use of benzodiazepines and antidepressants was similar to that reported for antipsychotics and sedatives/hypnotics (Table 2). The results from the Bayesian meta-analysis were compared with those obtained using a frequentist approach and were similar in direction and magnitude. Overall, the authors concluded that the use of psychotropic medications is associated with a statistically significant increase in falls among older adults.

Table 2: Risk of Falls in Older Adults Using Nine Drug Classes, from Woolcott et al.[7]

Drug Class	Bayesian OR (95% CrI)	Number of studies
Benzodiazepines	1.57 (1.43 to 1.72)	11
Antidepressants	1.68 (1.47 to 1.91)	9
Antihypertensives	1.24 (1.01 to 1.50)	6
Diuretics	1.07 (1.01 to 1.14)	9
Beta-blockers	1.01 (0.86 to 1.17)	4
Sedatives/hypnotics*	1.47 (1.35 to 1.62)	7
Neuroleptics/antipsychotics	1.59 (1.37 to 1.83)	4
Narcotic analgesics	0.96 (0.78 to 1.18)	4
Non-steroidal antiinflammatory drugs	1.21 (1.01 to 1.44)	4

CI = confidence interval; CrI = credible interval; OR = odds ratio.
*The authors defined this as benzodiazepines, barbiturates, chloral hydrate, or hydroxyzine.

In 2007, Hartikainen et al.[8] conducted a systematic review to assess the association between medication use and the risk of falls in older adults. Limitations with the reporting of this systematic review include a failure to provide the eligibility criteria for including studies, methods for study selection and data extraction, and instruments and methods for risk of bias assessment. The authors specified that the population of interest was adults older than 60 years. Four of 29 included studies had a population younger than 65 years.

Seventeen studies reported an association between benzodiazepines and fall or fall-related fractures, and three studies reported no association. Fourteen of these studies included patients who were 65 years or older, and three included patients who were at least 60 years of age. The authors noted that the risk of falls was increased after a new prescription and with long-term use, and was independent of the product's half-life (for example, long-acting versus short-acting). Twelve studies reported an association between the use of antidepressants and the risk of falling, and five studies found no association. The authors concluded that the use of psychotropic drugs seems to be associated with an increased risk of falling. However, they noted that the available evidence was often low quality and inconsistent.

4.1.2 Risk of cognitive decline

In 2005, Verdoux et al.[9] conducted a systematic review to investigate if an exposure to benzodiazepines is associated with an increased risk of cognitive decline. Primary studies were selected for inclusion if they met the following criteria: published in English in a peer-reviewed journal; involved participants who were recruited from the general population; the length of follow-up was at least one year in duration; documented benzodiazepine use at baseline and follow-up; standardized cognitive assessment at baseline and follow-up; and the association between benzodiazepine use and change in cognitive performance explored. There are several methodological limitations with this review: the literature review was conducted in one database (MEDLINE from 1966 up to April 2004), there was a failure to fully report the methods that were used for study selection and data extraction, there was no mention of a formal risk of bias assessment, and non-English language publications were excluded.

The review included six prospective cohort studies involving patients older than 60 years. All studies compared current or former users of benzodiazepines with non-users. Overall, the results of the individual studies were inconsistent with two studies reporting that benzodiazepines were associated with less risk of cognitive decline, two studies reporting no statistically significant association, and three studies reporting an increased risk of cognitive decline. Furthermore, the studies that reported a statistically significant increase in cognitive decline differed in the at-risk populations (new, chronic, or former users). The authors stated that the discrepancies in these findings prevent conclusions from being made about the direction and magnitude of a potential association between benzodiazepine use and cognitive decline.

The inconsistent findings may be due to the heterogeneity in study design. The studies varied in sample size (range of 242 patients to 3,309 patients), length of follow-up (range of two years to six years), adjustment of confounding factors, and methods for outcome assessment (for example, Short Portable Mental Status Questionnaire or categorical diagnosis of dementia by a physician). The authors noted that selection bias may be present in the included studies because all failed to provide details about the proportion of individuals who refused to participate. This could favour the inclusion of patients who had less exposure to benzodiazepine use and less cognitive decline, or less exposure to benzodiazepine use or less cognitive decline, thereby underestimating the strength of association between the drug and the primary outcome. Well-designed studies are needed to accurately assess the impact of benzodiazepine use on cognitive decline in older adults.

4.1.3 Risk of fractures

In 2007, Takkouche et al.[10] conducted a systematic review and meta-analysis to assess the risk of fractures among users of psychotropic drugs. The drug classes that were included in the review were benzodiazepines, antidepressants, non-barbiturate antiepileptic drugs, barbiturate antiepileptic drugs, antipsychotics, hypnotics, and opioids. The literature search involved many databases and was conducted without language restriction. Published studies were included if they met the following criteria: original data were presented from case-control or cohort studies, the outcome of interest was defined as fracture (falls not followed by fractures were not included), the exposure of interest was a psychotropic medication, and relative risk (RR) estimates with confidence intervals (CIs) were provided or enough data were provided to calculate them. Studies that did not provide adjusted or crude data of RR and cross-sectional studies were excluded. The study selection was performed independently by two reviewers. An appropriate instrument was used to assess the risk of bias of each included study; however, it was unclear if this was done by multiple independent reviewers. Publication bias was assessed using appropriate methods (examination of funnel plots and Egger's et al.'s regression test[25]).

