Reviewer’s report

Title: A Systematic Review of Evidence-based Treatment for Depersonalization-derealization Disorder (DPRD)

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Reviewer: Antonio Mantovani

Reviewer’s report:

General:
The interesting aspect of this article is the aim directed to review the therapeutic options for a condition, Depersonalization-Derealization Disorder (DPRD), highly distressing and for which no definitive treatments exist. However, the methodology used is biased by the inclusion of unpublished data that in my opinion should be excluded. The results and conclusions are based on 4 RCTs without taking into account many open-label published results that would be really helpful to discuss. In order to provide both researchers and clinicians with suggestions and recommendations to use for the design of new RCTs and for the clinical treatment of a condition highly prevalent (0.8-2.8%) in the general population, it is advisable to restructure the manuscript including the abstract. Therefore, major compulsory revisions should be made before the article can be published.

Specific:
Abstract.

Background:
- Please specify whether it is the clinical features or the pathophysiology of DPRD that is not well understood.

- In my opinion both open-label and placebo-controlled trials should be included. More so, because the authors review all clinically significant studies.

Methods:
- All treatment trials, with particular emphasis on RCTs, were analysed. Specifically, pharmacotherapy, psychotherapy, somatic interventions and combination treatments were included in the review.

- Unpublished trials should be excluded.

- The inclusion criteria should include not just the 4 RCTs, but all clinically significant studies.

Results:
- Please report briefly results of all clinically significant studies.

- Data from these trials suggest that SRIs, Lamotrigine alone or in combination with SSRIs, anticonvulsants, opiate antagonists, and repetitive transcranial
magnetic stimulation (rTMS) are promising treatments for DPRD.
- Last sentence should be deleted.

Conclusions:
- Although the treatment strategies above specified are promising, large RCTs should be conducted to support their definitive efficacy.

Keywords
Please delete redundant keywords.

Background
- Reference no. 1 does not exist. Please replace it with Spiegel et al. (2011): Dissociative disorders in DSM-5.
- In the second sentence perhaps the authors refer to the four symptoms cluster dimensions of DPRD (Sierra et al. 2005), as desomatization and deaffectualization are terms not in use for the description of DPRD.
- Some grammar errors need attention: “Depersonalization is disordered”, “condition in its own right”, “in the region of 20%-40%.”
- Clozapine is not a benzodiazepine, instead it is an atypical neuroleptic medication. Please correct.
- The word serotonergics does not exist; perhaps the authors meant medications with serotoninergic activity. Please correct.
- Please provide the reference of Pikwer (2011) for the glutamatergic hypothesis of DPRD.
- “The latter two” should be replaced with “the last two.”

Methods
Identification of studies:
- The search terms used are redundant; please delete the unnecessary duplications.
- Unpublished trials should be excluded.
- The criteria reported for trials inclusion appear to be correct here; however, the list (1, 2, 3) is missing criterion “c.”

Outcome measures and effect variables:
Primary outcomes
- CGI-I stands for clinical global impression-improvement subscale. Please correct.

Secondary outcomes
- Last sentence does not make sense: specific severity measures for each of the other anxiety disorders should be reported.

Data collection:
Selection of studies
- All treatment studies and not just RCTs should be included, as reported in the “Identification of studies” section.

Results
Results of the search
- According to the criteria of selection specified in the Methods, Figure 1 should be corrected.

Description of included studies
- This section should be revised. In particular, the dosages of lamotrigine reported (i.e. 181 mg/day and 196 mg/day) do not seem to reflect what it is reported in the methodology of the referred studies: Sierra et al. (2003) and Aliyev et al. (2011). In the first clinical trial it looks like the participants were put on 250 mg/day of lamotrigine, whereas in the second one lamotrigine dose was 300 mg/day. Please revise.

Description of excluded studies
- This section should be revised according to the selection criteria reported in the Methods.

- The clinical trial with temporo-parietal junction stimulation cannot be an ongoing study as the results have been published by Mantovani et al. (2011). Please correct.

Effect of interventions
Pharmacotherapy versus placebo.
Primary outcome measures.
With regard to the results by Simeon et al (2004), it seems incorrect the report of an improvement in depersonalization severity by using the CGI-I that is a measure of improvement in the clinical global impression. Please correct.

Clinical trials specified in criterion “c” of the Methods should be reported in this section, with detailed information about the results obtained with SRIs, SSRIs plus lamotrigine, anticonvulsants, opiate antagonist, and temporo-parietal junction stimulation. Please revise.

Discussion
The statement that “the data do not provide support for the efficacy of any pharmacotherapy or psychotherapy in DPRD” is incorrect, as the RCT with lamotrigine versus placebo was successful (p< 0.001). A possible reason for the different outcomes between the study by Aliyev et al. (2011) and by Sierra et al. (2003) maybe the higher dosage of lamotrigine administered (300 mg/day versus 250 mg/day) and the larger sample size (40 subjects versus 9) in the first one. The clinical results of SRIs, SSRIs in combination with lamotrigine, lamotrigine alone, anticonvulsants, opiate antagonists, and repetitive transcranial magnetic stimulation (rTMS) are promising and should be further evaluated in large RCTs.
Conclusion
In my opinion, the conclusions should report the potential clinical value of SRLs, SSRIs plus lamotrigine, lamotrigine alone, anticonvulsants, opiate antagonists, and rTMS. However, I agree that larger RCTs are needed in order to confirm the published results, and that further research on the physiopathology of DPRD is required.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests