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

Eli Somer¹
Email: somer@research.haifa.ac.il

*Taryn Amos-Williams²
Email: tarynamos@gmail.com

Dan J. Stein²
Email: Dan.Stein@uct.ac.za

¹School of Social Work, University of Haifa, Israel
²Department of Psychiatry, University of Cape Town, South Africa

*Corresponding author

Abstract

Background
Depersonalization-derealization disorder (DPRD) is a distressing and impairing condition that is not well understood. Nevertheless, given the growing interest in its pathogenesis, and publication of a number of treatment trials, a systematic review of controlled pharmacotherapy and psychotherapy trials is timely.

Method
A systematic search of articles on DPRD published from January 1980 to August 2012, using Cochrane methods, was conducted. All randomized
controlled trials (RCTs) of pharmacotherapy (for example SSRIs), psychotherapy (for example behavioural modification and cognitive restructuring programs), or a combination of these modalities for the treatment of depersonalization disorder were included in the review, including all participants diagnosed with depersonalization disorder (i.e. DSM-III-R, DSM-IV, ICD-9 or ICD-10) irrespective of age, in- or outpatient status, or presence of comorbidity. Searches were carried out on The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 8), MEDLINE, PsycINFO, the metaRegister of Controlled Trials database (mRCT), the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). The bibliographies of all identified trials were checked for additional studies and authors were contacted for published and unpublished trials. No restrictions were placed on language and setting. Data extraction sheets were further designed to enter specified data from each trial and risk of bias information was identified. Of the unique 1296 papers that were retrieved, four studies met the inclusion criteria and were reviewed.

**Results**

The four trials were of fluoxetine, lamotrigine (2 studies) and biofeedback. Data from these trials is not consistently in favor of the efficacy of any particular intervention. Efficacy may have, for example, been limited to sample size and gender disparity.
Conclusions

There is insufficient evidence to support the efficacy of any particular pharmacotherapy or psychotherapy in DPRD. Further research on the treatment of depersonalization-derealization disorder is sorely needed.

Keywords

Depersonalisation disorder, depersonalization disorder, derealisation disorder, derealization disorder, depersonalisation-derealisation disorder, depersonalization-derealization disorder, depersonalisation syndrome, depersonalization syndrome, derealisation syndrome, derealization syndrome, depersonalisation-derealisation syndrome, depersonalization-derealization syndrome, drug, pharmacotherapy, medication, randomised control trial, randomized control trial, RCT, treatment.

Background

Depersonalization disorder (DPRD), renamed depersonalization-derealization disorder in DSM-5 [1], is an alteration in the perception or experience of the self and the environment. Individuals with depersonalization feel uneasily estranged and separated from their selves (depersonalization) and their surroundings (derealization), experiencing a sense of disembodiment (desomatization) and a diminution or loss of emotional reactivity (de-affectualization) [2-4]. Depersonalization is disordered when it occurs as a persistent, pervasive phenomenon, causing subjective distress and functional impairment. 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: depersonalization-derealization disorder [6].

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 is in the region of 20%–40% [7-9]. 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 [8]. A possible reflection of how unfamiliar professionals are with DPRD is the outcome of a case series reported by Baker et al [10], in which the mean duration of symptoms was over 12 years at the time of first contact with a specialist depersonalization clinic. The disorder might be much more prevalent than commonly thought. Thus, in one survey, DPRD occurred in 80% of psychiatric inpatients, 12% of whom were assessed as suffering from a severe and persistent form of the disorder [11].

Historical reports of the use of barbiturates, amphetamines and antipsychotics in the treatment of DPRD do not suggest any consistent benefit [12, 13]. Subsequent single case reports suggest potential efficacy for a wide variety of treatments including benzodiazepines (phenazepam and clozapine, [14]; clonazepam, [15]), tricyclic anti-depressants (desipramine, [16]), serotonergic drugs (fluoxetine, [17, 18]; fluoxetine and buspirone, [19]), SNRIs (venlafaxine, [20]), a combination of benzodiazepines and serotonergics (citalopram-clonazepam, [21]), anti-convulsants (lamotrigine, [22]),
(methylphenidate, [23]), and opiate antagonists (naltrexone, [24]). Other tried psychiatric interventions included electroconvulsive therapy (ECT) [25] and transcranial magnetic stimulation [26]. Psychotherapy case reports have indicated that psychodynamic psychotherapy [27] and hypnosis-based treatment, combined with Eye Movement Desensitization and Reprocessing (EMDR), [28], may be useful.

Several small open-label studies have also been conducted. Based on the hypothesis that emotional numbing is an opiate-mediated phenomenon, nalmefene, an oral opiate antagonist, was administered and reported to lessen depersonalization symptoms in some combat veterans suffering from PTSD [29]. Although the duration of the response was not clearly described, a marked decline in chronic depersonalization was reported in subjects treated intravenously with naloxone, another opiate antagonist [30]. In a later open prospective trial of naltrexone administered to 12 participants with DPRD who completed at least 4 weeks of naltrexone treatment, four (33%) showed marked improvement with a 50% to 90% reduction in symptoms [31].