This review did not specify an age threshold in the eligibility criteria and included studies regardless of patient age. There were 23 studies that investigated the association between benzodiazepine use and the risk of fractures, including 16 case-control studies and seven cohort studies. Fourteen studies specified that patients had to be older than 65 years, two involved patients at least 60 years of age, one included patients at least 55 years, and six did not provide an age threshold for inclusion. In comparison with non-users, the RR for fractures in benzodiazepine users was 1.34 (95% CI 1.24 to 1.45) based on random effects meta-analysis. These results were similar when the analysis was stratified according to the risk of bias assessment, study design, setting, and use of short-acting or long-acting agents. Drugs from the benzodiazepine class in the reference case meta-analyses included those with different pharmacokinetic properties. This was reflected in the high statistical heterogeneity (Ri 0.57, P = 0.00001) for the reference case, which was reduced when the trials were stratified according to short-acting (Ri 0.3, P = 0.23) and long-acting agents (Ri 0.3, P = 0.19).

Fifteen studies examined the association between the use of antidepressants and the risk of fracture. Pooling showed a statistically significant increase in fracture risk with antidepressant use relative to non-use (RR 1.60; 95% CI 1.38 to 1.86]. This finding was consistent when the data were stratified by study design, setting (hospital or general population), or type of antidepressant. The authors reported that there was no evidence of publication bias for the benzodiazepines and for the antidepressants. The results of these meta-analyses appear in Appendix 4. The authors concluded that the use of psychotropic medications may be associated with the development of fractures and that larger prospective studies could be designed to provide a more accurate assessment of this clinically important outcome.

4.1.4 Risk of Mortality

In 2009, Charlson et al.[12] conducted a systematic review examining the association between benzodiazepine use and mortality. The literature search involved many databases. A formal risk of bias assessment was conducted using a comprehensive checklist. There are several methodological limitations with this review, including the failure to provide a clear description of eligibility criteria, failure to fully report the methods that were used for study selection and data extraction, and the exclusion of non-English language publications.

The authors identified one population-based survey and three cohort studies that assessed the risk of mortality in older adults (Table 3). The three cohort studies reported that there was no statistically significant association between the use of benzodiazepines and an increase in all-cause mortality among older adults. One study also assessed the risk of fracture-related

mortality and reported a RR of 2.71 (95% CI 0.37 to 19.76) for benzodiazepine use compared with no use. The population-based study provided a comparison of the risk of mortality related to benzodiazepine poisoning in patients at least 60 years of age with those younger than 60 years. The authors reported a statistically significant increased risk of mortality in patients who are older than 60 years (RR 7.1 [95% CI 3.2 to 15.5]). The number of events in each study was not reported. Therefore, the non-statistically significant findings may be due to inadequate statistical power. Given the observational study designs and the large number of unadjusted confounders, the authors concluded that there are insufficient data to accurately assess the relationship between benzodiazepine use and mortality.

4.1.5 Risk of adverse events in the treatment of insomnia

In 2005, Glass et al.[11] conducted a systematic review and meta-analysis to evaluate the risks and benefits of using sedative hypnotics for the treatment of insomnia in older adults. Active and placebo-controlled randomized studies were eligible for inclusion if they met the following criteria: published in English; mean age of participants was at least 60 years; investigated the use of a sedative hypnotic given for at least five consecutive nights; included a washout period after previous drug treatments; and excluded patients with psychiatric disorders, concurrent use of drugs affecting the central nervous system, and severe or acute physical illnesses that could disrupt sleep. Studies of barbiturates and chloral hydrate were excluded. The literature search involved many databases. Study-level risk of bias was assessed using an appropriate method (Jadad scale[26]). However, it is unclear if these findings were used in the meta-analysis. Study selection, data extraction, and risk of bias assessment were conducted independently in duplicate or triplicate. Publication bias was assessed using examination of funnel plots and Egger's regression test.[25] The methods that were used to pool data were appropriate and well reported. However, studies were pooled at the drug class level. Therefore, the benzodiazepine group consisted of short-acting agents (triazolam, midazolam, brotizolam, lormetazepam, loprazolam), intermediate-acting agents (nitrazepam, temazepam, flunitrazepam), and long-acting agents (flurazepam and quazepam).

Table 3: Risk of Mortality Among Patients Taking Benzodiazepines, Charlson et al.[12]

Author	Year	Sample Size	Age	Summary of Results
Vinkers	2003	599	> 85 years	• All-cause mortality* RR 0.68 (95% CI 0.44 to 1.04) • Fracture-related mortality† RR 2.71 (95% CI 0.37 to 19.76)
Hogan	2003	2,914	> 65 years	• All-cause mortality Users (54.8%) versus non-users (53.2%); P = 0.48
Rumble	1992	1,042	≥ 65 years	• Mortality of hypnotic users* OR 1.20 (95% CI 0.83 to 1.73)
Rogers	2007	72,694	> 20 years	• Acute poisoning mortality† (≥ 60 years versus < 60 years) RR 7.1 (95% CI 3.2 to 15.5)

CI = confidence interval; OR = odds ratio; RR = relative risk.
*Adjusted.
†Unadjusted.

