Author's response to reviews

Title: Evidence-based Treatment for Depersonalization-derealization Disorder (DPRD)

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Author's response to reviews: see over
Dear Dr. Marshall,

**RE: MS: 2201249988486663 - A Systematic Review of Evidence-based Treatment for Depersonalization-derealization Disorder (DPRD)**

Thank you for the helpful comments of the reviewers. We have addressed these as follows:

- The search strategy does not include the term “psychotherapy” or “psychological intervention”. Nevertheless this was one of the aims of the study. “Treatment” as a search term might not cover such types of interventions adequately.

As indicated in the article’s original abstract, we did include the term “Psychotherapy” in our search terms. We have now amended the omission on page 7 and correctly added the term to the described search terms.

- "Depersonalization disorder can occur in the context of major depression, panic disorder, posttraumatic stress disorder, schizophrenia, stress and fatigue [5], or it may occur as a primary phenomenon, in which case it is classified as a condition in its own right". The first occurrence of the word 'disorder' here is incorrect- it is not 'depersonalization disorder' that occurs in these other conditions, but depersonalization as a symptom (or set of symptoms).

We have changed the text to (p.4): Depersonalization symptoms can occur in many neurological (e.g. migraine and epilepsy, [5]) and psychiatric conditions (e.g. major depression, panic disorder, posttraumatic stress disorder, schizophrenia, stress and fatigue, [6]), or it may occur as a primary phenomenon, in which case it is classified as depersonalization-derealization disorder [7].

- Also, the way it is currently phrased it sounds as though that list of conditions that may involve depersonalization is an exhaustive one- but it is not, in fact there are so many neurological and psychiatric disorders where depersonalization can occur that I would replace the list of conditions with something like 'can occur in many neurological (give examples) and psychiatric (give examples) conditions'.

The revised text also incorporates this suggestion.

- It is an excellent idea to avoid a pooling of data in meta-analysis. The authors report in a narrative review the findings of the single studies. However, a critical appraisal is missing for each study. The general discussion at the end of the MS is not clearly related to the findings.

A critical appraisal of each study can be found in the section under ‘other biases’ (p.14-15) as well as in the ‘discussion section’ (p.17-18). The discussion has been aligned to the findings:
Other biases
All four studies were posed with several limitations. In the biofeedback study [59], half the patients (17 participants) were on various medications and this can affect autonomic response; however, both conditions had similar proportions of medicated and non-medicated patients, and statistical analysis did not find medication status to be a significant confound. There was a preponderance of men in the DPRD group compared to the control group, but significant between-group effects were still evident after covarying for age and sex. Only thirty two participants were randomized, this is small in comparison to other clinical trials. Finally, the experimenter was not blind to patient allocation; it is theoretically possible that non-explicit clues as to the biofeedback condition were inadvertently revealed, potentially affecting results. This study was also implemented over four weeks which may have been short for evidence of an effect.

The two studies investigating lamotrigine also had important limitations. The first study [61] consisted of eighty men, but no female participants, so preventing generalization of results to women. Some patients were also allowed to take clonazepam for insomnia and hydroxyzine for the treatment of a rash in concurrent with lamotrigine. Furthermore, the study only reported on those participants who completed the study. The second study [40] used both males and females in their analysis, but only fourteen participants were randomized over twelve weeks, and dropout rates were high.

In the SSRI study [60], fifty-four patients were treated over ten weeks with 10-60mg of fluoxetine or matching placebo. Some participants were treated with psychotherapy (e.g. cognitive behavioral therapy) for three months, and were nevertheless included in the analysis. Intention-to-treat analysis was used, with last observation carried forward for those participants who did not complete the study. This study was also characterized by high withdrawal rates. Well-validated measures were used and the independent evaluator was masked to side effects and medication adjustment.

Discussion
To the best of our knowledge, this is the first systematic literature review on the treatment of depersonalization-derealization disorder. Four RCTs (all with duration of 12 weeks or less) were found and included in the study (180 participants; age range 18-65 years). These four RCTs included one psychotherapy (i.e. biofeedback) and three pharmacotherapy (i.e. lamotrigine and fluoxetine) trials, with comparison groups.

