REPLY TO REVIEWERS

Reviewer 1

Overall this is a well written case report, albeit of quite a simple case without any histological results which would have strengthened the report by more definitively ruling out alternative diagnoses (although I acknowledge the patient's improvement after escitalopram withdrawal. Please make more explicit in the case presentation the fact that she had started escitalopram 2 weeks prior to presentation (perhaps around line 61 or 62). This fact was mentioned in the abstract and in the diagram, but should be explicitly stated in the main body of the text. Otherwise this is of publishable quality.

REPLY: Thank you for the positive comments. We have now made clear in the case presentation that, "She had started escitalopram and olanzapine two weeks prior to presentation."

Reviewer 2

Overall this is a nice case report however the major limitation in this case is how the authors precluded Olanzapine as a culprit for this DILI, the exact time points for the start and the stop of each drug should be defined.

REPLY: Thank you for the comment. We have now explained that, "Although olanzapine has also been linked to reports of DILI[4], it was precluded as a culprit drug in this case because the patient had previously taken it with no issues. She was treated with oral olanzapine 10 mg once nightly and oral fluoxetine 20 mg once every morning in February 2018 for psychotic depression, with good resolution of symptoms and the drugs were subsequently tapered and stopped by December 2018."

The exact time points for the start and stop of each drug were defined in Figure 1.

Second: the authors stated that "Measurements of LFT could be considered after initiation of antidepressant treatment, especially in patients with pre-existing liver disease", how did they reach this conclusion? Please correct.

REPLY: Thank you for the comment. We agree with reviewer that this is still an area of contention. Published guidelines at present do not have recommendations regarding routine monitoring, except for a few drugs in particular (e.g. anti-tuberculosis drugs). Hence we have tempered our comments accordingly, "Although thought to be generally safe and with minimal drug-drug interactions, clinicians should be aware of the possibility of escitalopram-induced liver injury when initiating depressed patients on antidepressant treatment. This requires extra vigilance as most patients may remain asymptomatic. It is still controversial whether routine monitoring is recommended, especially in patients with pre-existing liver disease. Fortunately, DILI is typically reversible after withdrawal of the implicated drug and patients should have a favourable outcome."

Reviewer 3

This manuscript reports an escitalopram-induced liver injury case. Previously to this case, only one case of liver injury associated to escitalopram had been published despite the wide use of escitalopram suggesting that escitalopram-induced liver injury is a very rare event. This case is interesting but a more precise evaluation of escitalopram causality is needed before conclude that the drug is the culprit of the injury.

Concretely: 1 - in the case description more data about a possible allergic nature of the injury such as eosinophils counts and presence or absence of skin rashes in addition to the fever must be provided.

REPLY: Thank you for the comment. We have stated in the case presentation that, "On physical examination, she had an average build (body mass index 22.8 kg/m2), was not jaundiced, had no rash present" and "Total whites were not raised at 5.4 x 10^9 cells/L and eosinophils count were within normal limits as well (0.33 x 10^9 cells/L)."

2 - According to temporal relationship among drug intakes and liver injury detection olanzapine and escitalopram were started less than 30 days previous to injury detection. Even more, olanzapine increased dose in that period. Why olanzapine was not considered suspected of causing the injury and only escitalopram treatment was retired? What about the interaction between olanzapine and escitalopram as the responsible of injury?

REPLY: Thank you for the comments. We have now explained that, "Although olanzapine has also been linked to reports of DILI[4], it was precluded as a culprit drug in this case because the patient had previously taken it with no issues. She was treated with oral olanzapine 10 mg once nightly and oral fluoxetine 20 mg once every morning in February 2018 for psychotic depression, with good resolution of symptoms and the drugs were subsequently tapered and stopped by December 2018."

In our discussion section, we also explained that, "we are unable to entirely exclude the fact that olanzapine may have also contributed to her liver injury as olanzapine also undergoes extensive hepatic metabolism by CYP1A2 and to a lesser extent by CYP2D6[11]. Olanzapine has also been reported to cause transient serum liver enzyme elevations[4]."

3 - Authors must apply the CIOMS/RUCAM scale of hepatotoxicity to quantitatively assess the causality of suspected drug induced liver injury in this case. The causality for escitalopram, olanzapine and the interaction between both drugs should be assessed and items and points resulting for each drug must be showed in the text.

REPLY: Thank you for the comment. We have now added that, "The Roussel Uclaf Causality Assessment Method (RUCAM) scoring[5] also helps clinicians determine how likely the diagnosis of DILI is. The components considered are: (1) time to onset (+1 or +2); (2) course (-2, 0, +1, +2 or +3); (3) risk factors (2 scores: 0 or +1 each); (4) concomitant drugs (0, -1, -2 or -3); (5) nondrug causes of liver injury (-3, -2, 0, +1, or +2); (6) previous information on the hepatotoxicity of the drug (0, +1, or +2); and (7) response to

rechallenge (-2, 0, +1, or +3)[5]. Applying the RUCAM scoring to our patient, escitalopram yielded a total score of at least 5, suggesting that it was a 'probable' cause of DILI."

4 - The termination date of fluoxetine treatment by the patient must be indicated in the text. If termination date was less than 3 months previous to injury detection and according to the long half-life of fluoxetine and its metabolite a consideration about a possible fluoxetine involvement in the development of injury must be done.

REPLY: Thank you for the helpful comment. We have now added the following information as requested, "She was treated with oral olanzapine 10 mg once nightly and oral fluoxetine 20 mg once every morning in February 2018 for psychotic depression, with good resolution of symptoms and the drugs were subsequently tapered and stopped by December 2018."

5 - In the conclusion section, authors state that "Measurements of LFT could be considered after initiation of antidepressant treatment, especially in patients with pre-existing liver disease". Why in patients with pre-existing liver disease? What information manage the authors to state this recommendation?

REPLY: Thank you for the comment. We agree with reviewer that this is still an area of contention. Published guidelines at present do not have recommendations regarding routine monitoring, except for a few drugs in particular (e.g. anti-tuberculosis drugs). Hence we have tempered our comments accordingly, "Although thought to be generally safe and with minimal drug-drug interactions, clinicians should be aware of the possibility of escitalopram-induced liver injury when initiating depressed patients on antidepressant treatment. This requires extra vigilance as most patients may remain asymptomatic. It is still controversial whether routine monitoring is recommended, especially in patients with pre-existing liver disease. Fortunately, DILI is typically reversible after withdrawal of the implicated drug and patients should have a favourable outcome."