Overall, this is a well-conducted meta-analysis with a low risk of bias.[27] However, this study has limited applicability to the research questions because the trials focused on the short-term treatment of insomnia as opposed to the treatment of anxiety, the primary outcomes for clinical efficacy in this review are related to sleep (quality of sleep, amount of sleep, and number of awakenings), and the primary meta-analyses were done by pooling data for all sedative hypnotics (benzodiazepines, benzodiazepine-receptor agonists, and an antihistamine). Despite this apparent indirectness,[28] there is potentially useful information about the adverse events observed with the short-term use of benzodiazepines and similar sedative hypnotics (Table 4).
Of the 24 randomized controlled trials that were included in the review, 21 included a benzodiazepine treatment group. Sedative hypnotics were associated with more cognitive, psychomotor, and overall adverse events compared with placebo. There were no statistically significant differences between benzodiazepines and benzodiazepine-receptor agonists (zopiclone, zolpidem, and zaleplon). The authors concluded that the benefits associated with sedative use are marginal and outweighed by the risks, especially if patients are considered to be at a higher risk for falls or cognitive impairment.

4.2 Guidelines and Recommendations

Nine evidence-based guidelines and recommendations addressed the use of benzodiazepines by older adults for dementia,[13-16] mood and behavioural disorders,[17] panic disorder,[18] and sleep disorders[19-21] (Appendix 5). The recommendations in each guideline focus on patient safety and the potential adverse effects of these drugs in older adults. Two guidelines[19,20] caution that the adverse effects of benzodiazepines generally seem to be worse in older adults. One of these guidelines recommends that dosages be reduced for older adults and that short- or intermediate-acting agents are preferable. This is consistent with the product monographs for these agents.[2]

Dementia, particularly Alzheimer disease and vascular dementia, can be associated with behavioural and psychological symptoms, including depression, agitation, psychosis, wandering, aggression, and incontinence. The Social Care Institute for Excellence and the National Institute for Health and Clinical Excellence have published a guideline on the treatment and diagnosis of dementia that addresses the use of benzodiazepines by these patients.[14] The guideline was developed with an objective of providing advice on supporting people with dementia and their care givers in health and social care. This guideline was developed using a rigorous methodology in accordance with the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria.[29] The guideline offers recommendations on training and competencies for health care professionals prescribing medications for the management of disruptive behaviour in people with dementia. The guideline noted that for patients with Alzheimer disease or vascular dementia and clinically significant agitation, there is moderate-quality evidence suggesting that benzodiazepines administered through intramuscular injection may have beneficial effects in reducing psychotic symptoms and aggression or agitation that outweigh the risk of adverse events. The Scottish Intercollegiate Guidelines Network's (SIGN) guideline for the management of patients with dementia[15] was developed using rigorous methods. The guideline states that no systematic reviews or randomized controlled trials examined the use of benzodiazepines in the management of dementia symptoms.

Table 4: Adverse Events for Benzodiazepines in the Treatment of Insomnia[11]			
Outcome	**Number of Studies (n)**	**Comparison**	**Results (95% CI)**
All adverse events	16 (2,220)	Sedative hypnotics versus placebo	NNH: 6 (4.7 to 7.1)
Cognitive effects	10 (712)	Sedative hypnotics versus placebo	OR: 4.8 (1.5 to 15.5)
Psychomotor effects	13 (1,016)	Sedative hypnotics versus placebo	OR: 2.3 (0.9 to 5.4)
Daytime fatigue	7 (829)	Sedative hypnotics versus placebo	OR: 3.8 (1.9 to 7.8)
All adverse events	6 (648)	BzRA versus benzodiazepines	OR: 1.1 (0.6 to 2.8)
Cognitive effects	4 (268)	BzRA versus benzodiazepines	OR: 1.1 (0.2 to 7.8)
Psychomotor effects	6 (625)	BzRA versus benzodiazepines	OR: 1.5 (0.8 to 2.9)

BzRA = benzodiazepine receptor agonist; CI = confidence interval; NNH = number needed to harm; OR = odds ratio.

The search identified two guidelines from Canadian organizations that were developed with rigorous methodology. The Canadian Coalition for Seniors' Mental Health published guidelines addressing the assessment and treatment of mental health issues in long-term care with a focus on managing mood and behavioural symptoms.[17] The guideline recommends that health care professionals weigh the potential benefits of pharmacologic intervention against the potential for harm. Short- or intermediate-acting benzodiazepines are noted as a therapeutic option for the treatment of long-term care residents with severe behavioural symptoms. The Guidelines and Protocols Advisory Committee in British Columbia prepared guidance on the recognition, diagnosis, and management of cognitive impairment in the elderly.[13] The guideline addresses interventions for the behavioural and psychological symptoms of dementia and states that benzodiazepines are not recommended because of their high potential for adverse events such as confusion and falls.