Data on lamotrigine for DPRD was inconsistent with one trial indicating that lamotrigine was not significantly better than placebo when applied as a singular treatment for DPRD, and one trial showing a statistically significant difference in improvement (i.e., 50% reduction in the CDS) compared placebo [61]. Fluoxetine was not demonstrated to be efficacious in treating depersonalization disorder. However, there was a tendency for depersonalization symptoms to improve in subjects with a comorbid anxiety disorder [60]. Finally, electrodermal biofeedback was not effective in increasing SCR (a physiological marker of emotional response) or in decreasing trait measures of depersonalization (CDS). However, SCR biofeedback did result in lower state scores on the CDS.

The RCTs included here demonstrated ‘low’ or ‘unclear’ risk of bias. Three studies provided evidence for random generation sequence [40, 60, 61], four for allocation concealment, two for blinding [59, 61], and all four for incomplete outcome data; consistent with ratings of a
“low” risk of bias. All four studies had missing study protocols so that selective reporting could not be assessed; this is consistent with an ‘unclear’ risk of bias (see table 2).

The literature has shown that depersonalization symptoms can be induced by serotonin receptor agonists such as meta-chlorophenylpiperazine [65], and by substances which act as serotonin agonists such as cannabis [17], lysergic acid diethylamide, and “ecstasy” [66]. Serotonin reuptake inhibitors (SSRIs) were reported to be associated with positive treatment outcome in eight individuals with DPRD and comorbid obsessive-compulsive and panic disorders in a case series [66]. Furthermore, in a double-blind crossover trial consisting of eight weeks of desipramine and eight weeks of clomipramine, there was limited evidence that clomipramine was more efficacious than desipramine. Nevertheless, in the only randomized controlled trial of a SSRI in DPRD, fluoxetine was not found efficacious.

The literature has a number of important limitations. There are a small number of studies with small samples (sample size 80; 14; 54; 32). There are differences across trials in sample characteristics (more male than female participants), and timing of interventions (12 weeks; 10 weeks; 4 weeks respectively). Further research is necessary, particularly in light of the methodological differences between studies.

Given the limited data available, there is arguably a need for additional research on lamotrigine, other anticonvulsants, SSRIs, opiate antagonists, and repetitive transcranial magnetic stimulation (rTMS).

- A closer look at table 2 shows that the presented results do not match with the description in the text. In the text the authors report that each trial is reported as low in outcome assessment. In the table the opposite is the case. This issue should be clarified before the appropriateness of the interpretation of the general findings can be done.

The text (p.12-15) has been made consistent with the table 2 (p.30):

Risk of bias within studies
The overall risk of bias was evaluated as ‘high’, ‘low’ or ‘unclear’ according to the five criteria stipulated by the Cochrane Handbook for Systematic Reviews of Interventions [64]: random sequence generation, allocation concealment, blinding (performance bias and detection bias), blinding of outcome assessment, incomplete outcome data (attrition bias), and selective reporting (reporting bias) (see table 2).

Random sequence generation
Three trials were rated as having a “low” risk of bias on the basis of random sequence generation (i.e. use of a randomization table, list or code) [40, 60, 61]. One trial was rated “unclear” [59], as the trial indicated that the participants were randomized however the procedure was not clearly defined.

Allocation concealment
All four studies were rated as having a ‘low’ risk of bias on the basis of allocation concealment. The pharmacological studies all used identical appearing capsules for the medication and placebo groups [40, 60, 61]. For the psychotherapy study, biofeedback and sham was presented on an identical interface [59].
Blinding of participants, assessors and personnel
Two trials were rated as having a ‘low’ risk for performance and detection bias. In the first trial both the patient and the treating psychiatrist were blinded to treatment [61], whereas the second study was patient blind [59]. The additional two trials were rated ‘unclear’ [40, 60], as they did not provide evidence to determine if blinding occurred.

Blinding of outcome assessment
Each trial was rated as having a “low” risk of bias on the basis of blinding of the outcome assessment. For the biofeedback group procedures were identical to those in experimental group [59]. There was no clear need for the outcome assessments to be blind in the additional three trials [40, 60, 61].

