Author's response to reviews

Title: Predictors of the short-term responder rate of Electroconvulsive therapy in depressive disorders - a population based study.

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Author's response to reviews: see over
The Editor
BMC Psychiatry
Manuscript: Axel Nordenskjöld, Lars von Knorring, Ingemar Engström. Predictors of the short term responder rate in Electroconvulsive therapy in depressive disorders – a population based study

This manuscript has been submitted for publication in BMC Psychiatry. After peer review we received the following comment from the Editor:

Please note that we think it may be possible to revise your manuscript to address these comments but that this would require longer than our standard revision period. However, we are willing to consider your manuscript further once all the concerns have been addressed. Therefore, if you are able to address all of these concerns, please do submit a new manuscript to BMC Psychiatry. If you are able to do this, a full covering letter, explaining the revisions made, should accompany the submission.

We have read the comments from the reviewers and would like to thank you for the possibility to submit a revised manuscript for consideration.
We have gone through the comments from the reviewers with great interest and care. We have revised the manuscript thoroughly based on the comments from the reviewers and do hope that you now may be able to accept the manuscript for publication in BMC Psychiatry. All three authors have taken part in the revision.
The authors respond point by point to the he comments from the reviewers below.

Reviewer: Kristian Wahlbeck
Reviewer’s report:
First reviewers general comment:
The manuscript is a clinically relevant pragmatic patient cohort study, which outlines electroconvulsive treatment (ECT) outcome predictors in a naturalistic setting in Sweden. It is based on sound data and methods, but the reporting needs some revision. The reporting is overall clear and the language is satisfactory.

Authors response:
The reporting is adjusted as the reviewers suggests.

1. Use of the term "effectiveness". This is a non-controlled study, and thus effectiveness of treatment cannot be compared and established. The authors should replace the word "effectiveness" in the title with, for instance, "outcome". Likewise, the first sentence of the abstract states that the aim is to investigate effectiveness. The current study design does not allow this, and the sentence is also in conflict with the stated aim in the text (see final sentence of the Introduction section)

Authors response:
Effectiveness has been removed from the title and the text. Responder rate is used in the title and in the two first sentences in the abstract. In the last sentence of the abstract “better outcome” is used instead of “more effective”.

First reviewers comment 2:
Abstract needs to be somewhat expanded: in the methods section time of follow-up needs to be added, and the results section should, in addition to reporting the univariate analyses, shortly mention also the outcome of the regression analysis.

Authors response:

“Within one week” is added in the second sentence in the methods section of the abstract. The logistic regression analysis is added in the last sentence of the results section.

First reviewers comment 3:
Methods section needs to be elaborated to include definitions and descriptions of all included variables. A description on how severity of depression (a variable in the analyses) was defined is missing. Neither are the treatment variables “inpatient/outpatient” and “voluntary/involuntary” described. (Sometimes ECT is started as an in-patient treatment, but the continued after hospital discharge, how were the patients classified? Does involuntariness mean that the ECT-treatment was given without consent by the patient?). Was there any quality control regarding measurement of the core variable, i.e. clinical response (were nurses provided with any training in use of CGI-I? Was inter-rater reliability established? Was CGI-I validated against change in GAF scores?). How were out-patients assessed? (If in-patients were followed up, and out-patients were assesses immediately, this would introduce a source of bias when comparing the two groups).

Authors response:
Definitions and descriptions of the included variables are added in the paragraph “Variables and measures”. It includes definitions of “severity”, “inpatient/outpatient” and “voluntary/involuntary”. The absence of test of the inter-rater reliability of the CGI-I is mentioned in the last sentence of first paragraph in the “Validation of measures” paragraph and in fourth sentence in the weaknesses paragraph in the discussion. A new paragraph “validation of measures” is added and it includes a comparison of CGI-I to GAF and MADRS scores. That all patients were assessed within a week of ECT is added in second sentence in the variables and measures paragraph.

First reviewers comment 4. How did the authors reach to the conclusion that “there were no statistically significant differences between patients with and without CGI-I ratings”? Authors should note that this is not proof of similarity between groups –to show similarity, adequate statistical tests for similarity need to be applied.

Authors response:
In the “Methods/included and excluded patients” section information of the clinical characteristic of the patients excluded from response analysis is added.

