Reviewer’s report

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

**Version:** 2  **Date:** 1 June 2015

**Reviewer:** Christine M. M Hunt

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The authors clearly defined the important study goal: to examine duloxetine hepatic safety in a large, geographically diverse US insured population (comprising 3-4% of US population). This 6 year propensity-matched cohort study (2004-2010) appropriately compared the incidence of liver injury, liver failure and liver-related death with initiation of duloxetine vs other antidepressants in depressed patients without known baseline liver injury, and additionally compared it to rates of liver injury in untreated patients with depression. # 20,000-30,000 patients/drug-treatment group or control population were compared, and were well-matched with propensity scoring (which included assessment of 100 most common drugs coprescribed with duloxetine). The study was designed similarly to Xue et al (2011), which examined the initial 2 post-marketing years in a population with #11,000 person-years of duloxetine exposure (vs #7,000 in current 6 year study).

The study title and abstract are clear and explicit about the study aims, population, and findings. The study is well-written and clear. The authors appropriately cite prior work, including the 2 year post-marketing cohort study (Xue 2011), which reported an increased risk of non-serious hepatotoxicity with duloxetine in comparison to venlafaxine, as well as Shin (2013) who reported adjusted rates of duloxetine-associated liver injuries in 2432 patients of 57.3 per 100 000 persons with 95%CI (0, 149.2).

Multiple study limitations are outlined in the discussion, including: insufficient size to demonstrate a statistically significant difference across treatment groups, and the post-hoc review of a clinically significant hepatic injury ascribed to duloxetine, which was re-examined due to claims data – however, comparator events were not re-examined, therefore, this decreased the incidence of clinically significant duloxetine-induced hepatic injury.

1. The major study limitation is that it’s underpowered to assess differences in clinically significant liver injury between groups, due to the large numbers of patients needed to evaluate this rare event. For example, duloxetine-induced liver injury is reported to affect:
   - 57.3 per 100 000 persons with 95%CI (0, 149.2) adjusted rates of

However, only #7500-10,000 duloxetine person-years were captured in the current study – inadequate to identify clinically significant liver injury between groups.

2. An additional notable limitation is that the study followup was for only 15 days after duloxetine treatment cessation. This limited study period precluded assessment of potential duloxetine chronic liver injury, reported in Fontana RJ et al. "Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset."Gastroenterol 2014;147:96-108. In this prospective series, 2 duloxetine-induced chronic liver injury events were reported among 113 chronic drug-induced liver injury events, in addition to 5 duloxetine-induced acute liver injury events within 484 acute drug-induced liver injury events overall.

Other limitations include:
3. identifying potential cases on the basis of ICD-9 diagnosis or procedure codes. Use of ICD-9 codes may under-estimate the event rate. As observed by Jinjuvadia K et al. ("Searching for a needle in a haystack: use of ICD-9-CM codes in drug-induced liver injury." The American journal of gastroenterology 2007;102: 2437-2443), <1% of acute liver injury ICD-9 codes are related to drug-induced liver injury.

4. Additionally, few patients had liver chemistries evaluated, although Line 123 states: “The secondary outcome was non-serious asymptomatic hepatic enzyme elevations.” Yet, Supplemental Table 2c reports that <1 in 20 (4.1%) duloxetine patients had liver chemistries performed.

5. the apparent use of Lilly hepatologists to adjudicate cases. The authors should indicate whether independent adjudication occurred to avoid potential bias.

6. Only 74% of medical records were obtained, limiting adjudication of potentially important study events.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
In the past 5 years, the reviewer has been a consultant to Furiex, Otsuka and was a full-time GSK employee until Aug 2012.

No stocks, patents or other financial competing interests affected by this paper.

No non-financial competing interests related to this paper.