Author’s response to reviews

Title: Real-Life Assessment of Aripiprazole Monthly (Abilify Maintena) in Schizophrenia: A Canadian Naturalistic Non-Interventional Prospective Cohort Study

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To: "Ashok Malla" ashok.malla@mcgill.ca

From: "BMC Psychiatry - Editorial Office" Joselito.Acosta@springer.com

Subject: Your submission to BMC Psychiatry - BPSY-D-18-00965

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Real-Life Assessment of Aripiprazole Monthly (Abilify Maintena) in Schizophrenia: A Canadian Naturalistic Non-Interventional Prospective Cohort Study

Sally Mustafa, PhD; Joanna Bougie; Maia Miguelez; Guerline Clerzius; Emmanouil Rampakakis; Jean Proulx; Ashok Malla

BMC Psychiatry
Dear Dr Malla,

Your manuscript "Real-Life Assessment of Aripiprazole Monthly (Abilify Maintena) in Schizophrenia: A Canadian Naturalistic Non-Interventional Prospective Cohort Study" (BPSY-D-18-00965) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Psychiatry, once you have carried out some essential revisions suggested by our reviewers.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/bpsy/ for any additional comments that were saved as attachments. Please note that as BMC Psychiatry has a policy of open peer review, you will be able to see the names of the reviewers.

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A decision will be made once we have received your revised manuscript, which we expect by 05 Feb 2019.

We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

René Ernst Nielsen, MD, PhD

BMC Psychiatry

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Technical Comments:

Editor Comments:

Dear authors

Thank you very much for submitting your manuscript to BMC Psychiatry.

The reviewer’s have raised a few minor points which need to be adressed before a possible acceptance for publication.

Best

René Ernst Nielsen

MD, PhD, Associate Professor
BMC Psychiatry operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Lone Baandrup (Reviewer 1): This is a prospective cohort study of subjects with schizophrenia treated with AOM after the discretion of their treating physician. The study is open-label and uncontrolled. The study investigates pragmatic functional outcome measures in an unselected clinical sample. The study aims to add data on effectiveness of AOM as a supplement to RCTs with narrow eligibility criteria and thus questionable external generalizability.

The study is funded by the pharmaceutical industry and thus needs to clearly document that design, analyses and interpretation is not biased. To ensure this, I recommend the following adjustments:

1) Background section: The trial was registered at clinicaltrials.gov. Not all secondary outcomes registered in the protocol are reported in the manuscript. The introduction states that only 'clinically relevant' outcomes are reported. To avoid presentation bias, all planned outcomes should be reported. One of the non-reported pre-planned outcomes is 'remission' which is indeed clinically very relevant in a pragmatic study like this and thus the authors' reason for not reporting all pre-planned outcomes does not seem justified. All planned outcome should be reported and commented on in order to be sure that not only outcomes with favorable results were reported. Of course, increasing the number of outcomes should be accompanied by considerations of the need to adjust for multiple comparisons.

We understand the reviewer’s concern about potential bias through not presenting all outcomes. The remaining preplanned secondary outcomes as per trial registration were added, namely, remission, relapse and medication adherence. Remission and relapse added information are on the following pages: page 5 last paragraph continuing to page 6, page 7 paragraph 2 lines 5 & 6, page 9 section 1.2.3. and page 11 line 5. Adherence information are added on: page 5 lines 7 & 8 and page 8 lines 3, 4 & 5 in addition to a supplementary table.

2) Methods section: The original power analysis should be reported including the adjustments that were made due to the interim analysis.

The required information was added; page 6 last paragraph continuing to page 7.
It should also be stated who was in the committee deciding to stop the study pre-term due to better than expected results.

This decision was made by the study sponsor in consultation with the investigators. This statement was added on page 4, paragraph 1, lines 8 & 9. If the reviewer is referring to a steering committee, as would be the case often for an RCT, no such steering committee existed for this open label study.

3) Limitations section: The results reported in the manuscript show very high effect sizes compared with RCTs and the limitations of the current design should be briefly stated.

Further elaboration on limitations was added on page 13 last paragraph continuing to page 14.

