Author's response to reviews

Title: Predictors of psychiatric hospitalization during 6 months of maintenance treatment with olanzapine long-acting injection: post hoc analysis of a randomized, double-blind study

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Author's response to reviews: see over
Dear Editor

Thank you for your consideration of our manuscript and the helpful comments from the reviewers. We have addressed each of the comments (as documented below) and hope that you find the revised manuscript worthy of publication in BMC Psychiatry.

EDITORS COMMENTS:

1. The authors should add baseline BMI to table 1 and comment on the lack of significant difference in the discussion of the paper.

Reply: Done as requested. Table 1 includes baseline BMI and the Results section states: “There were no statistically significant differences between the groups on any of the baseline sociodemographic or clinical characteristics.”

2. Was there any difference in duration of illness between the two groups?

Reply: There was no difference in duration of illness, which was 13.4, 13.5 and 13.5 years for the three treatment groups, respectively.

REVIEWER'S REPORT

REVIEWER: Rune Kroken

A well-written report in a topic of great clinical significance for patients with schizophrenia. The use of inpatient treatment is costly, and differs between health systems and nations. The manuscript needs some improvement before publication. The two-fold goal can be reconsidered; the design of the study is more suitable for the investigation of predictors for hospitalisation than for the comparison of oral to LAI antipsychotics.

Major compulsory revisions

Introduction:

1. The main topic is predicting hospitalisation, but there is no overview over previous literature on this topic in the introduction, e.g. suicidality or previous hospitalisation.

Reply: We have included in the Background a paragraph (with additional references) about factors associated with hospitalization in schizophrenia and the risk of suicide. The Background text now states:

“Loss (or lack) of medication efficacy and medication non-adherence tend to act synergistically to increase the risk of relapse and hospitalization. Even in patients receiving continuous medication, it has been estimated that 3.5% of patients will relapse per month, and this rate increases to 11% per month among non-adherent patients [3]. Substantial inpatient hospitalization cost savings can thus be realized by linking better pharmacological treatments with more effective strategies to manage medication non-adherence in the management of patients with schizophrenia [3,7]. High severity of
positive symptoms, lack of insight, not living with the family, frequent past episodes, addiction to illegal drugs, and global illness severity have all been associated with a higher risk of hospitalization [8]. Suicide behavior, which may be present in over 50% of patients [9] and may cause a 10–13% mortality rate in schizophrenia [10], is also associated with a high risk of hospitalization, as hospitalization is a frequent treatment intervention for suicidal patients."

New references added:

2. As a subgoal in the study is to compare olanzapine oral and LAI, some central papers regarding the use of RCTs to study the effects of oral vs. LAI antipsychotics could have been referred to.

Reply: We have added several recent references to studies comparing antipsychotics in oral vs. long acting injection formulations. The Background section has been revised to state:

“Prior research has shown differential rates of hospitalization among oral antipsychotics, as clozapine and olanzapine were found to be associated with a lower rehospitalization rate compared with other oral antipsychotics [11,12]. Long-acting injection (LAI, depot) antipsychotic formulations are recommended for the treatment of non-adherent patients [13], as depot medications ensure adherence during the injection duration and may help reduce the risk of relapse [14–16]. It has been reported that LAI formulations can reduce the risk of relapse in patients with adherence difficulties [17]. The comparative effectiveness of oral vs. LAI antipsychotics in reducing patients’ relapse and hospitalization rates has been a topic of controversy. A recent literature review and meta-analysis [18] found that LAI antipsychotics were associated with a lower risk of relapse but the limited data on hospitalization did not reveal significant differences between the two formulations. These findings, along with other recent publications [19,20], help highlight that the lack of observed differences in treatment outcomes between oral and LAI antipsychotics may be driven by reliance on randomized clinical trials, which tend not to enroll non-adherent schizophrenia patients, the very group of patients for whom LAI antipsychotics are most appropriate.”