A different body of research suggests that glutamate might be relevant to the pathophysiology of depersonalization and dissociation. Sub-anesthetic doses of the N-methyl D-aspartate receptor antagonist ketamine were shown to induce subjective experiences characteristic of depersonalization [32]. It is believed that the altered state of consciousness induced by ketamine is mediated by increased glutamate release in response to NMDA receptor blockades, with a consequent excess of glutamate activity at non-NMDA
glutamate receptors [33]. Several studies have reported on the use of lamotrigine in DPRD, a drug reported to inhibit glutamate release by acting at the presynaptic membrane to attenuate the effects of ketamine on conscious experience and cognition [34, 35]. While a crossover, double-blind study on nine patients with DPRD, failed to show any beneficial effects of lamotrigine [36], lamotrigine was reported to benefit some patients with chronic DPRD [22, 37] when used as an add-on therapy.

There have also been some publications on psychotherapy research in DPRD. One psychoanalytic case study was mentioned earlier [27], and two additional case reports representing behavioral therapy [38] and directive therapy [39] have been published. However, the latter two reports focused on depersonalization as a co-morbid, secondary disorder. 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.

Given the growing interest in the psychobiology and management of DPRD, it is timely to conduct a systematic review to determine the efficacy of medication, psychotherapy or a combination of both treatment modalities in combating depersonalization-derealization disorder, relative to placebo and other comparison groups.
Methods

Identification of studies

The literature search was carried out using the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 8), MEDLINE, PsycINFO, the metaRegister of Controlled Trials database (mRCT), the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP), for articles published from January 1980 to August 2012. The following search terms were used: “depersonalisation disorder” OR “depersonalization disorder” OR “derealisation disorder” OR “derealization disorder” OR “depersonalisation-derealisation disorder” OR “depersonalization-derealization disorder”, OR “depersonalisation syndrome” OR “depersonalization syndrome” OR “derealisation syndrome” OR “derealization syndrome” OR “depersonalisation-derealisation syndrome” OR “depersonalization-derealization syndrome”, AND “drug” OR “pharmacotherapy” OR “medication” OR “treatment”, AND “randomised control trial” OR “randomized control trial”, OR “RCT”. The initial search yielded 1296 studies, of which four met study criteria and were included in the review. The bibliographies of all identified trials were checked for additional studies and the authors were contacted for published and unpublished trials. No restriction was placed on language and setting. Studies employing cross-over and parallel designs were potentially considered for inclusion, as well as unpublished trials.

Criteria for considering studies for this review included (a) all randomized
controlled trials (RCTs) of pharmacotherapy, psychotherapy, or a combination of these modalities for the treatment of depersonalization disorder, (b) all participants diagnosed with depersonalization disorder according to the criteria of the Diagnostic and Statistical Manual (DSM-III-R [41] or DSM-IV [42]), or the International Classification of Diseases (ICD-9, [43] or ICD-10 [44]) 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 junction 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. 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**

Treatment response was reported if studies used the Clinical Global Impressions scale (CGI-I), a widely used categorical measure of treatment response in which responders are defined as having a change item score of 1 = "very much" or 2 = "much" improved (CGI; [45]), or by a 50% reduction
reported by the Cambridge Depersonalization Scale [46].

The effect of intervention on symptom severity was determined from standardized instruments such as the Cambridge Depersonalization Scale, the Dissociative Experiences Scale (DES, [47]), or the Depersonalization Severity Scale (DSS, [48]).

**Secondary outcomes**

Depression was reported if studies provided data on the 17-item Hamilton Rating Scale for Depression (HRSD; [49]), the Beck Depression Inventory; [50]), or a similar scale. Anxiety was measured with the standard Hamilton Rating Scale for Anxiety (HRSA; [51]) the Beck Anxiety Inventory [52], or a similar scale. Symptom improvement in other anxiety disorders similarly employed customary "gold-standard" severity measures.

**Meta-analysis**

The analytical summary of the selected studies was considered but high heterogeneity across studies prohibited combining results to produce a single overall estimate of effect.

**Data collection**

**Selection of studies**

RCTs that were potentially eligible for inclusion after an initial screening of their abstracts by one of the authors (ES) were assessed based on information included in the main body of the trial report, or the abstract in
cases where the article was not accessible. 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 & TA-W). The reviewers contacted investigators by email in an attempt to obtain missing information. A narration of each trial is provided in the results section.

Results

Results of the search

MEDLINE, ClinicalTrials.gov, WHO trials and PsycINFO, searches retrieved 1147 and 149 unique articles, respectively. The search of the CCDAN Controlled Trials Registry yielded 2 additional results. Reviews of reference lists of key studies identified one more study, resulting in a total of 1296 unique abstracts (see figure 1). Of the 14 open and cross-over trials, one was a double-blind, placebo-controlled study that was selected for this review. Four double-blind, placebo-controlled studies (three randomized and one cross-over) were finally selected for independent assessment by two raters (ES and DS).