Two relevant guidelines were published by the American Psychiatric Association (APA).[16,18] Both were developed using a rigorous methodology, based on the criteria of the Appraisal of Guidelines for Research and Evaluation instrument.[29] One guideline focused on the treatment of patients with dementias.[16] In the section about the treatment of psychosis and agitation, the following advice is provided:

> "Data demonstrating benefit from BZDs are modest, but BZDs occasionally have a role in treating patients with prominent anxiety [III] or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure such as a tooth extraction or a diagnostic examination [II]. Adverse effects of BZDs include sedation, worsening cognition, delirium, increased risk of falls, and worsening of breathing disorders. Lorazepam and oxazepam, which have no active metabolites, are preferable to agents with a longer half-life such as diazepam or clonazepam [III]." (p 13)[16]

The second guideline focuses on the treatment of patients with panic disorder. This guideline advises that an antidepressant is the recommended first-line pharmacotherapy for geriatric patients with panic disorder, citing co-occurring mood disorders as the primary reason. Furthermore, the APA recommends that benzodiazepine use be avoided whenever possible, indicating that the use of long half-life benzodiazepines and long-term use in general can be problematic in older adults. If a benzodiazepine is used, the APA notes that these

patients may be at a higher risk for falls and fractures and that monitoring is needed.

The National Institutes of Health in the United States published a State-of-the-Science Conference Statement on the manifestations and management of chronic insomnia in adults.[20] This statement was prepared using a rigorous method that involved a systematic review. However, this document offers little information about the use of benzodiazepines by older adults other than noting that adverse effects seem to be worse in the elderly. The American Medical Directors Association[19] released a guideline addressing the treatment of sleep disorders in long-term care. The guideline recommends that the continuous use of benzodiazepines be discouraged because of the risk of side effects, physiological tolerance, and adverse effects upon discontinuation. Neither the age range to which the recommendation applies nor the level of evidence was provided in support of the statement. In 2007, Montgomery and Lilly[21] prepared a systematic review and offer clinical guidance about the treatment of insomnia in patients 65 years age and older. The review was prepared in accordance with the BMJ's Clinical Evidence method.[30] The authors concluded that the use of benzodiazepines may improve sleep outcomes, but are likely to cause adverse events in patients 65 years and older.

4.3 Limitations

Six systematic reviews and meta-analyses addressed the association between benzodiazepine use in older adults and falls,[7,8] cognitive decline,[9] fractures,[10] cognitive and psychomotor adverse events,[11] and mortality.[12] However, no studies addressed the research questions about the safety, comparative efficacy, and cost-effectiveness of using benzodiazepines in older adults to manage disruptive behaviour or treat anxiety.

A limitation of the available evidence is the lack of clarity and consistency in defining older adults. Hartikainen et al.,[8] Woolcott et al.,[7] Verdoux et al. ,[9] and Glass et al.[11] all specified that the population of interest was patients older than 60 years of age. The World Health Organization notes that most developed countries considered a cut-off age of 65 years when defining an elderly or older person. The United Nations' cut-off age is 60 years.[31] The studies in this review did not provide justifications for selecting 60 years of age as an appropriate threshold. Takkouche et al.[10] did not specify an age threshold in their eligibility criteria and included studies regardless of patient age. Most of the studies (70%) that were included in the review by Takkouche et al.[10] involved patients older than 60 years. However, there is uncertainty about the population in the remaining studies. This could limit the generalizability of the findings to a population entirely comprised of older adults. No studies addressed the potential for withdrawal, abuse, and addiction in older adults using benzodiazepines.

The included reviews did not provide the indication for benzodiazepine use in the patient populations. Therefore, the quality of evidence in this rapid review is limited by a lack of direct relevance to the population of interest for this review (i.e., older adults with anxiety, behavioural problems, and/or depression). In addition, there were no economic evaluations of the use of benzodiazpines in older adults. In 2005, Mamdani et al.[6] speculated that, although benzodiazpines are inexpensive, they may carry an additional hidden cost in the increased health care resources that are used to treat adverse events. Given the increased adverse events reported in the systematic reviews and the high prevalence of benzodiazepine use in older adults, formal economic evaluations of each indication would be beneficial.

The evidence base for the systematic reviews consisted almost entirely of observational studies. Most studies made statistical adjustments for a range of potential confounding factors. However, the dosage of benzodiazepines was not addressed in the meta-analyses because of a lack of reporting in the primary studies.[7,10] Confounding by indication may have occurred because patients who were prescribed benzodiazepines may have underlying symptoms (for example, anxiety or agitation) that carry an increased risk of falls.[10] Benzodiazepines in the meta-analyses included

those with different pharmacokinetic characteristics (short-, intermediate-, and long-acting). This was noted as a source of statistical heterogeneity in one report. However, a subgroup analysis that stratified results according to benzodiazepine properties showed that the risk of fractures was similar in each group.[10] The lack of consistency about the definitions of benzodiazepine users and non-users could affect the events rates for either comparator.[12]