Incomplete outcome data (attrition bias)
All four studies were rated “low” for attrition bias because all outcomes were reported on. For two studies, dropouts were excluded from the analysis, with no reasons given for dropouts [40, 61]. No baseline scores were reported on in one study using lamotrigine [61].

Selective reporting (reporting bias)
For selective reporting, all four studies were rated as having an “unclear” risk of bias, because there was no protocol available to determine if all outcomes were measured.

- The conclusions are not related to the findings. Why is psychobiological research indicated? Why should one study etiology of DPRD after these results? This comment is also connected to the research aim. The interest in psychobiology is a weak argument for conducting this study.

We have revised the text to decrease the emphasis on psychobiological research (p.7): Nevertheless, the disorder remains a poorly understood condition that has received relatively little research attention. Lack of awareness of DPRD may contribute to a high rate of misdiagnosis [9]. With growing interest in the management of DPRD, it is timely to conduct a systematic review to determine the efficacy of medication, psychotherapy, somatic interventions and a combination of treatment modalities for depersonalization-derealization disorder, relative to placebo and other comparison groups.

Conclusion (p.18-19)
There is inconsistent evidence to support the efficacy of lamotrigine in DPRD, with no evidence to support the efficacy of fluoxetine and biofeedback. Given the limited data available, further exploration of lamotrigine, other anticonvulsants, SSRIs, opiate antagonists, and repetitive transcranial magnetic stimulation (rTMS) in larger trials may be useful. Indeed, a great deal of further research on the pathogenesis and treatment of depersonalization-derealization disorder is required.

- The authors state a high prevalence of DPRD, which is disputable given a reference of 1970 as argument for the clinical importance of the topic.

The argument has been supported by referencing more recent prevalence rates (p.4-5): DPRD is frequently a chronic disorder, affecting between 1% and 2.4% of the general population with a gender ratio of about 1:1, although its comorbidity with depression and anxiety falls between the percentage ranges of 20–40 [8-10]. Depersonalization and derealization symptoms seem to be more common among women (26.5%) than men (19.5
It was estimated in one survey that DPRD occurred in 80% of psychiatric inpatients and that 12% among them suffered from a severe form of this condition [12]. Lifetime prevalence of depersonalization and derealization symptoms of 31 and 66% were found in surveys conducted among non-clinical respondents and a lifetime prevalence of depersonalization and derealization symptoms of 42 to 91% was reported in psychiatric settings [13]. Severe clinical depersonalization was identified among 1.9% of German participants [14] and among 5% of psychiatric outpatients in New York [15].

(p.7) Nevertheless, the disorder remains a poorly understood condition that has received relatively little research attention. Lack of awareness of DPRD may contribute to a high rate of misdiagnosis [9]. With growing interest in the management of DPRD, it is timely to conduct a systematic review to determine the efficacy of medication, psychotherapy, somatic interventions and a combination of treatment modalities for depersonalization-derealization disorder, relative to placebo and other comparison groups.

- The reviewer has strong concerns to recommend mindfulness interventions in this group. Is this a random choice or is there any evidence for this recommendation. From a clinical perspective DPRD is rather a contraindication for MBSR.

As suggested by the reviewer we have removed reference to MBSR (p.16-20):

- The flow chart of study inclusion is inconclusive. How can the authors decide, whether an appropriate outcome was assessed from the abstract? It is unusual to mix categories within one global “exclusion rating”.

We followed the usual Cochrane methodology, which is now described in the text:

Selection of studies (p.10): In order to determine whether studies were eligible for inclusion, the Cochrane steps of a systematic search was followed. This entailed the screening of titles and abstract for face validity within the selected databases. Included, excluded and unclear studies were color coded, and the full text articles for each study were retrieved. After full text screening, studies were further included or excluded based on the study criteria for the review. This process was completed by one of the authors (ES). Spreadsheet forms were designed for the purpose of recording descriptive information, summary statistics of the outcome measures, risk of bias data, and associated commentary (ES & TW). The reviewers contacted investigators by email in an attempt to obtain missing information. A narration of each trial is provided in the results section.

- What is the difference between “or” and “and” in the full text screening.

