Article details: 2013-0076	
Title	Utilization of benzodiazepines and related drugs: a Canadian population-based study, 1997–2012
Authors	Silvia Alessi-Severini PhD, Matthew Dahl BSc, James M. Bolton MD, Murray W. Enns MD, David M. Collins PhD, Dan Chateau PhD, Jitender Sareen MD
Reviewer 1	John-Michael Gamble
Institution	University of Alberta, Public Health Sciences
General comments	This is a well-written descriptive population-based epidemiologic study that contributes novel information about the utilization of benzodiazepines and Z-drugs by one Canadian province over a time period of 16 years. These are important classes of medications to document patterns of utilization, as they are frequently prescribed in Canada. The major findings were that the prevalence of benzodiazepine in those over 65 years of age declined substantially between 1996 and 2012, and the prevalence of Z-drugs increased in the same age group. Interestingly, the overall prevalence of benzodiazepines increased only slightly over the study timeframe. Although I feel this manuscript is well written and makes an important contribution to the descriptive literature around the utilization of benzodiazepine and related drugs, I do have some suggestions that may be helpful to the authors. General Comments 1. Description of statistical analysis: Although the statistical analysis conducted appears robust and appropriate, the description of the analysis is very brief. First, I would expect to see details around the assumed distribution of the dependent variable and what type of correlated structure was used for the GEE. Second, It would also be helpful to see a description of the how the denominators were calculated for incidence and prevalence. Third, I would like to see more explanation of how the statistical model was built to test the influence of socioeconomic variables on the utilization of benzodiazepines and Z-drugs. Fourth, I suggest including an explanation of the planned stratified analyses that are presented in the results. 2. Prescribers analysis: Although the authors include a brief section in their results on 'prescribers', this analysis could be further expanded, which would strengthen the paper. I would have liked to see if the trends in prescribing for benzodiazepines and Z-drugs changed over time according to physician specialty as defined in the paper. In other words, have the prescribing patterns over time differed according to which type of physician is prescribing? 3. Combination of all Z-drugs and benzodiazepines into one category: Given that the prescriptions for zopiclone represent the majority of Z-drug use and zaleplon was discontinued in 2007, I suggest the authors provide more detail around this issue. It would be helpful to know the proportion of Z-drug records that are due to zopiclone. Based on figure 1 and 2, it does not appear that the discontinuation of zaleplon in 2007 or introduction of zolpidem in 2011 had any major impact on the overall use of Z-drugs. Ideally, the authors would include a table or figure showing Z-drug use by drug. Likewise, it would be interesting and in my opinion, strengthen the paper, to see benzodiazepine usage stratified by drug or at least the most prevalent drugs in the class. Specific Comments: 1. Abstract, methods section: I suggest including the study design within the abstract as well as the time interval that was used for the analysis. 2. Abstract, results section: I suggest replacing the term elderly with the specific age category used in the study (i.e., ≥65). 3. Abstract, conclusion: I suggest revising the sentence in the conclusion to include the notion of change over time. As it stands, it is not clear that BZDs are prescribed less frequently over time in elderly patients if the conclusion sentence is read on its own. 4. Introduction, general: Well written and concise. Reference number 6 appears to be missing.

	5. Methods, page 4, line19: Please define the term index year and specify if it is a calendar or fiscal year. 6. Methods, page 5, line 42: Please revise the statement "Zolpidem has never been approved for sale in Canada" as it is incorrect. Health Canada approved the drug zolpidem (Sublinox) in 2011 (NOC: July 11, 2011). 7. Methods, page 6, analyses section: As discussed above, please expand this section. 8. Results, page 7, last paragraph: Please specify if these denominators were for calculating prevalence or incidence. I would like to see more explanation of how the denominators were calculated in the methods as mentioned above. 9. Results, page 8, prescribers section: I suggest changing the title as this section does not describe the association between type of prescriber and benzodiazepine/ Z-drug use. This analysis could be further developed and strengthen the paper as described above.
