Author's response to reviews

Title: Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection. I: analysis of cases.

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Version: 2 Date: 12 May 2010

Author's response to reviews: see over
12 May 2010

Melissa Norton, MD
Editor-in-Chief, BMC Psychiatry
BioMed Central Ltd, Floor 6
236 Gray's Inn Road
London, WC1X 8HL, United Kingdom

Re: MS# 5816706623192332

Dear Dr. Norton:

Thank you very much for your review of our manuscript, “Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection: I. analysis of cases.” Please find below a point-by-point response to the reviewers’ comments. All changes to the manuscript have been marked with track changes. Page numbers in the response refer to the page numbers in the track-changes version. Please let us know if there is anything else that we need to provide.

Thanks again to you and all three of the reviewers for the helpful feedback.

Sincerely,

Holland Detke, PhD
Senior Clinical Research Scientist
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Comments from the Editorial Team

1. Document ethics committee approval and informed consent.

Response: We have added the following statement to the Methods section, p.6:
“All study protocols were approved by institutional review boards at each site. After receiving a complete description of the study, all patients and/or their authorized legal representatives provided written informed consent before participation.”

2. Please also ensure that your revised manuscript conforms to the journal style.

Response: We have reformatted the title page and reference section to conform to the journal style and have added a Trial Registration section to the abstract.

Comments from Referee 1 (D. Taylor)
No changes requested.

Comments from Referee 2 (W. Cronenwett)
Minor Essential Revisions:

1. Consistency with symbol usage in the term "Post-injection delirium/sedation syndrome." The slash character is missing from the title of Appendix A.

Response: Corrected. Slash has been added.

2. Page 11: "characterized as convulsive movements:" indicate that this was not a diagnosis, but a description. Perhaps "described by witnesses as convulsive movements."

Response: We have revised the sentence as suggested (p.12).

3. Break out the recommendations for monitoring patients post-injection ("Risk Management") into an Appendix B, or alternatively, present as a table or box within the main text. These recommendations are important and will be sought by clinicians reading the paper; they should be given appropriate prominence by repeating in a table or box in bullet list form.

Response: Good suggestion. We have added an Appendix B as well as a statement on p.20 at the end of the Risk Management section referring the reader to this appendix along with some additional text about what to do if a PDSS event is suspected: “These precautions are summarized in Appendix B. Note that if a PDSS event is suspected, close monitoring and supervision of the patient should continue until examination indicates that signs and symptoms have resolved. Also, if parenteral benzodiazepines are required for the management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression are recommended.”

Appendix B is as follows:
Safety Precautions for Each Administration of Olanzapine Long-Acting Injection

**Before the injection:**
- Determine that the patient will not travel alone to their post-injection destination.

**During the injection:**
- Aspirate the syringe for several seconds following insertion of the needle into the muscle to ensure that no blood appears before injecting the medication. If any blood is aspirated into the syringe, discard the syringe, reconstitute a new vial of olanzapine LAI, and inject into the alternate side of the buttock.

**After the injection:**
- Patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

**Before leaving the healthcare facility:**
- Confirm that the patient is alert, oriented, and without signs or symptoms of a post-injection delirium/sedation syndrome (PDSS) event.*
- Advise patients to be vigilant for symptoms of a PDSS event for the remainder of the day and be able to obtain medical assistance if needed.

**After leaving the healthcare facility:**
- Patients should not drive or operate machinery for the remainder of the day.

* If post-injection delirium/sedation syndrome is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. If parenteral benzodiazepines are required for the management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

**Discretionary Revisions:**

1. Page 18: "more prone to bleeding or vessel injury." For additional clarity, indicate whether there is a hypothesized mechanism for this, and if one exists, what it might be.

**Response:** We have now added information about the hypothesized mechanism here. Because this lengthened the paragraph significantly, we divided the paragraph in two. The requested information is in the second of these (on pp.18-19), which now reads (italics represent newly added text):

   “Nevertheless, another finding which suggests that there may also be individual patient factors which could affect the occurrence of PDSS is the fact that one patient in the clinical trials experienced this event twice. Examination of medical history and concomitant medications indicated that this patient had a number of chronic conditions (including diabetes, arthritis, alcoholism, and hypertension) and may have been in poorer general health than the other PDSS patients, although such conditions are not at all uncommon in patients with schizophrenia and are certainly represented among the patients who did not experience PDSS. It is important to note that McDonnell et al [5] found olanzapine pamoate to be significantly more soluble in blood, such that accidental contact of the medication with a large quantity of
blood may produce higher than expected olanzapine plasma concentrations in a manner that would be consistent with the clinical presentation and timing of the symptoms of PDSS. Thus, a patient who was more prone to bleeding and/or vessel injury might theoretically be at greater risk for this accidental occurrence. Chronic salicylate usage has been associated with increased clotting time and risk of bleeding (Goldsweig et al 1976; Weis & Aledort 1967; Weis et al 1968), as has alcoholism (Mukamal et al 2005; Iber et al, 1986). Also, chronic diabetes can result in vascular fragility (Hart & Cohen, 1969; Purushothaman et al 2007). Thus, any or all of these factors may have created a predisposition toward excessive bleeding and/or increased likelihood of vessel injury in this patient. Beyond the idiosyncratic situation with this particular patient, the hypotheses generated by this case may converge with the statistical findings of greater age and lower BMI as weak risk factors for PDSS if one assumes that greater age is associated with a higher likelihood of poorer general health and likelihood of vascular fragility and if lower BMI is associated with higher likelihood of vascular injury during the injection. However, none of these hypotheses have been able to be confirmed. Further research on a larger number of cases is needed to explore more fully the possibility of specific risk factors.”

2. It was considered that this article be merged with I: Analysis of Cases, but I recommend against that. I favor publishing these two articles as related, independent manuscripts.

Response: We agree with this perspective and will assume that this is the prevailing decision of the editorial board as well since the overall letter did not request that the papers be merged.

Comments from Referee 3 (J.M. Olivares)
Dr. Olivares suggested that this paper be summarized in the first paper (analysis of cases).

Response: Again, we will assume that the prevailing decision of the editorial board was that the papers should not be merged. Additional description of the findings from the companion paper (McDonnell et al [5]) are now included on pp.18-19 (see response to Dr. Cronenwett above), which we hope will suffice to address this comment.