Reviewer’s report

Title: High daily doses of benzodiazepines among Quebec seniors: Prevalence and correlates

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Reviewer: Prof nicholas moore

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until I see revised version

Good study, but difficult to understand and extract the marrow. Needs more work for the expression of the results.

This is an interesting report, that needs some reworking, both conceptually and in the presentation:

a) in the introduction, the authors say that benzos are associated with a number of adverse outcomes, then cite
- hip fracture: controversial, not associated with benzos as a group (several refs including pierfitte et al, BMJ 2001; 322:704-708, and Sgadari A, Lapane KL, Mor V, Landi F, Bernabei R, Gambassi G. Oxidative and nonoxidative benzodiazepines and the risk of femur fracture. J Clin Psychopharmacol 2000; 20: 234-239 ), may be associated with subgroups such as long-acting, short-acting, high doses, those with oxidising mechanisms, etc...Just citing one ref may not be enough;
- motor vehicle accidents: there is a more recent paper in the Lancet a year or two ago, by Tom MacDonald's group.
- Accidental falls: agreed
- Accidental poisonings possibly

Hospitalisation for depression and attempted suicide, on the other hand, may be a case of reverse causality: anxiety and depression are associated with hospitalisation and suicide. they are often treated with benzodiazepines. Indeed at one time it was recommended to use benzos in the more suicidal patients.... Because of their effects on cognition and desinhbition, there has been much discussion recently as to whether benzos do increase the risk of suicide in depressive patients, and to my knowledge this has not been clearly resolved. That benzos are found in more than 90% of cases of voluntary drug overdoses is probably more a reflection on the wide use and availability of these drugs than on their role in the suicide attempt per se. It may also be an indication that depression is too often misdiagnosed or underdiagnosed, and treated (!) with benzos, which are ineffective, rather than antidepressants, especially in the elderly, where there is in addition a wide mistrust of antidepressants because of the poor tolerability of the earlier drugs. Suicide would then be more a results of lack of treatment efficacy than of risk related to the drug. Anyhow, I would leave that out, it is another debate.
What should be included in the elderly is the effects of benzos on memory and cognition with a possibly increased risk of dementia (Lagnaoui et al, J clin epidemiol, in press); This is certainly underestimated and may be the more serious risk in a rapidly aging population.

b) When the authors say: "due to the widespread use of benzos among seniors, even a relatively low prevalence of use may have a substantial impact on public health". I am not sure I understand. Isn't this contradictory? how can a low prevalence of use be associated with widespread use?

c) The definition of high daily doses rests on what was prescribed, not what was actually used. This may be the major caveat for the paper: is there a limit on the duration of a prescription in canada? ie, can a prescription be for example for 3 months or more? In France some drug have limited duration prescriptions, and prescribing high doses could be a way to prescribe for longer periods. I remember in a different setting a patient who was prescribed 8 tablet of morphine per day one week a month. This corresponded in fact to regular use of 2 tablets daily, but since morphine cannot be prescribed for more than 7 days here, prescribing such large intermittent doses enabled the patient to consult just once a month insted of every week. This is an extreme example,of course, and may not be relevant, but I think that the definition of high doses could include at least two prescriptions redeemed within a time-frame that implies that these high doses were actually used. If a one-month high-dose prescription is filled every other month, then the actual dose used may be half that prescribed. What was the actual number of DDDs bought over the study period? This is in fact the limit of prescription or pharmacy-based studies, that no one knows what the real usage is.

One indicator for different usage patterns is the mean number of prescriptions per person. Overall 607 patients received 5638 prescriptions (mean 9.3); 108 high-dose patients received 787 prescriptions (7.3 per patient), so that 499 low-dose patients received 4851 prescriptions, i.e. 9.7 per person: low-dose patients received in the mean 2.4 more prescriptions than high-dose patients. This is, of course, assuming that high-dose patients received only high-dose prescriptions. So that in fact the yearly coverage of the high-dose patients may have been lower than expected, or at least not really that much higher than that of the low-dose. Is this correct?

d) the results are not easy to read through. Table 2 should have the percentages computed vertically not horizontally, because the source of patient selection was based on drug usage, not on populations. eg, the percentages should give the gender ratio in the low and high users, not the distribution of women between the high and low dose groups. Thus 90% of high dose prescribers and 86% of low-dose prescribers were men may be better than 82% of men and 86% of females were low-dose prescribers. This is especially true for the prescribers since there may be duplication of prescribers, if there were fewer than 607 prescribers for the 607 patients. High-dose prescribers could in fact have concentrated a proportionally much smaller number of actual different prescribers than low-dose prescribers. Unusual prescribing is usually limited to a small number of high-volume prescribers (see W. Inman's work on PEM studies and early prescribers of new drugs)

For the rest of the table I am not sure whether row of column percents are more useful or appropriate. Table 3 should indicate odds ratios and confidence intervals, rather than parameter estimates and SE: one can always recompute one from the other, but the OR and CI are more informative and much easier to use than the parameter estimates.

Figure 1 is not really appropriate. It would be much simple to put actual figures in a table, for example in table 1, giving total number of prescriptions and % high dose prescriptions for example, and total number of patients using the drug, and % high dose users.

The conclusions of the paper are clear (but not clearly put):
- prescribers avoid high doses of benzodiazepines in the elderly above 75 years of age.
- specialists use lower doses than GPs (maybe they also use more other psychotropics than just
benzos)
- when a patient has cognitive impairment, GPs avoid high doses even more, and the prescription of high doses in these at-risk patients is done mainly by specialists.

I find these conclusions rather encouraging.

**Competing interests:**

None declared.