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Six systematic reviews and meta-analyses addressed benzodiazepine use in older adults. No studies addressed the safety, comparative efficacy, and cost-effectiveness of using benzodiazepines in older adults to manage behaviour or treat anxiety. The included systematic reviews and meta-analyses report that benzodiazepine use by older adults is associated with an increase in falls and fractures. However, the impact of these drugs on cognitive decline and mortality is unclear. This increased risk of falls was similar to the risk that was observed with other drugs commonly used in older adults, including antidepressants, antihypertensives, diuretics, beta-blockers, sedatives, hypnotics, antipsychotics, and non-steroidal antiinflammatory drugs. Most of the systematic reviews had inclusion criteria that focused on the occurrence of outcomes related to safety in older adults. The review that focused on the treatment of insomnia was the only one with a clear and consistent reason for benzodiazepine use. Furthermore, the evidence base for the reviews consisted of observational studies and was subject to a range of confounding factors, the exception being the review of insomnia treatments, which was derived from randomized controlled trials. No studies directly compared the safety and effectiveness of benzodiazepines against antidepressants in older adults who were treated for anxiety. The use of benzodiazepines and antidepressants was shown to lead to an increased risk of falls and fractures that was similar in magnitude to that observed with other psychotropic medications such as antipsychotics and sedatives/hypnotics. This increase in clinically important adverse events could consume additional health care resources. However, this rapid review was unable to identify any formal analyses about the cost-effectiveness of using benzodiazepines in older adults. A high-quality economic evaluation based on robust clinical data would be beneficial and would help ascertain if benzodiazepine use by older adults has significant budgetary implications in Canada.

All the included clinical practice guidelines recommended that health care professionals use caution when considering the use of a benzodiazepine in older patients. However, there was a lack of consistency in the messaging and recommendations on the place in therapy for these agents in the treatment of anxiety and behavioural symptoms associated with dementia. One stated that benzodiazepines are not recommended because of their high potential for adverse effects,[13] another indicated that there was insufficient evidence to formulate a recommendation, and the remaining guidelines recommended a limited role for benzodiazepines.[14,16,17] The guideline for the treatment of panic disorder recommends that an antidepressant be used as first-line pharmacotherapy in geriatric patients and that benzodiazepine use be avoided whenever possible. The remaining recommendations in each guideline focused on issues related to safety in older adults, with most guidelines emphasizing that the adverse effects of benzodiazepines generally seem to be worse in older adults.[2]

The available evidence suggests that benzodiazepines are associated with an increase in clinically important adverse events such as falls and fractures. Large, well-designed trials that address the treatment of older adults with anxiety would be needed to accurately assess the safety, clinical effectiveness, and cost-effectiveness of using benzodiazepines for these indications. However, given the potential risk

that is associated with benzodiazepine use in older adults, the feasibility of such a study is questionable.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	BIOSIS Previews <1989 to 2010 Week 36> EMBASE <1996 to 2010 Week 32> Ovid MEDLINE <1950 to Present (24 Aug 2010)> Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 24, 2010
Alerts:	Monthly search updates began August 24, 2010 and ran until October 4, 2010.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; economic studies; guidelines.
Limits:	Publication years January 1, 2005 – August 24, 2010, English language
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.mp.	Mapped Word
.jw.	Journal Word
.md.	Methodology field
.pt	Publication type
.rn	CAS registry number
use prmz	Select MEDLINE results
use emef	Select EMBASE results
use b10o89	Select BIOSIS results

MULTI-DATABASE STRATEGY	
Line #	Search Strategy
1	exp Benzodiazepines/ or (benzodiazepine* or Alprazolam or Bromazepam or Chlordiazepoxide or Clobazam or Clonazepam or Clorazepate or Diazepam or Flurazepam or Lorazepam or Midazolam or Nitrazepam or Oxazepam or Temazepam or Triazolam or ativan or xanax or lectopam or rivotril or valium or anexate or dalmane or mogadon or restoril or librax or nitrazadon or diazemuls or BZD).ti,ab. or (12794-10-4 or 28981-97-7 or 1812-30-2 or 58-25-3 or 58-25-3 or 22316-47-8 or 1622-61-3 or 57109-90-7 or 439-14-5 or 17617-23-1 or 846-49-1 or 59467-70-8 or 146-22-5 or 604-75-1 or 846-50-4 or 28911-01-5).rn.
2	*benzodiazepine/ or *bromazepam/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *clorazepate dipotassium/ or *diazepam/ or *flurazepam/ or *lorazepam/ or *nitrazepam/ or *oxazepam/ or *temazepam/
3	exp Aged/ or geriatrics/ or (elderly or elder or elders or aging or older adult* or older people or older patient* or older person* or older women or older men or older individual* or geriatric* or gerontology or senior citizen or senior citizens or seniors or septuagenarian* or octogenarian* or nonagenarian*).ti,ab.
4	(elderly or elder or elders or aging or older adult* or older people or older patient* or older person* or older women or older men or older individual* or geriatric* or senior citizen or senior citizens or seniors or septuagenarian* or octogenarian* or nonagenarian*).ti,ab.
5	1 and 3
6	limit 5 to english language
7	limit 6 to yr="2005 -Current"
8	7 use prmz
9	1 and 4
10	9
11	limit 10 to english language
12	limit 11 to yr="2005 -Current"
13	[12 use b10o89]
14	2 and 3
15	limit 14 to english language
16	limit 15 to yr="2005 -Current"
17	[16 use emef]
18	8 or 13 or 17
19	remove duplicates from 18
	Systematic review / health technology assessment / meta-analysis filter
20	meta-analysis.pt.
21	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
23	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or