First reviewers comment 5. All means should be accompanied by a measurement of variance (SDs if normally distributed). (for instance, in the section Methods/ECT-treatment variances need to be added)
Authors response:
The ECT parameters were recalculated and the SDs are added in the Methods/ECT-treatment section.

First reviewers comment 6. There is a dose-response relationship in ECT. The authors have not reported the number of ECT sessions in the the subgroups. They should add this information to the section Results/Treatment factors. If there is a difference in number of sessions between subgroups analysed, this may be a significant predictor that needs to be added to the regression analysis.

Authors response:
The number of ECT sessions in the most important subgroups are added in the Results/Treatment factors section. The regression analysis was recalculated with and without number of ECT-sessions added as a co-variable but number of ECT-sessions was not a significant predictor of the outcome.

First reviewers comment 7. In the Discussion section, authors state that good results in inpatient care, as compared to outpatient care, may be confounded by the severity of disease. This explanation does not seem plausible, as the inpatient status remained significant even in the regression analysis, when controlling for depression severity, and the sentence should be withdrawn. The authors should expand their discussion on the unexpected finding of superior outcome in in-patient settings –were there any systematic differences in the ECT received by in-patients vs. out-patients? (e.g.in number of ECT sessions?)

Authors response:
In the fourth paragraph of the discussion we argue there may be some problems to fully correct for severity in the regression analysis and there may be a risk of confounding. We discuss the finding that outpatients in fact received more ECT than inpatients disregarding the hypothesis that outpatients received fewer ECT.

First reviewers comment 8. In the Discussion section, authors claim that the responder rate in patients with schizo-affective disorder did not differ from the rate in other diagnostic groups. This may depend on the choice of model in the chi-square analysis. Would the finding remain statistically non-significant even if the schizoaffective group would be compared with the rest of the diagnostic groups, i.e. if df=1?

Authors response
The proposed comparison is performed in the sixth sentence in the “Results/age sex and diagnosis” section. The result is mentioned in the eighth paragraph of the discussion.

First reviewers comment:9. In the discussion off limitations, the authors need to fully discuss the impact of length of follow-up. Will any longer follow-up study be made available?

Authors response:
The limitation of the follow-up time is discussed in the last paragraph of the discussion. The register is growing and we plan further longer follow-up studies which is also added.

First reviewers comment 10. The conclusions need to clearly reflect that the high responder rates are derived from a very short follow-up. It needs to be clearly acknowledged (both in the conclusion section of the abstract and in the text) that this study does not provide any information on treatment outcome in the long run.

Authors response:
It is added in the first sentence in the abstract and in the last paragraph of the discussion that the study focuses exclusively on the short time outcome and is not informative about the longer term outcome.

Minor Essential Revisions
First reviewers comment 11. The term "response rate" should probably better be "responder rate"?

Authors response:
The term response rate is changes to responder rate through out the text.

First reviewers comment 12. Background, third sentence, delete word "very". A response rate of 60-70 % is not "very high".

Authors response:
The word very is deleted.

First reviewers comment 13. Methods, first sentence states that the study population consists of people with "major depression". This is not quite right, as the authors included also e.g. depressive type of schizoaffective disorder.

Authors response:
In the first sentence in the methods section schizoaffective disorder, depressed type is added.

First reviewers comment 14. Methods/ECT-treatment. Authors state that in 13 % of treatments bitemporal approach was used at least once. Later on, in the results section, it turns out that also bifrontal techniques were in use. In how many cases was this electrode placement used?

Authors response:
In the Methods/ECT-treatment section second paragraph first sentence information about the extent of bifrontal ECT is added.

Discretionary Revisions
First reviewers comment 15. The discussion could be expanded by a more detailed discussion of the findings of this study in relation to previous studies. Why did some previous studies (references #8 and #9) not report the same findings?

Authors response:
The discussion is expanded in the second paragraph in the discussion mentioning references #8 and #9.

First reviewers comment: 16. Tables 1 and 2, which both present unifactorial analyses, could be merged.

Authors response: Tables 1 and 2 are merged.

Reviewer: Ulrik Fredrik Malt
Second reviewers general comment:
There are few clinical studies on the outcome of ECT. Thus this study is of interest. The major strength of the study is the sample size (>900) and the naturalistic design. However, limitations are many. The major limitation is the assessment method, or better, the lack of reliable and valid assessment methods. This study is based on info provided by different hospitals about diagnoses and outcome only. There are no systematic assessments beyond that of CGI. E.g. no semi-structured or structured interviews were applied. This makes it impossible to draw any conclusion about the predictive power of psychiatric co-morbidity like anxiety disorders and personality disorders. There is also no info about how severity of the current episode was measured (MADRS? Ham-D? IDS?). Most patients used concomitant drugs, but no further info is provided.

