Reviewer's report

Title: Hepatic Outcomes Among Adults Taking Duloxetine: a Retrospective Cohort Study in a US Health Care Claims Database

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Reviewer: James H Lewis

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The authors have undertaken a review of a large insurance database for instances of hepatic injury due to duloxetine, and make a comparison to venlafaxine and SSRIs. I have a number of questions:

1. The cases selected for further chart review were adjudicated by two hepatologists, but the methods fail to state what causality assessment methodology was utilized – was it RUCAM, expert opinion or a combination as is done by the DILIN group?

2. Multiple concomitant medications were taken by these patients (table 4 and supplemental table 1), and several are also potentially hepatotoxic (e.g. diclofenac, INH, phenytoin, valproate, chlorpromazine, etc), how were these excluded (relates to comment #1)?

3. With respect to the supplemental tables, there is such a thing as too much information – it would be much more useful (and reader friendly) if the authors would summarize the most important points to be derived from the supplemental material – otherwise it is difficult to know if anyone should even spend the time to review them.

4. The authors have nearly as many more exclusions as actual duloxetine–associated liver injury patients! (table 1). It would have been very informative to know if underlying liver disease was a risk factor for any of the DILI patients. Certainly, duloxetine is used in patients with liver disease in real life. Can they offer any statements about its use in this setting? Is there any labeled warning that contraindicates its use? If so, their study might have been in a position to possibly refute such a the warning.

5. What clinical signature emerged for the DILI from duloxetine, venlafaxine and SSRIs? And how did these biochemical and clinical findings compare to the published reports and case series in the literature?

6. Is the study powered to be able to exclude a case of acute liver failure or hepatic-related death? If so, have they analyzed the published reports of severe liver injury and can they provide an alternative explanation for the events?

7. Table 3 would benefit from having the percentages of patients included (rather than just the raw numbers)
8. Why consider hepatic outcomes “irrespective” of alternative etiologies (on page 8 line 268). This seems to just muddy the waters when the goal is to describe DILI specifically related to the drugs in question. Unless they are aware of some factor that raises the risk of an hepatic event in patients using these medications, that analysis seems irrelevant.