New references added:
18. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S: Oral versus depot antipsychotic drugs for schizophrenia--a critical systematic review and


This topic is further expanded in the Discussion section, which states:

“This finding is likely driven by the study design, a randomized clinical trial (RCT) of stable, mildly ill and mostly adherent outpatients. In this sample, the hospitalization rate was relatively low, which lowers the power of finding significant findings. Although non-adherent patients are typically the ones chosen for depot formulations in clinical practice, they are often reluctant to enroll in RCTs. This interpretation seems consistent with a recent study that found differences in effectiveness when comparing results from RCTs and observational studies, with observational studies finding larger medication differences [20]. A large review of RCTs comparing oral with LAI treatment found significant differences in relapse rates between RCTs of depot and oral antipsychotics, but did not find differences in hospitalization rates or other outcome parameters [18]. As mentioned above, naturalistic studies have shown differences in hospitalization rates between oral and depot formulations. For example, Tiihonen and colleagues conducted retrospective analyses of Finnish databases and found depot therapy to be associated with a significantly lower risk of hospital admission compared with oral formulations of the same compounds [11,12]. In another similar study in Hungary, depot antipsychotics were found to have a lower hospitalization rate than many other oral antipsychotics [19]. Similar findings were observed in the Schizophrenia Outpatients Health Outcomes (SOHO) Study [35], a large pan-European, naturalistic, prospective, observational study of schizophrenia patients. That analysis of SOHO focused on non-adherent patients who were initiated on typical antipsychotics in oral or depot formulations (n = 431) and found that patients initiated on depot formulations had a significantly lower rate of hospitalization and a lower mean number of hospitalizations following 6 months of treatment. The potential confounding impact of clinical trials versus naturalistic practice settings will require further research to clarify the relative advantage of depot versus oral atypical antipsychotics in reducing the risk of hospitalization among patients with schizophrenia. Observational studies may be better suited to study the impact of depot therapy on treatment outcomes among non-adherent patients because these patients tend not to participate in RCTs.”

2. The first lines of the methods section is also given in the introduction, there should be no need to do so.

Reply: The respective lines of the Methods section have been deleted.

Methods:
1. It would have been nice to know how many sites in which countries participated, and the number of patients per site, and the length of the follow-up in each group.

Reply: We have added more information to the Methods section (the detailed information requested was not available). The Methods section now states:

“This multicenter study was conducted by 113 investigators at 112 study sites in 26 countries. The countries which participated in the study were Spain, France, Sweden, Norway, Austria, Belgium, Finland, Netherlands, Germany, Portugal, Italy, Russia, Hungary, Turkey, Greece, Romania, Poland, Israel, Argentina, Brazil, Puerto Rico, United States, Mexico, Australia, South Africa, and Taiwan.”

2. Should there be a subheading called "Variables" in the method section? Much of the text in the "Study design" and some in the "Statistical analysis" section could have been labeled so.

Reply: We have included a subheading called “Variables” which includes some text of the methods and statistical analysis section.

3. Did the study assess the use of alcohol or drugs?

Reply: Sorry, the study did not assess the use of alcohol or drugs.

Results:

The section is perhaps too long, the paper would benefit of a more condensed version.

Reply: The Methods section has been shortened, deleting the following:

“Age ranged from 38.8 to 39.5 years and the proportion of males ranged from 64.9% to 66.7%. Mean PANSS overall scores were 57.8 in the sub-therapeutic olanzapine-LAI group, 56.1 in the oral olanzapine group, and 55.4 in the olanzapine-LAI group.”

We have not deleted any more text from the Results section because either it presents data not shown in the tables or summarizes the main findings of the tables.

Minor points:

Figures: X-axis: days?

Reply: Yes, days. The title of the figure now indicates that the X-axis is in days.

REVIEWER: Istvan Bitter

Reviewer's report:

The authors address an important practical question, namely the predictors of hospitalizations during maintenance treatment with the long acting formulation of a frequently used antipsychotic, olanzapine.
The manuscript is clearly written, the main message (in addition to prior hospitalizations suicidality at baseline is a strong predictor of hospitalization) is important for the praxis.