Reviewer 2	Hugo Lövheim
Institution	Geriatric Medicine, Community Medicine and Rehabilitation
General comments	I think this manuscript is a well-written and interesting report. I have a few suggestions to possibly improve it, but think it might be acceptable for publication after a minor revision. I would like you to include a calculation of incidence and prevalence for "any BZD or Z drug", to see if the total number of people using any of these drugs have increased or decreased. I think the very first sentence in the introduction should be changed. Even if there is undoubtedly many newer drugs since the first benzodiazepine in 1960, there is also many older, such as barbiturates, sedative antihistamines, classic antipsychotics, tricyclic antidepressants (about the same age) etc, not to mention morphine known for thousands of years. I suggest you just write "Benzodiazepines have been used for decades..." The abbreviation BC should be spelled out the first time it appears in the introduction.
Reviewer 3	Dick Bijl
Institution	
General comments	General impression. This study describes the utilization of benzodiazepines and Z-drugs in Canada in period 1997 to 2012. The topic is relevant and important for doctors, pharmacists, policy and guideline makers. Yet, the information provided in the article is very limited, it only mentions utilization c.q. the users. No information is provided on defined daily doses (DDD's), prescribed daily doses (PDD's), the indications, nor about the length of use or the comorbid conditions of the users, and other confounding factors or the limitations of the database. It is not clear whether the databases used do not contain this information or that the authors did not analyze them. Therefore, we do not know whether there are accompanying trends or confounders, such as shorter or longer duration of use, higher or lower daily use, shifts in indications, off-label prescriptions or off-label use. That information would greatly add to the impact of the paper. If the authors can provide these data and analyses, then the impact of the paper would increase. If the authors cannot give additional data and analyses, I think the message should be reduced to one page or it could be published as a letter. I have also added detailed comments below. Especially troublesome is the way in which the evidence regarding the effectiveness and adverse events of the drugs is reported. It is not correct to summarize case reports, observational data and evidence from randomized trials as if these represent the same level of evidence. Per page/line.

	4/4-5 BZD's have been used as effective agents for decades. In the case of insomnia there are no data this is actually true for use longer than 3-4 weeks or long-term use. 4/21 Reference 9 is not convincing. This article describes only case reports of addiction, clinical studies were excluded. A more extensive literature search and pharmacovigilance search would be needed to support this statement. Furthermore, the study was sponsored by the producer of zolpidem/zopiclone. 4/26 Advised against long-term use. In the Netherlands the use of BZD's should be limited to 2 to 4 weeks, which cannot be called 'long-term' use. 4/35-36 May not be generalizable to Canada. The authors should give arguments. 5/12 New users. Can the authors make plausible that chronic users or addicts are not captured, for instance those that have collected the drugs in the year before the study. And can these drugs be obtained from the USA freely? 5/36 Have there been major changes in the database since 1996 and if so was there a new validation study? 6/7 Outpatient drug use. We need to know what part this is of the total drug use in the region or in Canada. 6/40 It would be interesting to know why this drug was not approved in Canada. 6/58 Are prisoners regarded as outpatients? 7/10 The paragraph Analyses should be extended with analyses on DDD's, duration of use, comorbid conditions, the indications of the prescribed drugs, and confounders as mentioned above. 9/44 Have repeat-prescriptions been taken into account? 10/11 Share similar activity. This is assumed and/or this is based on animal studies. 10/14 They have been marketed. Yes, but the reader would like to know what is the evidence behind this marketing. 11/2 There are too many limitations to justify more than one or two pages for the article. 11/29 Perceived by general practitioners as more effective. Make critical remarks on this. GPs should deal with the evidence in order to stay credible. If GPs prescribe non-evidence based drugs that cost more than the standard drugs, re-imbursement should stop. It could be inferred. This is a weak inference and should be made clear be real data. Reference 31 is a study under German GP's and I do not know whether they are representative for the rest of the Western GP's. In any case I do not think so. 11/49 GPs in Manitoba, like elsewhere in the Western world, are very susceptible to marketing and this should be added. References. 