MULTI-DATABASE STRATEGY	
	overview*)) or (pool* adj3 analy*)).ti,ab.
25	(data synthes* or data extraction* or data abstraction*).ti,ab.
26	(handsearch* or hand search*).ti,ab.
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
28	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
29	(meta regression* or metaregression* or mega regression*).ti,ab.
30	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
31	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
32	(cochrane or health technology assessment or evidence report).jw.
33	(meta-analysis or systematic review).md.
34	or/20-33
	Economic filter
35	*Economics/
36	exp "Costs and Cost Analysis"/
37	(sensitivity analysis or sensitivity analyses).ti,ab.
38	(cost or costs or costing or cost-effective$).ti,ab.
39	or/35-38
	Guideline filter
40	exp clinical pathway/
41	exp clinical protocol/
42	exp consensus/
43	exp consensus development conference/
44	exp consensus development conferences as topic/
45	critical pathways/
46	exp guideline/
47	guidelines as topic/
48	exp practice guideline/
49	practice guidelines as topic/
50	health planning guidelines/
51	exp treatment guidelines/
52	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
53	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab.
54	(standards or guideline or guidelines).ti.
55	((practice or treatment*) adj guideline*).ab.
56	(CPG or CPGs).ti.
57	consensus*.ti.
58	consensus*.ab. /freq=2
59	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab.

MULTI-DATABASE STRATEGY	
60	recommendat*.ti.
61	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab.
62	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab.
63	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab.
64	or/40-63
	Randomized controlled trial filter
65	Randomized Controlled Trial.pt.
66	Randomized Controlled Trials as Topic/
67	Randomized Controlled Trial/
68	Randomization/
69	Random Allocation/
70	Double-Blind Method/
71	Double Blind Procedure/
72	Double-Blind Studies/
73	Single-Blind Method/
74	Single Blind Procedure/
75	Single-Blind Studies/
76	Placebos/
77	Placebo/
78	(random* or sham or placebo*).ti,ab,hw.
79	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
80	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
81	or/65-80
82	19 and (34 or 39 or 64 or 81)

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
The Cochrane Library Issue 8, 2010	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	August 16, 2010 – August 26, 2010
Keywords:	benzodiazepine, elderly, drug names for benzodiazepines produced by Canadian manufacturers
Limits:	Publication years January 1, 2005 – August 26, 2010

The following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/index.php/en/cadth/products/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economic
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals

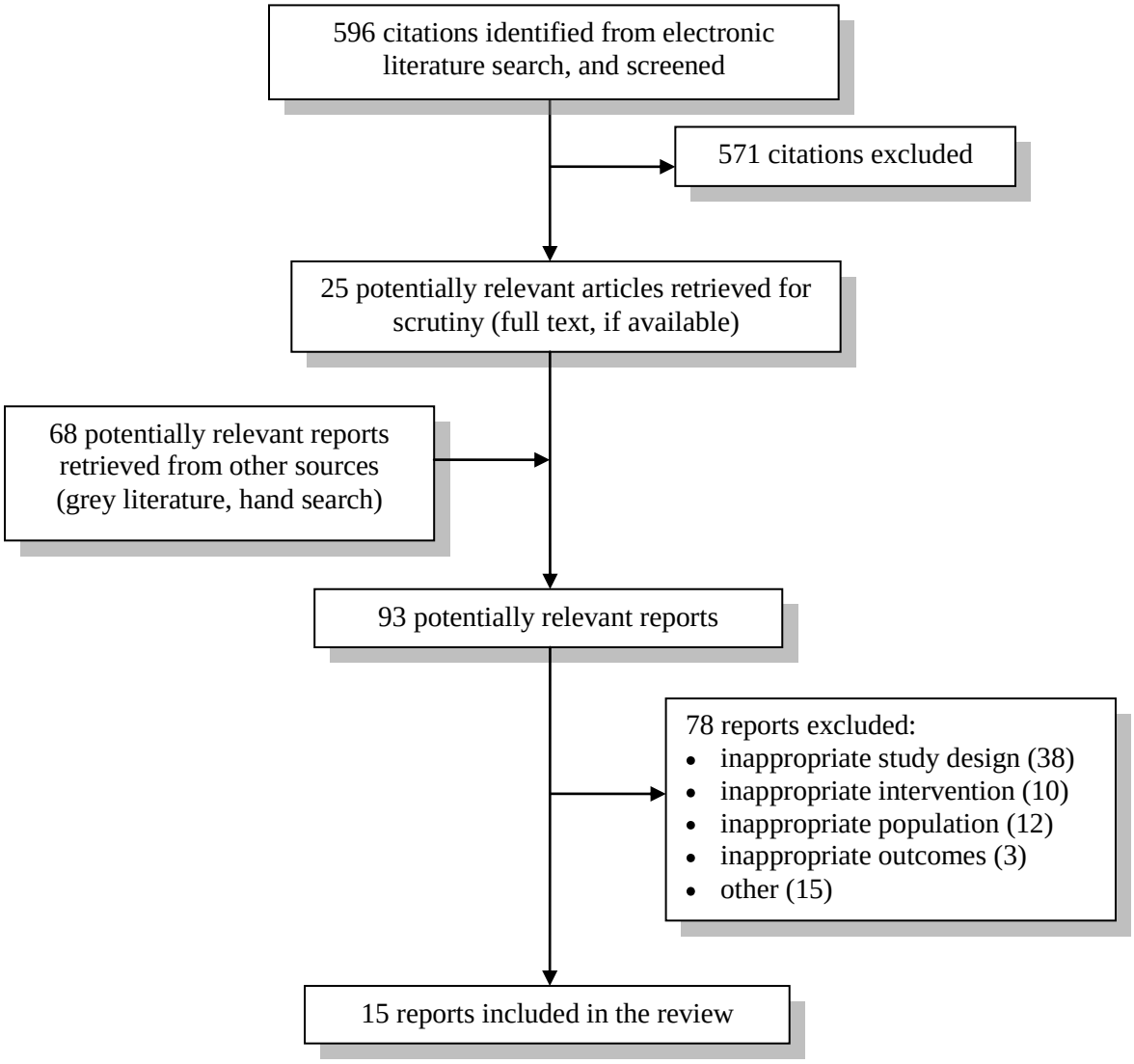
APPENDIX 2: ELIGIBILITY CRITERIA

Studies that met of the inclusion criteria and none of the exclusion criteria as summarized below were included:

Inclusion criteria	
Population	• Older adults who are receiving benzodiazepines (≥ 60 years) • Subgroup of interest is patients ≥ 75 years
Interventions	• Short-acting benzodiazepines • Intermediate-acting benzodiazepines • Long-acting benzodiazepines • Antidepressants (SSRIs, TCAs, MAOIs, SNRIs)
Comparators	• Benzodiazepines (any dose) • Antidepressants (any dose) • Non-benzodiazepine use (with or without a placebo)
Outcomes	• Patient safety (e.g., falls, addiction, or other adverse events) • Clinical effectiveness (e.g., quality of life, reduced anxiety, or depression) • Cost-effectiveness • Evidence-based recommendations and clinical practice guidelines
Study design	• Health technology assessments • Systematic reviews and meta-analyses • Randomized controlled trials (including parallel and crossover) • Economic evaluations (including cost-effectiveness, cost-benefit, cost-utility) • Evidence-based guidelines
Exclusion criteria	
	• Studies where patients are treated for conditions other than anxiety or disruptive behaviour and safety data are not reported (e.g., clinical focus is on short-term management of insomnia and adverse events are not reported). • Studies conducted in healthy patients.

SSRIs – selective serotonin reuptake inhibitors; TCAs – tricyclic antidepressants; MAOIs-monoamine oxidase inhibitors; SNRIs - Serotonin–norepinephrine reuptake inhibitor

APPENDIX 3: SELECTION OF PUBLICATIONS



APPENDIX 4: RISK OF FRACTURES IN PATIENTS TAKING PSYCHOTROPIC DRUGS (TAKKOUCHE ET AL.)[10]

Drug Class	Fixed Effects RR (95% CI)	Random Effects RR (95% CI)	Number of Studies
Benzodiazepines			
All studies	1.29 (1.24 to 1.35)	1.34 (1.24 to 1.45)	23
Short-term benzodiazepine	1.24 (1.16 to 1.33)	1.25 (1.14 to 1.37)	9
Long-term benzodiazepine	1.29 (1.21 to 1.38)	1.31 (1.20 to 1.43)	10
Cohort studies	1.30 (1.18 to 1.43)	1.31 (1.18 to 1.45)	7
All case-control studies	1.29 (1.23 to 1.35)	1.36 (1.23 to 1.51)	16
Population-based case-control	1.28 (1.22 to 1.34)	1.33 (1.20 to 1.49)	10
Hospital-based case-control	1.47 (1.22 to 1.78)	1.46 (1.09 to 1.96)	6
Hip fractures	1.29 (1.23 to 1.36)	1.38 (1.24 to 1.54)	19
Antidepressants			
All studies	1.53 (1.48 to 1.58)	1.60 (1.38 to 1.86)	15
Cohort studies	1.28 (1.04 to 1.58)	1.28 (1.04 to 1.58)	3
All case-control studies	1.54 (1.49 to 1.59)	1.66 (1.41 to 1.96)	13
Population-based case-control	1.40 (1.35 to 1.45)	1.54 (1.25 to 1.90)	9
Hospital-based case-control	1.90 (1.79 to 2.01)	1.88 (1.73 to 2.04)	4
SSRI antidepressant	1.84 (1.72 to 1.96)	1.91 (1.43 to 2.55)	4
Non-SSRI antidepressant	1.32 (1.26 to 1.38)	1.44 (1.27 to 1.63)	11
Tricyclic antidepressant	1.31 (1.25 to 1.38)	1.58 (1.24 to 2.00)	4
Hip fracture	1.54 (1.49 to 1.59)	1.68 (1.44 to 1.96)	16
Additional drug classes*			
Non-barbiturate antiepileptic drugs	1.19 (1.16 to 1.23)	1.54 (1.24 to 1.93)	13
Barbiturate antiepileptic drugs	3.19 (2.29 to 3.41)	2.17 (1.35 to 3.50)	5
Antipsychotics	1.46 (1.34 to 1.59)	1.59 (1.27 to 1.98)	12
Hypnotics	1.47 (1.40 to 1.54)	1.15 (0.94 to 1.39)	13
Opioids	1.32 (1.24 to 1.40)	1.38 (1.11 to 1.67)	6

CI = confidence interval; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.
*Only the base case is shown