I have only a few comments/questions. (MER: minor essential revisions; DR: Discretionary Revisions)

1. The 1:2:1:2:1 random assignment would deserve a short explanation (DR)

Reply: Considering the complexity of the study (2 study phases, 5 treatment groups) we simplified the section, stating:

“The study had an open-label stabilization phase (4–8 weeks) followed by a double-blind randomized phase (24 weeks). During the stabilization phase, all patients were switched to open-label oral olanzapine monotherapy at a dose of 10, 15 or 20 mg/day. Patients who met the stabilization criteria were randomly assigned to double-blind therapy with one of the following five treatments: low-dose olanzapine-LAI (150 mg/2 weeks, n = 140), medium-dose olanzapine-LAI (405 mg/4 weeks, n = 318), high-dose olanzapine-LAI (300 mg/2 weeks, n = 141), oral olanzapine (a stabilized dose of oral olanzapine, 10, 15 or 20 mg/day n = 322) and a sub-therapeutic (very low) dose of olanzapine-LAI (45 mg/4 weeks, n = 144).”

2. “Suicide threat” sounds stigmatizing. I suggest to replace the term (e.g. with suicidality?) and define it. (MER)

Reply: The study assessed only “suicide threat” and did not assess suicidality, which may include suicide threats, gestures and attempts. We opted, therefore, to keep the term “suicide threat” as used in the study.

3. What does it mean (suicide threat) “before baseline”? When? (MER)

Reply: “before baseline” refers to data assessed for the 12 months before patients’ baseline assessment. This information has been added to the text.

4. “Age ranged from 38.8 to 39.5 years.” Is it correct? Looking at the ages of the hospitalized (42.1, SD 9.6) and nonhospitalized patients (38.8, SD 11.4) (p.9) it seems to be an error. (MER if it is an error)

Reply: The age range (per Table 1) was for the 3 treatment groups (olanzapine-LAI, sub-therapeutic olanzapine and oral olanzapine). The mean age of the hospitalized subgroup was found to be older than the non-hospitalized patients. Please note that to comply with a request from another reviewer, we condensed the Results section and removed the text about mean age for the treatment groups because this was a duplication of information already included in Table 1.

5. As a feature of the design the patients were “stabilized” at the baseline, thus had low PANSS total scores, which limits further changes and explains the weak association with the risk of hospitalization – maybe it should be emphasized. (DR)
Reply: We thank the reviewer for this helpful comment. We have added this point to the limitations section (in the Discussion), stating: “Thus, as all patients were first stabilized on oral olanzapine and their baseline PANSS scores were within the mildly ill range, the chances of finding differences between the oral and depot formulations of olanzapine were much reduced. This may also explain the relatively low hospitalization rate observed in the study.”

6. Was the duration of the hospitalization really 1.5 versus 2.9 days? They are extremely short – this issue would need some explanation. (MER)

Reply: The calculation of the mean number of days includes both patients hospitalized and not hospitalized (calculation is number of days in the hospital including all patients divided by total number of patients in the group). This has been clarified by the addition of a footnote to Table 2.

7. The lack of significant difference in the efficacy (preventing hospitalization) between the oral and LAI formulation of olanzapine is not surprising considering the studied patient population (participants of a double blind RCT). Two recent papers (published after or round the submission of this manuscript) might help in better discussing the differences between RCT-s and real life (DR): Bitter et al: Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: A nationwide study in Hungary. European Neuropsychopharmacology (2013), http://dx.doi.org/10.1016/j.euroneuro.2013.02.003 (in press).

Reply: We thank the reviewer for this helpful suggestion. The two papers have been added to both the Background and Discussion sections of the manuscript.

REVIEWER: Naoki Hayashi

By utilizing the data obtained in the already published main study, the authors addressed the research question what clinical factors predict hospitalization of schizophrenic outpatients. The question is of great interest for the readers. The data collection process was well documented in the main RCT study. However the manuscript did not appear to be very well organized. Additionally, it needs to be questioned whether this study added new findings to those of the main study.

Major compulsory revisions:

1. There seemed to be no discussion about the finding concerning suicide threat as a predicting factor of hospitalization. This might be the important advantage of this study that the main study did not deal with.

Reply: The Background section have been revised to include additional information and references regarding the relationship between suicide threats and hospitalization.
The Background now states:

“Suicide behavior, which may be present in over 50% of patients [9] and may cause a 10–13% mortality rate in schizophrenia [10], is also associated with a high risk of hospitalization, as hospitalization is a frequent treatment intervention for suicidal patients.”