1. Animal study, not acceptable nowadays, should be replaced by a study in humans. 4. Refers only to observational data, so this is not hard evidence. Should have been mentioned in the text. 6. Is not referred to in the text. Is a review of interventions to prevent falls in elderly on psychotropic medications. 7. Cannot be found in Pubmed. The correct reference is Br J Clin Pharmacol. 4-11. The authors refer to these as 'evidence', yet the levels of evidence greatly vary from observational to randomized trials. This is not the way to express evidence. Did the authors perform an extensive literature search? 19-22. Only studies with negative results are mentioned. There are however studies with positive results: Curran HV, Collins R, Fletcher S, Kee SCY, Woods B, Iliffe S. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. Psychol Med 2003; 33: 1223-1237. Heather N, Bowie A, Ashton H, McAvoy B, Spencer I, Brodie J, et al. Randomised controlled trial of two brief interventions against long-term benzodiazepine use: outcome of

	intervention. Addict Res Theory 2004; 12: 141-154. Zitman FG, Couvée JE. Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off. Report on behalf of the Dutch Chronic Benzodiazepine Working Group. Br J Psychiatry 2001; 178: 317-324. Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Balkom AJLM van, Lisdonk EH van de, Breteler MHM, et al. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. Br J Psychiatry 2003; 182: 498-504. Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, Lisdonk EH van de, Balkom AJLM van, Hoogen HJM van den, et al. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. Drug Alcohol Depend 2005; 78: 49-56. Niessen WJM, Stewart RE, Broer J, Haaijer-Ruskamp FM. Vermindering van gebruik van benzodizepinen door een brief van de eigen huisarts aan chronische gebruikers. Ned Tijdschr Geneeskd 2005; 149: 356-361. Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Couvée JE, Balkom AJLM van, Zitman FG. Behandelmethoden om langdurig benzodiazepinegebruik te staken. Ned Tijdschr Geneeskd 2001; 145: 1347-1350. Kind regards, dr Dick Bijl, physician-epidemiologist
Author response	Reviewer 1: Synopsis: This is a well-written descriptive population-based epidemiologic study that contributes novel information about the utilization of benzodiazepines and Z-drugs by one Canadian province over a time period of 16 years. These are important classes of medications to document patterns of utilization, as they are frequently prescribed in Canada. The major findings were that the prevalence of benzodiazepine in those over 65 years of age declined substantially between 1996 and 2012, and the prevalence of Z-drugs increased in the same age group. Interestingly, the overall prevalence of benzodiazepines increased only slightly over the study timeframe. Although I feel this manuscript is well written and makes an important contribution to the descriptive literature around the utilization of benzodiazepine and related drugs, I do have some suggestions that may be helpful to the authors. General Comments 1. Description of statistical analysis: Although the statistical analysis conducted appears robust and appropriate, the description of the analysis is very brief. First, I would expect to see details around the assumed distribution of the dependent variable and what type of correlated structure was used for the GEE. Second, It would also be helpful to see a description of the how the denominators were calculated for incidence and prevalence. Third, I would like to see more explanation of how the statistical model was built to test the influence of socioeconomic variables on the utilization of benzodiazepines and Z-drugs. Fourth, I suggest including an explanation of the planned stratified analyses that are presented in the results. Modification has been made to address these comments. See specifics throughout the paper and response to individual points. 2. Prescribers analysis: Although the authors include a brief section in their results on 'prescribers', this analysis could be further expanded, which would strengthen the paper. I would have liked to see if the trends in prescribing for benzodiazepines and Z-drugs changed over time according to physician specialty as defined in the paper. In other words, have the prescribing patterns over time differed according to which type of physician is prescribing? We appreciate this comment. However, this request exceeds the scope of our initial objectives. We have modified the sub-heading as it is more appropriate to define it as "prescription" as it is simply a description of the prescribers' specialty. 3. Combination of all Z-drugs and benzodiazepines into one category: Given that the

