Reviewer’s report

Title: Antidepressant use and risk of adverse outcomes in people aged 20 to 64: cohort study using a primary care database

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Reviewer: Patrick Souverein

Reviewer's report:

The authors describe an observational study on antidepressant use and risk of adverse outcomes in people 20-64 years using data from a primary care health care database in the UK. Rationale for the study was that in younger subjects, which form a substantial proportion of users, there is lack of data on side effects. The authors conducted a cohort study on almost 240,000 patients and assessed various type of outcome events. A large number of results are presented.

General comments:

Given the focus on younger users of antidepressants and clinical implications of adverse reactions, I think the paper could benefit from showing more information on absolute risks/PARs. Now we only see hazard ratios and the description of of absolute risk in table 7 that are hardly put in context in the text.

What was the reason to look at individual antidepressants as well, besides looking at the classes? Did the authors have a priori evidence that risks would be different within eg. SSRIs/TCA's?

Many outcomes and comparisons were made in the paper; how did the authors take multiple testing into account?

Specific comments:

Design:

The authors conducted a cohort study among subjects 20-64 with a first diagnosis of depression. What was the reason for the 36 months before Dx exclusion criterion for use of antidepressants? There was a 12 months requirement for availability of prior history in the database. So, theoretically, a patient could be starting antidepressants 3 years before the diagnosis of depression, which seems odd.
Outcome: the road traffic accident outcome seems vulnerable for all kinds of misclassification given absence of data on whether or not the subject was the driver and whether or not he/she caused the accident in the first place.

Adverse drug reaction: this seems a broad type of outcome event with issues on how this is coded? Did the authors use specific Read codes for the rash etc or use specific drug-induced described Read codes here?

Exposure:

According to the section, the permissible gap between prescriptions was set at 90 days. This seems rather long, as my experience is that mean durations of prescriptions in the UK are more often like 30 days. Did the authors conduct sensitivity analyses to study the robustness of their exposure definition? Furthermore, it is not clear what happened with respect to add on/switching. The section only mentions the scenario of combined use when different drugs were issued on the same date, but how was this handled if this was not at the same date? Was this considered as switching? was this considered as add-on if the previous product has a new prescription within the 90 day window? Please explain. Also, what strategy was used to impute missing data on number of tablets to be be taken?

Data analysis:

Main analysis were based on the first 5 years; I'm not sure why this was restricted in the first place? As you have all the data available, why would things need to be complicated by restricting it arbitrarily to the first 5 years?

Why where the patients using MAO inhibitors physically excluded? You could have kept them in but have made the choice not to present? How did this work out if patients switched to/from a MAO inhibitor during follow-up?

The reference group are patients not using antidepressants. This constitutes a mixture of people with a diagnosis not being treated and past users of antidepressants. Not sure about having never-users in there; wouldn't it be better to start with a cohort of patients with a diagnosis who were actually treated? In other words, sensitivity analysis 3 would be my suggestion as primary analysis for the reasons provided by the authors themselves.
Results/discussion:

Table 1: number of non-white patients seems very low? Was this to be expected in such a multicultural country?

Table 2: unadjusted HR for TCA of 1.65 seems incorrect value imputed? Adjustment for confounding seems to have the greatest impact in the all-cause mortality? What where the major drivers for the HR to go down?

The most noticeable effects seem to be for fractures, which is a known association in many observational studies. In the IMI-PROTECT projects, antidepressants and hip fracture was one the five associations studied in several designs. Did the authors assess type of fracture and also looks at duration of use to assess effect on BMD?

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

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