New references added:

In another paragraph of the Background we included:

Loss (or lack) of medication efficacy and medication non-adherence tend to act synergistically to increase the risk of relapse and hospitalization. Even in patients receiving continuous medication, it has been estimated that 3.5% of patients will relapse per month, and this rate increases to 11% per month among non-adherent patients [3]. Substantial inpatient hospitalization cost savings can thus be realized by linking better pharmacological treatments with more effective strategies to manage medication non-adherence in the management of patients with schizophrenia [3,7]. High severity of positive symptoms, lack of insight, not living with the family, frequent past episodes, addiction to illegal drugs, and global illness severity have all been associated with a higher risk of hospitalization [8]. Suicide behavior, which may be present in over 50% of patients [9] and may cause a 10–13% mortality rate in schizophrenia [10], is also associated with a high risk of hospitalization, as hospitalization is a frequent treatment intervention for suicidal patients.

New references added:

The authors should also include the definition of “suicide threat” in the manuscript. In addition, is the term, “suicide attempt” in Line 7, Page 10 a synonym for “suicide threat”, or not?

Reply: Thank you for bringing to our attention that we have erroneously used the term “suicide attempt” (once, on page 10). This has been changed to “suicide threat” as the study only assessed “suicide threat” and “suicide threat” was included in the data collection form as is, without further definition or detail.

Minor Essential Revisions:
2. Why did not the authors refer Cox proportional hazard regression analysis in Abstract? It played an important role in the analysis of this study. In contrast, the authors referred to Kaplan-Meier product limit estimator in Abstract and Methods section, but seemingly only insufficiently presented its related results in Results section.

Reply: We thank the reviewer for pointing out the inconsistency. We have amended the abstract to include information on the Cox’s model. The revised text states:

“Logistic regression and Cox’s proportional hazards models were used to identify the best predictors of hospitalization. Comparisons between the treatment groups employed descriptive statistics, the Kaplan–Meier estimator and Cox’s proportional hazards models.”

3. The most of descriptions of Abstract Background subsection are to be placed in Abstract Methods subsection in nature? Additionally, those of Abstract conclusions subsection seemed only summarizing the results of this study. They should be an integration of the results and the present research conditions.

Reply: The abstract has been revised in line with the reviewer’s helpful recommendations. The abstract now states:

Abstract

Background: Hospitalization is a costly and distressing event associated with relapse during schizophrenia treatment. No information is available on the predictors of hospitalization during maintenance treatment with olanzapine long-acting injection (olanzapine-LAI) or how the risk of hospitalization differs between olanzapine-LAI and oral olanzapine. This study aimed to identify the predictors of psychiatric hospitalization during maintenance treatment with olanzapine-LAI and assessed four parameters: hospitalization prevalence, incidence rate, duration, and the time to first hospitalization. Olanzapine-LAI was also compared with a sub-therapeutic dose of olanzapine-LAI and with oral olanzapine.

Methods: This was a post hoc exploratory analysis of data from a randomized, double-blind study comparing the safety and efficacy of olanzapine-LAI (pooled active depot groups: 405 mg/4 weeks, 300 mg/2 weeks, and 150 mg/2 weeks) with oral olanzapine and sub-therapeutic olanzapine-LAI (45 mg/4 weeks) during 6 months’ maintenance treatment of clinically stable schizophrenia outpatients (n = 1064). The four hospitalization parameters were analyzed for each treatment group. Within the olanzapine-LAI group, patients with and without hospitalization were compared on baseline characteristics. Logistic regression and Cox’s proportional hazards models were used to identify the best predictors of hospitalization. Comparisons between the treatment groups employed descriptive statistics, the Kaplan–Meier estimator and Cox’s proportional hazards models.

