Reviewer's report

Title: Reconsidering the prognosis of major depressive disorder across diagnostic boundaries: full recovery is the exception rather than the rule

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Reviewer: Pamela Schettler

Reviewer's report:

OVERALL COMMENTS:

This manuscript provides an important perspective for understanding and effective clinical management of major depressive disorder (MDD). The authors have used a uniquely powerful database to characterize the course of MDD over a 6-year period in a large sample of patients recruited from community, primary care, and specialized mental health sources. They describe MDD course in both conventional terms (MDD status) over a 2, 4, and 6-year period and in terms of a much broader diagnostic view (including MDD plus all affective conditions as well as highly co-morbid anxiety symptoms) over the same follow-up periods. While an even longer timeframe has been presented in the literature on MDD course, the authors' inclusion of the presence and course of affective and anxiety disorders substantially increases understanding of chronicity of symptoms (and related impairment) experienced by most patients with MDD. Most useful, they have cogently presented the effects of including other affective symptoms, and then adding anxiety disorder symptoms, in within 2, 4, and 6-year timeframes.

This article is of immense value to clinical providers in general and mental health specialty practice, as well as to patients and their families. The comments below are suggestions for clarifying aspects of the presentation of methods and findings to improve the utility of this important information for a broad reading audience.

SUGGESTED CONCEPTUAL CLARIFICATION BASED ON DEFINITIONS USED:

1. Clarify the timeframe for having a '6-month MDD diagnosis' to qualify for entry to the study: In the section on Study Sample (line 115) does the text mean that the subject was in an MDD episode at baseline that had lasted at least 6 months, or does it mean that the subject had experienced an MDD episode of any duration during the past 6 months, and in either case was included if depressive symptoms were present at a clinically relevant level in the week prior to baseline assessment?

2. Specify the relationship of episodes and symptoms in the characterization of course: Recent literature has established that once symptoms meet diagnostic criteria for the start
of an episode has been defined using current diagnostic criteria, the presence of mild subthreshold symptoms of the episode is a strong risk factor for full episode relapse - thus challenging the long-standing convention that the end of an affective episode is defined by the presence of no more than mild symptoms of the episode for 8 consecutive weeks. From the section on definition of Course Trajectories (starting on line 144) it appears that the authors have used this stricter definition of the end of an episode. This should be clarified. The relationship between episodes and symptoms in this section also needs clarification. Was presence of an affective or anxiety 'disorder' or 'diagnosis' determined based on the subject having met criteria for an episode at some time during a given follow-up period (line 148-149)? Was the Life Chart method then used to identify months with 'at least mild' symptoms of affective or anxiety disorders (lines 150-155)? If so, were months counted that were prodromal to the start of an episode, as well as months with only mild symptoms during episode resolution? How about months between episodes when mild symptoms occurred that did not meet severity/duration criteria for an episode (which the statistical analysis section suggests on lines 187-189)? If so, was this done for anyone who had met diagnostic episode criteria at any time from baseline or during follow-up? Or just since the last assessment? If months with mild or worse symptoms were counted toward chronicity regardless of episode status, this would increase rather than decrease the value of the paper in providing an accurate picture of MDD chronicity; however, the relationship of symptoms and episodes needs to be clarified. This is important not only for clarification in the methods section but for full understanding of the results presented in the paper and discussion of MDD chronicity in the last section.

3. Timing of episodes in the definition of course trajectories: Was the longitudinal picture of illness course for each subject created by joining data from all follow-up assessments into a continuous record? Is the following interpretation of course trajectories (line 163-169) correct? If not, please clarify in the text! (1) Recovered means the intake episode(s) (MDD with possible additional anxiety episode) ended prior to the 2-year assessment and did not recur (at even a mild level?) thereafter. (2) Recurrent, without chronic episodes means that the intake episode(s) ended within the first 2 years and one or more additional episodes occurred between baseline/intake and the given follow-up assessment, but with no episode lasting as long as 2 years. (3) Recurrent with chronic episodes: The intake episode(s) ended and one or more additional episodes occurred between intake and the given follow-up assessment, and one or more of these episodes (intake or during follow-up) lasted at least 2 years. (4) Consistently chronic: The subject has been in a continuous episode since intake.
ADDITIONAL EDITORIAL SUGGESTIONS:

1. Results section of Abstract: If possible within the word limit, include the definitions of the categories in the categories, so it reads: "With the short, narrow perspective (MDD only from intake to 2 years)…" and "However, in the long broad perspective (any affective or anxiety episode lasting at least 2 years between baseline and a particular follow-up assessment)…"

2. In Conclusions section of Abstract (line 50) insert the word 'most' so it reads "suggests that most MDD patients have an unfavourable prognosis."

3. Line 81: Replace 'too' with 'unrealistically' so the sentence reads "…might incline towards outcomes that are actually unrealistically favourable."

4. Line 90: Replace 'vary' so the text reads "…changes seriously when we consider different clinically meaningful course perspectives."

5. Line 119: Replace 'whom' with 'who.'

6. Line 180: Add 'for n=712 subjects' so it reads "…(6-year follow-up of all affective and anxiety disorders, for n=712 subjects)."

7. Table 2 and lines 207-212: The title of Table 2 reads "Descriptive characteristics of course over 6-year follow-up (n=903)" and the text says the data is "Over the entire 6 years of follow-up" but the information in Table 2 includes subjects followed for only 2 or 4 years. It is strongly suggested that the authors include only data for n=712 subjects followed for the full 6 years in Table 2. Alternatively, they could show all data for 3 timeframes (2, 4, and 6 years). It would be easy to show follow-up diagnoses (top of the table) in 3 columns for 3 time frames. The bottom of the table (percentage of time with symptoms) could be presented in 3 sections (for 3 time frames) in a separate table (or else present the 2 and 4-year data in the Supplemental material).

8. Line 243: Replace 'fully recovered' with suggested text so it reads "…with only 17% of patients having early and sustained recovery…"

9. Lines 251-255: Text is confusing: You may want to say "…confirmed that, compared to those who recovered in the first 2 years and remained free of affective and anxiety
episodes until the 6-year follow-up, disability was consistently higher in subjects with recurrent non-chronic episodes…"

10. Line257: Consider adding at end something like: "Within all groups, average disability was most severe when subjects were in the intake MDD episode. Disability level was less severe, and at a stable level, at follow-up assessments which could occur at different points in time relative to episode status and symptom presence or severity."

11. Line 263: Change text to read "…with respect to either the time frame or the diagnostic conceptualisation."

12. Line 274: Better to say something like: "The impact on daily functioning was found to be parallel to the severity of illness trajectory."

13. Line 291: Change text to reads something like: "We showed that only a minority of depressed patients experience early and sustained recovery from all affective and anxiety conditions…"

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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