APPENDIX 5: SUMMARY OF GUIDELINES ADDRESSING THE USE OF BENZODIAZEPINES IN THE ELDERLY

Condition	Agency	Statements Concerning Benzodiazepines and Older Adults
Mood and behavioural disorders	Canadian Coalition for Seniors' Mental Health[17]	• "Carefully weigh the potential benefits of pharmacologic intervention versus the potential for harm. [A] • Appropriate first-line pharmacologic treatment of residents with severe behavioural symptoms with psychotic features includes atypical antipsychotics. [B] Atypical antipsychotics should be used only if there is marked risk, disability, or suffering associated with the symptoms. [C] • Appropriate first-line pharmacologic treatment of residents with severe behavioural symptoms without psychotic features can include (a) atypical antipsychotics [B] and (b) antidepressants such as trazodone or SSRIs [C]. • Pharmacologic treatment of residents with severe behavioural symptoms can also include (a) anticonvulsants such as carbamazepine [B] and (b) short- or intermediate-acting benzodiazepines [C]." (p. S62)
Dementia	BC GPAC[13]	• Pharmacotherapeutic interventions for BPSD: "Benzodiazepines are not recommended due to their high potential for adverse events such as confusion and falls" (p. 13)
Dementia	SCIE-NICE[14]	• "Healthcare professionals who use medication in the management of violence, aggression and extreme agitation in people with dementia should: be trained in the correct use of drugs for behavioural control, specifically benzodiazepines and antipsychotics; be able to assess the risks associated with pharmacological control of violence, aggression and extreme agitation, particularly in people who may be dehydrated or physically ill; understand the cardiorespiratory effects of the acute administration of benzodiazepines and antipsychotics and the need to titrate dosage to effect; recognize the importance of nursing people who have received these drugs in the recovery position and of monitoring pulse, blood pressure and respiration; be familiar with and trained in the use of resuscitation equipment; undertake annual retraining in resuscitation techniques; understand the importance of maintaining an unobstructed airway." (p. 263) • "In people with AD or VaD with clinically significant agitation, there is moderate quality evidence suggesting that both antipsychotic drugs and benzodiazepine drugs administered by IM injection, when compared with placebo, may produce benefits in terms of reduced psychotic symptoms and aggression/agitation that outweigh the risk of adverse events." (p. 258)
Dementia	SIGN[15]	• "No systematic reviews or RCTs examining the usefulness of benzodiazepines in the management of associated symptoms of dementia, including anxiety, were identified." (p. 20)

Condition	Agency	Statements Concerning Benzodiazepines and Older Adults
Dementia	American Psychiatric Association[16]	• "Data demonstrating benefit from benzodiazepines are modest, but benzodiazepines occasionally have a role in treating patients with prominent anxiety [III] or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure, such as a tooth extraction or a diagnostic examination [II]. Adverse effects of benzodiazepines include sedation, worsening cognition, delirium, increased risk of falls, and worsening of breathing disorders. Lorazepam and oxazepam, which have no active metabolites, are preferable to agents with a longer half-life such as diazepam or clonazepam [III]." (p. 13)
Panic disorder	American Psychiatric Association[18]	• "Given the high rates of co-occurring mood disorder in elderly patients with panic disorder, an antidepressant is recommended as first-line pharmacotherapy." [NR] (p. 45) • "Benzodiazepine use should be avoided whenever possible, since use of long half-life benzodiazepines and long-term benzodiazepine use can be problematic in geriatric patients." [NR] (p. 45) • "Geriatric patients taking benzodiazepines may be at higher risk for falls and fractures. [I]" (p. 14) • "Caution and careful monitoring is indicated when prescribing benzodiazepines to elderly patients. [I]" (p. 14)
Sleep disorders	American Medical Directors Association[19]	• "Continuous use of benzodiazepines should be discouraged in the long-term care setting because of the risk of side effects, physiological tolerance, and adverse effects on discontinuation." (ages not specified) [NR] • "Adverse effects generally appear to be worse in the elderly." [NR]
Chronic insomnia	National Institutes of Health[20]	• "Adverse effects associated with these medications include, residual daytime sedation, cognitive impairment, motor incoordination, dependence, and rebound insomnia. These problems appear to be worse in the elderly." [NR] (p. 16)
Insomnia in patients ≥ 65 years	Montgomery and Lilly, 2007[21]	• "Benzodiazepines may improve sleep outcomes but are likely to cause adverse events." [NR] (p. 1) • "Observational studies suggest an increased risk of falls, hip fractures, cognitive impairment, and car accidents." [NR] (p. 5) • "There is little evidence regarding the clinical benefits or adverse effects of benzodiazepine usage for greater than one month." (p. 5)

AD = Alzheimer disease; BC GPAC; British Columbia Guidelines and Protocols Advisory Committee; BPSD = behavioural and psychological symptoms in dementia; IM = intramuscular; NICE = National Institute for Health and Clinical Excellence; RCT = randomized controlled trial; SCIE = Social Care Institute for Excellence; SIGN = Scottish Intercollegiate Guidelines Network; VaD = vascular dementia.

[I] recommended with substantial clinical confidence; [II] recommended with moderate clinical confidence; [III] may be recommended on the basis of individual circumstances; [NR] level of evidence was not reported; [A] directly based on evidence from meta-analysis of RCTs or at least one RCT; [B] directly based on evidence from at least one controlled study or quasi-experimental study or extrapolated recommendation from higher quality evidence; [C] directly based on evidence from non-experimental descriptive studies or extrapolated recommendation from higher quality evidence.