4) Data sharing: Why can't the anonymized data be made available for e.g. meta-analytic purposes?

For ethical reasons, to ensure the privacy of the patient-level data utilized in the current study, and for reasons related to data ownership, data cannot be made available / may become available upon request. This statement was added on page 15 paragraph 3.

Pirathiv Kugathasan, MSc, PhD. stud. (Reviewer 2): Dear Authors,

The manuscript regarding the efficacy and effectiveness of Aripiprazole once monthly injectable formulation (AOM) has very important clinical features. While most evidence regarding the effect of antipsychotics are based on RCTs, real world evidence studies are needed to truly understand the real effect on a heterogeneous patient group. The results from this study clearly add valuable knowledge to the current literature of the pros and cons of using Aripiprazole in clinical practice. The manuscript is well written, easy to understand, and reports a clear message. However, there are place for improvement, so below you will find some suggestions and questions that need to be addressed.

#1 Methods - First paragraph. "..patients treated with AOM for schizophrenia for up to 24 months" and later in the inclusion criteria you write the following "Patients diagnosed with schizophrenia spectrum psychosis". It is important that you are clear about the definition of schizophrenia, as some studies prefer F20 (schizophrenia only), while others are more likely to
use schizophrenia spectrum disorders (F20-F25), and not to forget the few studies that uses psychosis both within schizophrenia and affective disorders. This is especially necessary to further discuss in the discussion section.

Schizophrenia diagnosis was the inclusion criterion for this study. This clarification has been made in the two indicated areas of the manuscript, namely, page 4 line 2 and paragraph 3 in addition to the Discussion section.

#2 Methods - Right before the description of population. There is an issue regarding the font in the last part of the section - please correct.

The font was 11 rather than 12, now corrected; page 4, paragraph 1.

#3 Methods - Right before the section of antipsychotic pharmacology. "Both serious as well as non-serious ADR were recorded." Can you please give examples from each of these categories?

Suicidality was given as an example of a serious ADR and mild nausea as a non-serious one; page 6 lines 8 & 9.

#4 Results - 1. Primary outcome; GAF. The citations need to have a reference. Please correct.

Reference was added, page 8, paragraph 2, reference # 24.

#5 Results - The type III test p-value. This kind of test is not described in the statistical analysis section, can you please provide an explanation of this test, because most often p-value and the significance is reported.

Type III test is the standard test used in linear mixed models to examine the significance of each partial effect, that is, the significance of an effect with all the other effects in the model. Acknowledging that this term may be confusing to the readers and that the statistical analysis section already provides sufficient information on the methodology used (linear mixed models adjusting for baseline scores were used for the primary analysis in this study’), in the revised manuscript we have replaced ‘Type III test p value’ simply with ‘p<0.001).

#6 Results - 2.2.2. BPRS - "There was no significant between." Please correct the language here.
Corrected, page 9, line 12.

#7 Results - 3. Adverse drug reaction. How do you distinguish between "new medication given" and "medication changed" for patients who are already on Aripiprazole?

These were changed to new concomitant medication and/or non-drug therapy given and concurrent concomitant medication switched, respectively for better distinguishing; page 10 lines 7 & 8.

#8 Discussion. This section "SOFAS is derived from GAF……. Measure in this study" does not belong here, should be described and explained in the methods section. Please correct.

Thank you for pointing this out. We have moved this now to page 5 lines 11, 12 & 13, its correct place.

#9 Conclusion - should be more precise and state the main findings and the corresponding clinical implications of them.

The conclusion section has been revised to reflect the reviewer’s suggestions; page 13.

#10 Limitations - This section is really weak, there should be more mentioned here. Among others 1) Are there any risk of selection bias for this particular treatment, 2) Is it really the true effect of the drug or the nature of the illness course or even an effect of another intervention, 3) discuss the scales measures, are they reliable? What other alternatives could have been used to assess the effectiveness?

We agree this section needs to be more elaborate. We have now rewritten this section and covered most, if not all possible biases; page 13 last paragraph continuing to page 14.
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