In doing a systemic research, we use MESH terms (i.e. keywords) to obtain the relevant information needed based on our study title. We use AND to include concepts that both need to be reflected in the title but OR if only one of the concepts need to be reflected in the title. This allows the database to generate as many articles as possible related to the search terms entered, study title and aim.

- The use of PRISMA might help for a stronger focus of the paper.

We have a PRISMA diagram on p.27 that represents the search.
• The authors should be encouraged to state more precisely, whether they had been involved in trials on the study aim.

We have added an explicit declaration in the Acknowledgement section of the article (p.19) stating no conflict of interest and no involvement in any of the trials by the reviewers.

• The reviewer is not clear, whether the assessment of performance bias is adequate. The assessor does not necessarily have to be blind. It is the treatment provider (performance). Assessment is covered by the next item.

The text has been clarified. (p.13):

• What is the difference between “BDI” and “BDI scores”.

There is no difference, and we now use the same terminology throughout.

• Content of table 1 should be improved by more relevant information (Setting, inclusion criteria, exclusion etc.). The authors do not want to run a meta-analysis which is reasonable, however the narrative description of the studies can be improved to make it accessible for readers.

As suggested, Table 1 now includes setting and dosage (p.28-29).

As suggested, the narrative section now addresses the inclusion and exclusion criteria of each study (11-12): Description of included studies
The search included four double-blind RCTs of treatment for depersonalization (180 participants). A placebo comparison group was employed in each study and the four studies consisted of one psychotherapy (biofeedback) and three pharmacotherapy trials (lamotrigine and fluoxetine). Each study was published in English and recruited outpatients from single centres. One trial was funded by the National Institute of Mental Health (NIMH) (the fluoxetine and placebo capsules were provided by Eli Lilly) and another by the Medical Research Council (MRC) [59, 60]. Countries in which studies were conducted included the United Kingdom [59, 40], the United States of America [60] and Azerbaijan [61].

The average sample size was 44 and ranged from 14 [40] to 80 [61]. Three studies consisted of both males and females, and one study males only [61] (mean age for all four groups: 36 years). Amongst others common inclusions criteria includes: adults aged 18–65 years; DSM-IV or PSE [40] diagnostic criteria for current depersonalization disorder; and written informed consent. Participants were excluded if they had a lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, organic mental disorder and substance use disorder [40, 59], eating disorder, acute or unstable medical illnesses [61], as well as those with a history of seizure disorder or major head trauma. Pregnant and lactating women were also excluded [60].

The duration of treatment for all interventions ranged between eight sessions of psychotherapy [59] to twelve weeks of pharmacotherapy [40, 61]. Dose of medication ranged from 10mg/day [60] to 300 mg/day [61]. Primary and secondary outcomes include CDS, DES [40, 59, 61], BAI [59] and BDI [40, 59], PES, CGI-I, DSS, HRDS, HRSA, LSAS, YBOCS and DSM-IV [40]. Two participants (one female and one male) dropped out of the sham condition in the biofeedback study. No side effects were reported in this study [59].
Fifteen dropouts were reported (three because of the development of a rash in the medication group) [61] compared to five dropouts [40] in two studies investigating lamotrigine. Seven participants further dropped out due to various side effects (i.e. dizziness, muscle aches, nausea, sedation, fatigue and neutropenia) in these 2 studies [40]. In addition, thirteen participants dropped out of the fluoxetine study. Side effects in at least 10% of the two study groups were reported in this trial [60].

- The methodology used is biased by the inclusion of unpublished data that in my opinion should be excluded.

We respectfully disagree with the reviewer. The Cochrane methodology specifically advises inclusion of unpublished trials, given that there is a bias for negative trials not to be reported. That said, we were unable to find any unpublished RCTs.

- 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.

In this article we follow the Cochrane methodology for systematic reviews. An important feature of this methodology, as well as related methodologies in the literature on systematic reviews, is a focus on randomized controlled trials. The argument is that these comprise the most rigorous studies, and that the reader should not be biased by open label studies. Accordingly, while we provide a short summary of open label studies, consistent with current approaches in the field, we focus primarily on reviewing the randomized controlled trials in the field.

