Author's response to reviews

Title: A randomized, double-blind, placebo-controlled study of intramuscular olanzapine in Japanese patients for schizophrenia with acute agitation

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Author's response to reviews: see over
Dear Editor,

Please find enclosed our response to reviewer comments for the manuscript (MS: 6891922947185256), “A randomized, double-blind, placebo-controlled study of rapid-acting intramuscular olanzapine in Japanese patients for schizophrenia with acute agitation” by Hideaki Katagiri et al., which we would like to resubmit for publication as an original manuscript in BMC Psychiatry. Our point-by-point response to reviewer comments is listed below.

**Response to Reviewers**

**Reviewer 1**

**Major compulsory revisions:**

1) Why did the authors include one patient was excluded from FAS analysis when they analyzed for the safety measures? The number of patients who were enrolled analysis would be better more clearly between 90 and 89.

- Added sentence, pg 15: To be statistically conservative, the FAS used for the safety analysis included all patients who received study drug.

2) Can we use the IM olanzapine for the patients with diabetes mellitus? The authors need to write the discussion about it.

- Olanzapine IM can be used but it is important to monitor the patient’s diabetes.
- Added text to the Discussion section, pg 21: Metabolic adverse events associated with glucose metabolism are often discussed as potential risks of olanzapine treatment.[27] Although there were no clear signals of adverse
events or laboratory changes associated with glucose metabolism in this study, it is important to monitor patients for adverse events and laboratory changes associated with glucose metabolism in clinical practice.

3) It was insufficient discussion about using IM not oral olanzapine in case of psychotic agitation.

- Added text, pg 5-6: Oral medications are considered to be preferable to parenteral administration.[14] Therefore, oral solutions have become used more frequently than injections to calm patients who have agitation, but patients with severe agitation do not always take oral medications. Antipsychotic injections allow physicians to treat patients, but also could be expected to calm patients more rapidly than oral medications.[15] Therefore, antipsychotic injections are still an option, especially to calm agitated patients who refuse to take medications.

Reviewer 2

Major Compulsory Revisions

None

Minor Essential Revisions

1) Page 5, line 3: “..should be sedated as soon as possible…”: The desired outcome of treatment of acute agitation is not sedation, but more a calming effect. The use of sedation as desired outcome should be changed.

- replaced sedation with calm
1. Added text, pg 5: In those cases, patients should be calmed as soon as possible to achieve a state of calm sufficient to minimize the risk posed to them or to others. Patients should be sedated as soon as possible.

2. Page 6, line 2: Please provide reference for antipsychotic injections sedating patients faster than oral medications.

   - Added a reference to this sentence: Antipsychotic injections allow physicians to treat patients, but also could be expected to calm patients more rapidly than oral medications.[15]


3. Page 7, lines 3-7: The sentence is non-sense. Please rephrase.

   - Revised, pg 7: The primary objective of the study was to confirm the efficacy of IM olanzapine (10 mg) was greater than efficacy of IM placebo in Japanese patients who had exacerbation of schizophrenia with acute psychotic agitation.

     Efficacy was measured by comparing the change from baseline to 2 hours after the first IM injection in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) total score.[21,22] We report the results of this study in this paper.

4. Page 9, line 14: Please clarify injection site (gluteal ?)

   - Added text, pg 9: All patients received at least 1 injection in the upper outer quadrant of the gluteus maximus muscles.

5. Page 16, line 12: Please provide p-value for 24-hour PANSS-EC score in the manuscript.

   - The p-value ($p=.008$) was added.
6) Page 17, line 11: Please provide p-value for difference in need of second injection between groups

- The p-value ($p=.2917$) was added.

7) Page 19, lines 9-10: Remove understrike

- Removed

**Discretionary Revisions**

8) Page 8, lines 1-3: You could provide data on distribution of patients in these three groups, for both placebo and olanzapine groups.

- We do not have this data.

9) Page 9, 6-9: You could provide data on the use of benzodiazepines in each treatment arm

- Thirty-seven patients (82.2%) in the IM olanzapine group and 28 patients (62.2%) in the IM placebo group used benzodiazepines within 24 hours before the first IM injection ($p=.059$). There were no notable differences between the IM olanzapine (20.0%) and IM placebo (17.8%) groups in the proportion of patients using benzodiazepines from 2 hours after the first IM injection ($p=1.0$). In terms of time to the first use of benzodiazepines (hours), there was no major difference between the IM olanzapine (mean=11.9 hours) and IM placebo (mean=8.7 hours) treatment groups.

- The usage of benzodiazepine 2 hours after the first injection was allowed not only when a new treatment was required for adverse events but also when the continued treatment with them was difficult to stop. This means that the usage of benzodiazepine before the first injection could influence the usage of
benzodiazepine after the first injection. We believe the results do not add relevant information so we prefer not to add them to the manuscript.