Results: Hospitalization was best predicted by suicide threats in the 12 months before baseline and by prior hospitalization. Compared with sub-therapeutic olanzapine-LAI, olanzapine-LAI was associated with a significantly lower hospitalization rate (5.2% versus 11.1%, p < 0.01), a lower mean number of hospitalizations (0.1 versus 0.2, p = 0.01), a shorter mean duration of hospitalization (1.5 days versus 2.9 days, p < 0.01), and a similar median time to first hospitalization (35 versus 60 days, p = 0.48).
Olanzapine-LAI did not differ significantly from oral olanzapine on the studied hospitalization parameters.

**Conclusions:** In clinically stable schizophrenia outpatients receiving olanzapine-LAI maintenance treatment, psychiatric hospitalization was best predicted by a history of suicide threats and prior psychiatric hospitalization. Olanzapine-LAI was associated with a significantly lower incidence of psychiatric hospitalization and shorter duration of hospitalization compared with sub-therapeutic olanzapine-LAI. Olanzapine-LAI did not differ significantly from oral olanzapine on hospitalization parameters.

4. In many parts of the manuscript, hospitalization and relapse were discussed in a parallel manner without sufficient attention to their difference. The authors need to organize the discussion by focusing their difference.

Reply: As suggested, we have better organized the Background and Discussion sections by differentiating the relapse and hospitalization. The Discussion section now states:

“The risk of hospitalization – as assessed here using four hospitalization parameters – however, was not found to differ significantly between the oral and LAI formulations of olanzapine. This finding is likely driven by the study design, a randomized clinical trial (RCT) of stable, mildly ill and mostly adherent outpatients. In this sample, the hospitalization rate was relatively low, which lowers the power of finding significant findings. Although non-adherent patients are typically the ones chosen for depot formulations in clinical practice, they are often reluctant to enroll in RCTs. This interpretation seems consistent with a recent study that found differences in effectiveness when comparing results from RCTs and observational studies, with observational studies finding larger medication differences [20]. A large review of RCTs comparing oral with LAI treatment found significant differences in relapse rates between RCTs of depot and oral antipsychotics, but did not find differences in hospitalization rates or other outcome parameters [18]. As mentioned above, naturalistic studies have shown differences in hospitalization rates between oral and depot formulations. For example, Tiitinen and colleagues conducted retrospective analyses of Finnish databases and found depot therapy to be associated with a significantly lower risk of hospital admission compared with oral formulations of the same compounds [11,12]. In another similar study in Hungary, depot antipsychotics were found to have a lower hospitalization rate than many other oral antipsychotics [19]. Similar findings were observed in the Schizophrenia Outpatients Health Outcomes (SOHO) Study [35], a large pan-European, naturalistic, prospective, observational study of schizophrenia patients. That analysis of SOHO focused on non-adherent patients who were initiated on typical antipsychotics in oral or depot formulations (n = 431) and found that patients initiated on depot formulations had a significantly lower rate of hospitalization and a lower mean number of hospitalizations following 6 months of treatment. The potential confounding impact of clinical trials versus naturalistic practice settings will require further research to clarify the relative advantage of depot versus oral atypical antipsychotics in reducing the risk of hospitalization among patients with schizophrenia. Observational studies may be better suited to study the impact of depot therapy on treatment outcomes among non-adherent patients because these patients tend not to participate in RCTs.”

New references added:


**Discretionary Revisions:**

5. The authors included solely Olanzapine LAI in the title, and explain the finding of Olanzapine LAI with more words than that of oral Olanzapine in Conclusion section though it could not be determined which was more excellent in terms of the findings of this study. Is it a neutral and balanced attitude?

Reply: The primary objective of this study was to provide novel information about olanzapine-LAI, aiming to identify the predictors of psychiatric hospitalization in the maintenance treatment of schizophrenia with olanzapine-LAI and compare olanzapine-LAI with a sub-therapeutic dose of olanzapine-LAI on hospitalization parameters. A secondary objective was to compare olanzapine-LAI with oral olanzapine on the hospitalization parameters. The title of the manuscript is consistent with the study’s primary objective. Please also note that the title of the manuscript is already quite long (“Predictors of psychiatric hospitalization during 6 months of maintenance treatment with olanzapine long-acting injection: post hoc analysis of a randomized, double-blind study”). We believe that the addition of information about the secondary comparison between olanzapine-LAI and oral olanzapine to the title would have made it much too long and cumbersome for the reader.