Considering the sample size, and the lack of large scale naturalistic studies, I still think the paper is worth publishing. However, a letter to the editor type of publication is probably the optimal solution. If BMC Psychiatry wants to publish it as a separate paper, they should request some modifications of the manuscript.

Authors response to the general comments:
We agree that the study is naturalistic and based on clinical information rather than structured interviews with the limitations that come with the design. We added the limitation in the weaknesses paragraph in the discussion. We believe that the study provides some information about the outcome in patients with clinically overt co-morbid diagnoses, and the information about co-morbid diagnosis is therefore not excluded. We added information about how the International Classification of Diseases severity of depression is compared to CGI-S, MADRS and GAF in the new section “Methods/validation of measures”. We also added information about the drugs used in the section “Methods/other treatments”. We have done some suggested modifications which are outlined below.

Second reviewers comment 1) The time of outcome assessment after the last ECT should be reported. The day after? After one week? After one month?

Authors response:
The time of outcome assessment is added in second sentence in the methods section of the abstract and second sentence in the Methods/variables and measures section.
Second reviewers comment 2) The authors must report how severity was assessed since this is a significant predictor.

Authors response:
How severity was assessed is added in the Methods/variables and measures section.

Second reviewers comment 3) A list of types of drugs used parallel to the ECT would be helpful.

Authors response:
The types of drugs used is added in the Methods/other treatments section.

Second reviewers comment 4) The authors should clearly state that no structured interviews or rating scales were used, and that the diagnosis was based on routine clinical procedures. This implies the authors must explicitly state that the diagnoses (e.g. major depressive episode vs bipolar spectrum depression) are rough estimates and not precise assessments. Further, the authors should not report any data relating to the predictive power of psychiatric co-morbidity (e.g. anxiety disorders, personality disorders).

Authors response:
The limitations of clinical diagnoses and explicitly the distinction between major depressive disorder and bipolar spectrum depression is added in the last sentence in the weaknesses paragraph in the discussion.
We agree that it is a limitation of the study to rely on clinical diagnoses only, and some co-morbid disorders risk going unnoticed in clinical practice. However, we believe that this study adds important information about the outcome in patients with clinically overt co-morbid diagnoses and the data is therefore reported.

Second reviewers comment 5) Another limitation that is not communicated is information about the presence of melancholic features. The authors should provide information about the number of subjects with such features. If not available, that should be listed as a limitation. For example 149 subjects were treated with ECT when seen for their first episode of major depression. This must imply melancholic or psychotic depressive episodes.

Authors response:
The absence of information about melancholic features is mentioned in the third sentence in the weaknesses paragraph in the discussion.

Second reviewers comment 6) The authors should discuss the implications of basing their findings on CGI only. Since no info about the interrater reliability of CGI is provided, we may assume that no formal reliability training was performed. The reliance on CGI only increases the risk for over-reporting response rate. A fact that should be mentioned as a limitation of the study.

Authors response:
In the added “Methods/validation of measures” section the CGI ratings are compared to GAF and MADRS ratings. The absence of measures of inter-rater reliability
measures and the risk of over-reporting response rate is added as limitations in the fourth and in fifth sentence in the limitations paragraph in the discussion.

Second reviewers comment 7) In-patients are mostly more severely depressed; have more somatic co-morbidity or are evaluated to have higher suicidal risk. Since “severity” is not assessed according to traditional scientific standards (e.g. HAM-D, MADRS), it is hard to interpret the findings of table 3 suggesting that inpatient status was a response predictor even when controlling for severity. In my opinion, that conclusion is not backed by data.

Authors response:  
In the fourth paragraph of the discussion we mention the differences between the symptoms among inpatients and outpatients and add the argument that there may be difficulty to fully correct for severity in the logistic regression analysis.

Second reviewers comment 8) Data about OR (table 3) should be re-calculated skipping info about personality disorder.

Authors response:  
The OR table (renamed table 2) is re-calculated with information about personality disorder skipped.

As requested the manuscript includes “tracked changes” so the changes to the manuscript from the last version can be compared.

Kind regards

Örebro, Sweden, March 13, 2012
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