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March 2, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15248-review_v2_noFC.doc).

Title: Transcranial Magnetic Stimulation for Geriatric Depression: Promises and Pitfalls

Authors: Priyadharshini Sabesan, Sudheer Lankappa, Najat Khalifa, Vasudevan Krishnan, Rahul Gandhi & Lena Palaniyappan.

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 15248

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated as suggested. I note that the edited version returned to us has our paper marked as a Retrospective Study. This isn't correct. Our paper is best classified as a Review.

2 Revision has been made according to the suggestions of all the three reviewers. Please **see below** our responses to the reviewer's queries. The reviewers' original queries are in bold font, our responses are in normal font, and excerpts from revised manuscript are italicized. In the manuscript, all changes are highlighted with a mark-up.

3 References and typesetting are now updated in line with the journal style.

Thank you again for publishing our manuscript in the *World Journal of Psychiatry.*

Sincerely yours,

Lena Palaniyappan, MRCPsych PhD

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RESPONSE TO REVIEWERS

Reviewer#1:
This is indeed a well organized and well written review on the subject. A few issues perhaps need to be clarified.

We thank the reviewer for highlighting the well-written nature of our work.

1. **If I am not mistaken, rTMS takes longer to elicit a response, and according to the authors the time to response may be even longer in the elderly. Since a rapid response is of the essence in severely ill patients with depression, would a delayed response not be a disadvantage, particularly compared to ECT?**

As the reviewer points out, rapid response is an important factor for which ECT is sought in the elderly. While the effect cannot be directly studies on the basis of data presented in meta-analyses, an important observation suggests that ECT may be superior to rTMS in terms of the rapidity of response. Xie et al. observed that when rTMS treatment period was less than 4 weeks, rTMS was significantly inferior to ECT. However, when the therapy period was increased to four weeks, the difference between rTMS and ECT began to decrease, suggesting that ECT results in far more cases of early response than rTMS. We have now added this information to the manuscript.

Rapidity of response is an important factor for which ECT is sought in the elderly. Difference in speed of response has not been studied directly in the 4 meta-analyses, but an important observation suggests that ECT may be superior to rTMS in terms of the rapidity of response. Xie et al. [47] observed that when rTMS treatment period was less than 4 weeks, rTMS was significantly inferior to ECT. When the treatment period was increased to four weeks, the difference between rTMS and ECT began to decrease, suggesting that ECT results in far more cases of early response than rTMS.

2. **The authors suggest that rTMS "could be offered after an unsuccessful or poorly tolerated trial of ECT." However, according to the authors rTMS is relatively ineffective compared to ECT in the treatment of psychotic depressions in the elderly. The efficacy in non-psychotic depressions in the elderly appears to be similar. Moreover, there appears to be a lesser incidence of cognitive impairment with rTMS. Given these differences between rTMS and ECT, I would have thought that a trial of rTMS should precede and not follow ECT, at least in the elderly with non-psychotic depressions.**

We fully concur with the views expressed by the reviewer. We have changed the manuscript to reflect this.

In contrast to working-age adult samples where TMS is considered as an alternative 'in line' with ECT, for *elderly depressed patients, given the indications for a superior efficacy of ECT, rTMS could be offered either after an unsuccessful or poorly tolerated trial of ECT. In some carefully selected cases of non-psychotic depression, rTMS could be an alternative to ECT when rapidity of response is not crucial but undesirable cognitive side effects to ECT are highly likely.*

3. **The varying definitions of TRD have been mentioned. Of note is the fact that out of the 4 RCTs listed in Table-2, 3 included patients who had failed to respond to a single antidepressant. Overall, 7 of the 12 trials reviewed included patients with only one failed antidepressant trial. There are also no studies "directly comparing subjects with TRD and without TRD in geriatric depression." Therefore, would it be prudent to conclude that: "Taken together, if there is any influence of the degree of treatment refractoriness on therapeutic response to rTMS, the size of this effect is likely to be small in the elderly?" Or, should it just be left at something like – the effect of treatment-resistance on rTMS treatment of depression in the elderly is still uncertain?**

We agree that careful conclusions must be drawn from the available evidence. We have changed this statement in line with the reviewer's suggestion.

Taken together, the influence of the degree of treatment refractoriness on therapeutic response to rTMS in the elderly is still uncertain

4. **Some other suggestions: The tables need to be formatted uniformly. All abbreviations used should be explained in the footnotes. In table-2 the 'methodology' column should come before the 'results' column.**

We thank the reviewer for these suggestions. We have now made changes to the tables as indicated.

<u>**Reviewer#2:**</u>

The paper by Sabesan is a quite informative review of the literature about the use of TMS in elderly patients.

We thank the reviewer for highlighting the informative nature of our work.

Two comments 1)The introduction lacks precision. Actually depression is a disorder of young adults. Prevalence of depression in the elderly is low compared to young adults. What makes the topic important is that if patients beyond 50 have a first episode of depressive disorder there is a much higher probability of treatment resistance and comorbidity with medical disorders (diabetes, heart disorders) or neurological disorders (cerebrovascular disorders, neurodegeneration) but less comorbidity with mental disorders. In addition there is the group of patients with depression of early onset that suffer from depression that persists into old age and that has a high rate of comorbid mental disorders. The authors should discuss how this heterogeneity influences the action of therapeutic agents. The expression "cerebrovascular insufficiency" has a specific meaning and should not be substituted for cerebrovascular disease.