	prescriptions for zopiclone represent the majority of Z-drug use and zaleplon was discontinued in 2007, I suggest the authors provide more detail around this issue. It would be helpful to know the proportion of Z-drug records that are due to zopiclone. Based on figure 1 and 2, it does not appear that the discontinuation of zaleplon in 2007 or introduction of zolpidem in 2011 had any major impact on the overall use of Z-drugs. Ideally, the authors would include a table or figure showing Z-drug use by drug. Likewise, it would be interesting and in my opinion, strengthen the paper, to see benzodiazepine usage stratified by drug or at least the most prevalent drugs in the class. The very limited contribution of zaleplon to the prevalence and incidence of use of the Z-drugs has been highlighted in the "Interpretation" section (pg. 10) with the sentence "It is important to note that zaleplon was discontinued in 2007 and that its utilization in Manitoba has been generally very low with prevalence never reaching the 1.0 per 1,000 mark between 2001/02 and 2007/08 and with incidence rates rapidly approaching 0.1 per 1,000 in 2005/06." Specific Comments: 1. Abstract, methods section: I suggest including the study design within the abstract as well as the time interval that was used for the analysis. Study design and time interval added to the abstract. 2. Abstract, results section: I suggest replacing the term elderly with the specific age category used in the study (i.e., ≥65). Done. 3. Abstract, conclusion: I suggest revising the sentence in the conclusion to include the notion of change over time. As it stands, it is not clear that BZDs are prescribed less frequently over time in elderly patients if the conclusion sentence is read on its own. Conclusion of the abstract has been modified to "Over time benzodiazepines have been prescribed less frequently to older patients in Manitoba; however, zopiclone prescribing has continued to rise for all age groups." 4. Introduction, general: Well written and concise. Reference number 6 appears to be missing. Thank you for noticing. Reference [6] has been added. 5. Methods, page 4, line19: Please define the term index year and specify if it is a calendar or fiscal year. Defined as "fiscal". 6. Methods, page 5, line 42: Please revise the statement "Zolpidem has never been approved for sale in Canada" as it is incorrect. Health Canada approved the drug zolpidem (Sublinox) in 2011 (NOC: July 11, 2011). We agree with the reviewer's comment. Thank you for the correction. We meant "during the timeframe of our study". In fact our data go only into the first quarter of 2012 and the product was not launched until the end of 2011 with basically no utilization showing in Manitoba. Modifications in the text have been made as previously mentioned. 7. Methods, page 6, analyses section: As discussed above, please expand this section. Addressed. 8. Results, page 7, last paragraph: Please specify if these denominators were for calculating prevalence or incidence. I would like to see more explanation of how the denominators were calculated in the methods as mentioned above. More details have been included and the denominators values moved to the Methods section. 9. Results, page 8, prescribers section: I suggest changing the title as this section does not

	describe the association between type of prescriber and benzodiazepine/ Z-drug use. This analysis could be further developed and strengthen the paper as described above. Explained above. Reviewer 2: I think this manuscript is a well-written and interesting report. I have a few suggestions to possibly improve it, but think it might be acceptable for publication after a minor revision. 1. I would like you to include a calculation of incidence and prevalence for "any BZD or Z drug", to see if the total number of people using any of these drugs have increased or decreased. We have added more information on the utilization of other agents; however, we have opted for not presenting the time course of all agents as this would create very confusing figures and would not provide any useful information (some agents have very low utilization and small variations in their prescribing overtime does not affect the final results and conclusions). 2. I think the very first sentence in the introduction should be changed. Even if there is undoubtedly many newer drugs since the first benzodiazepine in 1960, there is also many older, such as barbiturates, sedative antihistamines, classic antipsychotics, tricyclic antidepressants (about the same age) etc, not to mention morphine known for thousands of years. I suggest you just write "Benzodiazepines have been used for decades..." Agree. Corrected as suggested. 3. The abbreviation BC should be spelled out the first time it appears in the introduction. Done. Reviewer 3: General impression. This study describes the utilization of benzodiazepines and Z-drugs in Canada in period 1997 to 2012. 