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

Changed to (p.2): Depersonalization-derealization disorder (DPRD) is a distressing and impairing condition with a pathophysiology 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.

As stated above: In this article we follow the widely-accepted Cochrane methodology for systematic reviews; this focuses on randomized controlled trials.

Methods:

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

Text has been changed to (p.8): Criteria for considering studies for this review included (a) all randomized controlled trials (RCTs) of pharmacotherapy, psychotherapy, somatic
interventions and a combination of treatments for depersonalization disorder, (b) all participants diagnosed with depersonalization disorder according to the criteria of the Diagnostic and Statistical Manual (DSM-III-R [47] or DSM-IV [48]), or the International Classification of Diseases (ICD-9, [49] or ICD-10 [50]) irrespective of age, in- or outpatient status, or presence of comorbidity, (c) all medication agents and non-pharmacological interventions (e.g. selective serotonin reuptake inhibitors (SSRIs), anticonvulsants and opiate antagonists, temporo-parietal junct stimulation), and (d) RCTs of all forms of psychotherapy (e.g. behavioural modification and cognitive restructuring programs, relaxation, gestalt, interpersonal, supportive therapies, mindfulness, acceptance and commitment therapy, compassion-focused therapy). Both short- and long-term therapy were eligible for inclusion, as was group therapy in which cluster randomization designs were employed.

- Unpublished trials should be excluded.

As above, no unpublished trials were found (p.2, 8 & 10).

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

As stated above, in this article we follow the Cochrane methodology for systematic reviews.

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

Changed to: Results (p.3)

Four RCTs (all within the duration of 12 weeks or less) met study criteria and were included (180 participants; age range 18-65 years). The four RCTs included two lamotrigine studies, one fluoxetine study and one biofeedback study. Evidence for the treatment efficacy of lamotrigine was found in one study (CDS: p<0.001) with no evidence of effect for lamotrigine in the second study (CDS: p=0.61 or PSE: p=0.17). Fluoxetine and biofeedback were not more efficacious than the control condition, although there was a trend for fluoxetine to demonstrate greater efficacy in those with comorbid anxiety disorder. The 4 studies had 'low' or 'unclear' risk of bias.

- 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.

Added in the text where relevant (p.18): There is inconsistent evidence to support the efficacy of lamotrigine in DPRD, with no evidence to support the efficacy of fluoxetine and biofeedback. Given the limited data available, further exploration of lamotrigine, other anticonvulsants, SSRIs, opiate antagonists, and repetitive transcranial magnetic stimulation (rTMS) in larger trials may be useful. Indeed, a great deal of further research on the pathogenesis and treatment of depersonalization-derealization disorder is required.

- Last sentence should be deleted.

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

Changed to (p.3): Conclusions
The limited data from randomized controlled trials on the pharmacotherapy and psychotherapy of DPRD demonstrates inconsistent evidence for the efficacy of lamotrigine, and no efficacy for other interventions. Additional research on this disorder is needed.

- Keywords.
  Please delete redundant keywords.

Since American spelling was adopted throughout the article, redundant keywords spelled in American English were deleted while British English keywords were retained.

- 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.

The qualifying words “experiencing what was also described as…” were added (credit to Sierra has originally been provided).

- Some grammar errors need attention: “Depersonalization is disordered”, “condition in its own right”, “in the region of 20%-40%.”

Errors have been corrected.
These errors have been corrected (p.4):

- Clozapine is not a benzodiazepine, instead it is an atypical neuroleptic medication. Please correct.

Corrected (p.5).

- The word serotonergics does not exist; perhaps the authors meant medications with serotonergic activity. Please correct.

Changed to (p.5): Subsequent single case reports suggest potential efficacy for a wide variety of treatments including benzodiazepines (phenazepam, [18]; clonazepam, [19]), atypical neuroleptic medications (clozapine, [18]), tricyclic anti-depressants (desipramine, [20]), serotonergic activity drugs (fluoxetine, [21, 22]; fluoxetine and buspirone, [23]), SNRIs (venlafaxine, [24]), a combination of benzodiazepines and serotonergic activity drugs (citalopram-clonazepam, [25]), anti-convulsants (lamotrigine, [26]), (methylphenidate, [27]),
and opiate antagonists (naltrexone, [28]). Other tried psychiatric interventions included electroconvulsive therapy (ECT) [29] and transcranial magnetic stimulation [30]. Psychotherapy case reports have indicated that psychodynamic psychotherapy [31] and hypnosis-based treatment, combined with Eye Movement Desensitization and Reprocessing (EMDR), [32]), may also be useful.