We agree that depressive disorder as currently defined is more prevalent in the young than in the elderly. As the reviewer points out there are 2 groups of individuals among the depressed elderly; one with an early onset recurrent depression and other in whom depression occurs after the age of 50 for the first time (late-onset).
Compared to elderly patients with early-onset depression, patients with late-onset major depression often have greater vascular risk factors, show greater executive dysfunction, more psychomotor retardation, less agitation and guilt, and more disability. These factors in general predict poorer

response to antidepressants. Furthermore, even among the elderly depressed with early-onset depression, the prevalence of treatment resistance is substantial, and the risk of relapse despite successful treatment is particularly high, highlighting the critical need to focus on alternative treatments that have fewer propensities to affect cognitive faculties and physical frailty. We have included this information in the manuscript now. We have also replaced the term cerebrovascular insufficiency with cerebrovascular disorder as suggested by the reviewer.

Whilst depression is mostly a disorder of young adults (peak age of onset in 20s, with a trend towards more younger age of onset in younger cohorts), late-onset depression (after age 50) has a higher probability of medical comorbidity. There are 2 groups of individuals among those with geriatric depression: one with an early onset (<50 years) recurrent depression and other in whom depression occurs after the age of 50 for the first time (late-onset). Compared to elderly patients with early-onset depression, patients with late-onset major depression often have greater vascular risk factors[10], show greater executive dysfunction[11], more psychomotor retardation, less agitation and guilt, and more disability[12]. These factors in general predict poorer response to antidepressants[12]. Furthermore, even among the elderly depressed with early-onset depression, the prevalence of treatment resistance is substantial[8], and the risk of relapse despite successful treatment is particularly high[5], highlighting the critical need to focus on alternative treatments that have fewer propensities to affect cognitive faculties and physical frailty while reducing the persistence of symptom burden .

2) The review is apparently written by a group of great TMS fans. That is ok so far. Yet the pitfalls announced in the title seem to be neglected. Given the controversial status of TMS with respect to viewing it as a standard treatment more thoughts about this topic are needed.

We thank the reviewer for highlighting this issue. In our view, there are many factors that have contributed to rTMS not becoming a part of the stepped care approaches recommended by various guidelines, not all of them related to the quality of evidence. It is beyond the scope of our mini-review to discuss these factors, but following the reviewers suggestions we have made an attempt to present the issues that are most relevant to our paper. We have added the following text under the heading of 'Pitfalls' in discussions section.

While the potential of rTMS in the treatment of depression is acknowledged widely, it has not entered the standard stepped-care approach recommended for the treatment of depression in the elderly. An appraisal of the rTMS literature relevant to geriatric depression highlights several deficiencies and offers insight on the pitfalls of recommending routine use of rTMS in geriatric depression. Firstly, the practice of excluding older adults from rTMS trials has resulted in a dearth of good quality RCT data in this age group. The available evidence does not provide an unequivocal support for age related reduction in the antidepressant effect of TMS. In contrary, it hints at several possible mechanisms for the inconsistently observed differential treatment response. Secondly, there is a scarcity of experimental studies investigating the variations in TMS parameters to improve response rates in the elderly. Third, despite the numerous phenomenological and neurobiological differences between working-age adults and elderly with depression, moderators other than age have not been systematically studied in TMS studies of geriatric depression.

We have also added a statement of caution in the conclusion as below:

While it is premature to recommend rTMS for regular use in geriatric depression, continued exclusion of this group of depressed patients from a well-tolerated and safe treatment option for resistant depression on the basis of their age appears to be clearly untenable.

<u>Reviewer #3:</u>

The manuscript entitled "TMS for geriatric depression: promises and pitfalls" is a comprehensive, timely, and clinically important systematic (and partly narrative) review. As far as I know this is the first review on the topic of rTMS in late life depression. The MS is generally well-written and concise.

We thank the reviewer for highlighting the comprehensive nature of our work and commending on its timeliness and importance.

I only have minor points to consider: 1. Title - "Promises and pitfalls" could be deleted

We thank the reviewer for this suggestion, which we things is relate to the point #2 raised by reviewer #2. Our original manuscript lacked a clear-cut description of the pitfalls in relation to rTMS use in depression, but the current version has addressed this. As a result we have retained the title as it is to present a more cautious overview.

2. I recommend to use the more familiar abbrev "rTMS" instead of "TMS" as only studies applying repetitive TMS are considered in the MS.

We have made this change throughout the manuscript.

3. p.3, 1st paragraph, e.g., "reduced likelihood of treatment response" in addition with reference no.4 (Licht-Strunk et al. 2007) seems to be slightly outdated and simplified. The authors should at least cite some newer references (e.g. Tedeschini et al. J CLin Psychiatry, 2011). Thank you!

We thank the reviewer for highlighting this. We have made this change as suggested.