Author's response to reviews

Title: A pooled analysis of injection site-related adverse events in patients with schizophrenia treated with olanzapine long-acting injection

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Author's response to reviews: see over
Joshua Kantrowitz, MD  
Associate Editor, *BMC Psychiatry*

Re: Review of manuscript 1465050923954573, your email dated July 25, 2013

Dear Dr. Kantrowitz,

We would like to thank the reviewers for their thoughtful comments on our manuscript “A pooled analysis of injection site-related adverse events in patients with schizophrenia treated with olanzapine long-acting injection”. Below we have responded to each point with an explanation and, if necessary, exactly how the text of the manuscript was modified. We hope that the reviewers will find our answers to their concerns acceptable.

We hope you agree that our manuscript is improved and is acceptable for publication in *BMC Psychiatry*. If you have any additional concerns, please do not hesitate to contact us.

Sincerely,

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Reviewer: JB

The authors present a retrospective pooled analysis of injection related adverse events of olanzapine pamoate. The use of LAI medications is often limited by concerns about injection site pain/adverse events.

1. Please provide more information about the other medications. It would be helpful to have some understanding from the beginning of what the general range of injection-related AE's are for other medications. How many of these cited studies of other medications excluded studies in which active-solicitation was used (as was done in this report)?

Information about injection site-related adverse events is not widely reported, unfortunately. Indeed, that was one of the reasons that we chose to write this manuscript. We indicate whether or not active solicitation was used in the studies that we cite, if that information is available. We have modified the Background of the present manuscript to provide some indication to the reader about the incidence of injection site-related adverse events noted in the literature.

Page 4, paragraph 2, the following has been added:
“However, the extent of injection site-related AEs reported with injectable long-acting antipsychotic medications is not widely studied in the literature. Rates as low as 1.9% [7] and as high as 10% [8] have been reported in different papers.”


2. Was the one excluded duration result considered to likely be inaccurate? What is the justification for excluding the outlier?

The excluded data point was almost certainly an error (probably a running response for an adverse event that wasn’t closed). We have modified the sentence to make this clearer.

Page 8, paragraph 4, now reads in part:

“It should be noted that 1 data point was excluded from the data analysis because it was an extreme outlier and most likely an error (1097 days of injection site pain, which was greater than 300 times the median).”

Reviewer: JK

This report of the adverse events to olanzapine long-acting injection is of moderate interest, but the limited focus, as described below reduced my enthusiasm.

1. As written, it seems to suggest that injection site reactions are the only adverse reactions of note.

We have included an additional paragraph at the beginning of the Discussion to put injection site-related adverse events in better perspective.

Page 9, paragraph 2 has been inserted:

“The safety and efficacy of olanzapine LAI have been reported previously and have been shown to be similar to those of oral olanzapine ([10-12], with the exception being the occurrence of injection-related AEs. Injection-related AEs for olanzapine LAI can include AEs localized to the injection site itself but can also include PDSS events [13, 15]. The purpose of the present analysis was to focus specifically on injection site-related AEs, which are not well understood but may have an impact on patient satisfaction and treatment adherence.”


2. If the limited focus on injection site reactions is to be maintained, a more systematic comparison to other long acting preparations should be included so that the reader can have some context.

See reviewer JB, comment 1.

3. Specifically, I had some concerns about the limited focus on the most serious side effect (olanzapine long-acting injection)…

We are assuming that the reviewer is referring to post-injection delirium/sedation syndrome (PDSS) events. Two other articles have been published specifically about PDSS events, and these are cited in our manuscript.


4. …and moreover, the lack of formal pain assessment…

The present manuscript was based on a post-hoc analysis of 7 olanzapine LAI clinical trials, none of which were designed to formally assess injection site pain. However, adverse event severity and duration were included in the analysis to provide some indication of the extent of all of the injection site-related adverse events, including injection site pain. Note also that we pointed out the lack of formal assessment of pain in our original manuscript as a limitation: “First, although the majority of the injection site-related AEs were injection site pain, none of the studies included a formal assessment of pain severity.”
5. …and limited focus on adverse events titled "injection site." The authors presumably had access to all adverse event reports, and I would be more convinced if a manual search was conducted to ensure nothing was missed.

As mentioned in the methods section of the manuscript, “Only injection site-related AEs were assessed (i.e., AEs with Medical Dictionary for Regulatory Activities [MedDRA] preferred terms that contained the phrase “injection site”).” This is also pointed out in the Limitations section (page 11): “Finally, our event-term search strategy required “injection site” to be specified in the event term; however there may be other events in the database which were related to the injection but were excluded because the location of the reaction was not specified.” We searched on the phrase “injection site” because adverse events for which the location was not specified could be easily misinterpreted.

6. I was unclear as to why the focus was limited to injection site AE's, it is possible that other AE's such as sedation or weight gain would also affect the risk benefit profile of this medication.

Please see our response to comment #1. The adverse events related to oral olanzapine are well known and have been published on extensively. Our purpose in this paper was to address concerns related specifically to olanzapine LAI adverse events occurring at the injection site. We think this is an important topic because the potential misperception of the extent of these events may impact patient preference of oral versus LAI dosing.