1. The topic is relevant and important for doctors, pharmacists, policy and guideline makers. Yet, the information provided in the article is very limited, it only mentions utilization c.q. the users. No information is provided on defined daily doses (DDD's), prescribed daily doses (PDD's), the indications, nor about the length of use or the comorbid conditions of the users, and other confounding factors or the limitations of the database. It is not clear whether the databases used do not contain this information or that the authors did not analyze them. Therefore, we do not know whether there are accompanying trends or confounders, such as shorter or longer duration of use, higher or lower daily use, shifts in indications, off-label prescriptions or off-label use. That information would greatly add to the impact of the paper. If the authors can provide these data and analyses, then the impact of the paper would increase. We appreciate the comment. Unfortunately, the prescription database does not include information on diagnoses and therefore it is not possible to determine reasons for prescribing. The assessment of number of users is the most reliable parameter to assess utilization, as number of prescriptions, doses and length of therapy are highly variable and highly depending on the various diagnoses. The DDD assessment, while important as a measure of intensity of use, does not really help in answering the main question of our research project, which was to see if the prescribing of benzodiazepines and Z-drugs has changed over time in terms of new individuals started on the drugs. We appreciate the Editor's preference for not getting into speculations, however, it would appear that prescribing in Manitoba has been affected by the evidence of harm that have been presented for benzodiazepines and that zopiclone, perceived as being safer, has replaced benzodiazepines probably for the treatment of insomnia. Please refer to "Discussion" (pg. 11) for a brief mention of this interpretation. 2. Especially troublesome is the way in which the evidence regarding the effectiveness and adverse events of the drugs is reported. It is not correct to summarize case reports, observational data and evidence from randomized trials as if these represent the same level of evidence.

	We appreciate this comment; however, reports on various effects of psychotropic medications (motor vehicle accidents or cognitive deterioration) cannot really be measured through RCTs for obvious ethical reasons. In the introduction, we have included the words "at various level of evidence" (pg. 3) to clarify this issue. Per page/line. 3. 4/4-5 BZD's have been used as effective agents for decades. In the case of insomnia there are no data this is actually true for use longer than 3-4 weeks or long-term use. We appreciate the comment. The sentence has been modified as follows: "Benzodiazepines have been used for decades as effective agents for the treatment of seizure and anxiety disorders and for the short-term control of insomnia." 4. 4/21 Reference 9 is not convincing. This article describes only case reports of addiction, clinical studies were excluded. A more extensive literature search and pharmacovigilance search would be needed to support this statement. Furthermore,the study was sponsored by the producer of zolpidem/zopiclone. The reference has been replaced by a more recent clinical review that summarizes published evidence. 5. 4/26 Advised against long-term use. In the Netherlands the use of BZD's should be limited to 2 to 4 weeks, which cannot be called 'long-term' use. Replaced with "against use longer than 4 weeks". 6. 4/35-36 May not be generalizable to Canada. The authors should give arguments. Point well taken. The sentence has been removed. 7. 5/12 New users. Can the authors make plausible that chronic users or addicts are not captured, for instance those that have collected the drugs in the year before the study. And can these drugs be obtained from the USA freely? Unfortunately we do not have data to answer these questions. We can only capture prescriptions written in Canada and filled at a pharmacy in Manitoba since 1995. 8. 5/36 Have there been major changes in the database since 1996 and if so was there a new validation study? The prescription database started in 1996. No major changes have occurred. 9. 6/7 Outpatient drug use. We need to know what part this is of the total drug use in the region or in Canada. Manitoba has a population of approximately 1,200,000 (total Canadian population = 34,000,000). Since other provinces do not have comprehensive prescription databases and none of the provincial databases capture hospital use, it is not possible to accurately calculate proportions. We can only estimate that this represent approximately 3.5% of the patients filling prescriptions in the community. We have clarified the term outpatient and explained that in hospital use is not captured in our study. 10. 6/40 It would be interesting to know why this drug was not approved in Canada. The statement was not accurate. Zolpidem was in fact approved decades ago but never launched in Canada. The new sublingual formulation was approved in 2011 and was launched at the end of that year. Please refer to previous comments. 11. 6/58 Are prisoners regarded as outpatients? *(the editors found this point to be of lesser consequence) As ironic as it might sound, they are, unless they are hospitalized, in that case they become in-patients:-) 12. 7/10 The paragraph Analyses should be extended with analyses on DDD's, duration of use,