- Please provide the reference of Pikwer (2011) for the glutamatergic hypothesis of DPRD.

Added to text and reference list.

- “The latter two” should be replaced with “the last two.”

Done.

- **Methods**
  - **Identification of studies:**
    - The search terms used are redundant; please delete the unnecessary duplications.

We omitted British spelled search terms from the article’s text but indicated the following: “The following search terms (in both American and British English) were used:…”

- Unpublished trials should be excluded.

Changed to (p.3, 8 & 10): No unpublished trials were found (p.2, 8 & 10).

- The criteria reported for trials inclusion appear to be correct here; however, the list (1, 2, 3) is missing criterion “c.”

Changed to (p.8): Where possible, planned treatment comparisons included:
1. Pharmacotherapy versus placebo.
2. Psychotherapy versus sham interventions or waiting list.
3. Psychotherapy versus pharmacotherapy.

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

Corrected.

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

We have reviewed this section.

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

As stated earlier: In this article we follow the Cochrane methodology for systematic reviews.

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

We have reviewed this Figure.

- 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 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.

We have revised this section.

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

We have reviewed this section.

- 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.

Changed to (p.12): One open label trial on temporo-parietal junction stimulation [63] and cognitive-behavior therapy [46] was also excluded.

- 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.

Changed to (p.15): Fluoxetine (dose 10-60mg/day) was not superior to placebo on 3 primary outcome measures, except for a clinically minimal but statistically significantly greater improvement in CGI-I score in the fluoxetine group (2.9 v. 3.6) [60]. In participants with a comorbid diagnosis of depressive or anxiety disorder, those taking fluoxetine consistently tended to have better responses than those taking the placebo [60].
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.

As noted earlier in this article we follow the Cochrane methodology for systematic reviews.

- **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.

We have emphasized that the data on lamotrigine is inconsistent.

- **Conclusion**
  In my opinion, the conclusions should report the potential clinical value of SRIs, 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.

We have emphasized that the data on lamotrigine is inconsistent. Following the Cochrane methodology, we are only able to recommend a particular intervention definitively, if there are sufficient data to do so.

- In addition to the points raised by the reviewers, it has come to our attention in the assessment of your manuscript that a number of sentences used appear to be similar to previous publications. I have provided one example below and references to other publications where there appear to be similarities. Please revise your manuscript to remove overlap with the wording used in previous publications.

More recently, a cognitive behavioral model of depersonalization has been proposed [40]. This model is based on the idea that anxiety and depersonalization are intimately related, and that depersonalization is best conceptualized as related to anxiety disorders rather than to dissociative conditions.


"More recently, a cognitive? behavioural model of depersonalisation has been proposed (Hunter et al, 2003). It is based on the idea, touched on earlier in this article, that anxiety and depersonalisation are intimately related, and that depersonalisation is best conceptualised as related to anxiety disorders rather than to dissociative conditions".
Changed to (p.6): There have also been some publications on psychotherapy research in DPRD. One psychoanalytic case study was mentioned earlier [31], and two additional case reports representing behavioral therapy [42] and directive therapy [43] have been published. However, the last two reports focused on depersonalization as a co-morbid, secondary disorder. A cognitive–behavioral model of depersonalization has been developed, and comprises another potential form of treatment. This model is based on evidence that depersonalization is associated with anxiety rather than with dissociative conditions [44; 45; 46].

- Some overlap also appeared to be present with the following publications:  

Overlapping sentences were removed or altered. The manuscript was then scanned with eTBLAST and Dénjà vu (http://info.hsls.pitt.edu/updatereport/?p=2656) and matched with MEDLINE texts. Results showed that similarity ratios were substantially lower than the suggested threshold for unusual similarity.

We have also aligned the article to the BMC template as suggested.