	comorbid conditions, the indications of the prescribed drugs, and confounders as mentioned above. *(the editors are aware that this data might not be easily available) We appreciate the comment. Certainly more work could be done; however, as explained before these questions exceed the scope of our original project and research proposal. 13. 9/44 14. 10/11 animal studies. 15. 10/14 what is the evidence behind this marketing. 16. 11/2 There are too many limitations to justify more than one or two pages for the article. Like all studies, the present investigation has limitations, which are now more comprehensively outlined in the discussion of the paper. We have reduced the manuscript to comply with CMAJ required word limits. 17. 11/29 Perceived by general practitioners as more effective. Make critical remarks on this. GPs should deal with the evidence in order to stay credible. If GPs prescribe non-evidence based drugs that cost more than the standard drugs, re-imbursement should stop. It could be inferred. This is a weak inference and should be made clear be real data. Reference 31 is a study under German GP's and I do not know whether they are representative for the rest of the Western GP's. In any case I do not think so. The sentence has been change to reflect a non-generalized statement with the same reference. It was not our intention to propose changes in policy (i.e., restrictions in re-imbursement if prescribing not optimal). As explained in the discussion, our study did not look at appropriateness. 18. 11/49 GPs in Manitoba, like elsewhere in the Western world, are very susceptible to marketing and this should be added. While this might be true, our study did not assess influence of marketing on physicians in Manitoba. References. 1. Animal study, not acceptable nowadays, should be replaced by a study in humans. Point well taken. Reference replaced. 4. Refers only to observational data, so this is not hard evidence. Should have been mentioned in the text. As per previous reviewer's comment we have mentioned the different level of evidence reported. 6. Is not referred to in the text. Is a review of interventions to prevent falls in elderly on psychotropic medications. Corrected. 7. Cannot be found in Pubmed. The correct reference is Br J Clin Pharmacol. Thank you for the correction. 4-11. The authors refer to these as 'evidence', yet the levels of evidence greatly vary from observational to randomized trials. This is not the way to express evidence. Did the authors perform an extensive literature search? See earlier response to similar comment. 19-22. Only studies with negative results are mentioned. There are however studies Have repeat-prescriptions been taken into account?

	Share similar activity. This is assumed and/or this is based on They have been marketed. Yes, but the reader would like to know with positive results: Curran HV, Collins R, Fletcher S, Kee SCY, Woods B, Iliffe S. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. Psychol Med 2003; 33: 1223-1237. Heather N, Bowie A, Ashton H, McAvoy B, Spencer I, Brodie J, et al. Randomised controlled trial of two brief interventions against long-term benzodiazepine use: outcome of intervention. Addict Res Theory 2004; 12: 141-154. Zitman FG, Couvée JE. Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off. Report on behalf of the Dutch Chronic Benzodiazepine Working Group. Br J Psychiatry 2001; 178: 317-324. Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Balkom AJLM van, Lisdonk EH van de, Breteler MHM, et al. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. Br J Psychiatry 2003; 182: 498-504. Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, Lisdonk EH van de, Balkom AJLM van, Hoogen HJM van den, et al. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. Drug Alcohol Depend 2005; 78: 49-56. Niessen WJM, Stewart RE, Broer J, Haaijer-Ruskamp FM. Vermindering van gebruik van benzodizepinen door een brief van de eigen huisarts aan chronische gebruikers. Ned Tijdschr Geneeskd 2005; 149: 356-361. Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Couvée JE, Balkom AJLM van, Zitman FG. Behandelmethoden om langdurig benzodiazepinegebruik te staken. Ned Tijdschr Geneeskd 2001; 145: 1347-1350. Kind regards, dr Dick Bijl, physician-epidemiologist We appreciate the long list of important references. Our referencing was aimed at showing prescribing trends. We are aware that some strategies do work in modifying prescribers' habits; however, this aspect was not the aim of our paper. Nevertheless, we have included the Gorgels reference.