Description of included studies

One psychotherapy and three pharmacotherapy trials (32 participants; 144 participants) were eligible for inclusion in the review (see table 1). A 10-week double-blind comparison of the serotonin reuptake inhibitor (SSRI) fluoxetine with a placebo (mean dose: 48mg/day) in 50 patients with DPRD [53]. A 12-week double-blind, placebo-controlled, cross-over comparison of the
anticonvulsive lamotrigine (mean dose: 181 mg/day) [36] with a placebo, following a 2-week washout, in nine patients with DPRD. A later double-blind placebo-controlled 12-week randomization study of lamotrigine (mean dose: 196 mg/day) [54] in 80 male DPRD patients. The psychotherapy study selected for assessment in this review aimed to ameliorate disembodiment and emotional numbing symptomatology in DPRD by increasing physiological arousal levels through biofeedback. The study employed a randomized controlled biofeedback trial in 32 DPRD patients comparing skin conductance response biofeedback with sham biofeedback.

**Description of excluded studies**

Sixteen abstracts concerning case and retrospective studies on the treatment of DPRD were identified but excluded from this review due to inadequate sample size and lack of a control group. Described interventions included SSRI [55], benzodiazepines and anti-psychotics [14], an opioid receptor antagonist [29], lamotrigine as a single [37] or add-on treatment [22], the opioid receptor antagonists naloxone [30] and naltrexone [24, 31]. Temporoparietal junction stimulation [56] is reported as an ongoing open label trial in ClinicalTrials.gov and cognitive-behavior therapy [57].

**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 [58]: 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).

Random sequence generation
One trial was rated “high” because no information was provided to determine if randomization occurred [59]; one trial was rated “low” because the study used a randomization table [53]; and the additional two trials were rated “unclear” [36, 54]. Each study indicated that the participants were randomized however the procedure was not clearly defined.

Allocation concealment
One study was rated “high” because there was no indication within the study as to how the intervention was concealed [59]. The three additional trials were rated “low” because each trial provided both medication and placebo in identical-appearing capsules [36, 53, 54], presented in numbered or unmarked bottles.

Blinding (performance bias and detection bias)
One trial using lamotrigine provided information that the participant was blinded to the intervention [59], whereas the three additional trials provided information that both the participant and the assessor were blinded to the intervention and comparison [36, 53, 54].

Blinding of outcome assessment
Each trial rated “low” for the blinding of the outcome assessment [36, 53, 54, 59]. For the biofeedback group procedures were identical to those in
experimental 1 [59]. There was no need for the outcome assessments to be identical or blind in the additional three trials [36, 53, 54].

Incomplete outcome data (attrition bias)
All four studies were rated “low” for attrition bias because all outcomes were reported on [36, 53, 54, 59]. For two studies, dropouts were excluded from the analysis, with no reasons for dropouts [36, 54]. No baseline scores were reported in one study using lamotrigine [54].

Selective reporting (reporting bias)
For selective reporting, all four studies were rated “unclear” because there was no protocol available to determine if all outcomes were measured [59; 57; 56; 36].

Effects of interventions
Pharmacotherapy versus placebo
Primary outcome measures
Fluoxetine (mean dosage 48 mg/day) produced a statistically significant improvement in depersonalization severity, as rated by the improvement score of the Clinical Global Impression scale (CGI–I) (before correction for depression and anxiety effects, 2.9 vs. 3.6), without notable improvement in depersonalization symptom ratings [53]. However, categorical analysis of responder status indicated that fluoxetine cannot be regarded as efficacious in treating primary depersonalization [24% response rate on fluoxetine (n=6) and a 20% response rate on placebo (n=5) (x²=0.12, df=1, P=.73)]. End-point
CGI–I for depersonalization disorder differed marginally according to the presence or absence of clinical improvement (CGI–I) in comorbid anxiety disorders ($\chi^2=5.76$, d.f=2, $P=0.06$). That is, depersonalization was more likely to improve if comorbid anxiety disorder improved.

A 12-week double-blind, placebo-controlled, cross-over comparison of the anticonvulsive lamotrigine (mean dose: 181 mg/day) [36] with a placebo, following a 2-week washout, in nine patients with DPRD revealed that lamotrigine as a sole medication for DPRD was not significantly superior to the placebo as none of the nine patients was deemed a responder to the lamotrigine arm of the cross-over. Subsequently, 12 weeks of lamotrigine therapy resulted in a statistically significant difference in improvement (defined as a 50% reduction in the Cambridge Depersonalization Scale) in a lamotrigine group compared with that in the placebo group ([54]; $\chi^2=22.68$, df=1, $P<0.001$).

Secondary outcome measures
Those taking fluoxetine consistently tended to have better responses than those taking the placebo, as defined by CGI–I scores of 2 or 1 for the particular disorder: 50% vs. 0% for major depression, 75% vs. 25% for dysthymia, 50% vs. 40% for generalized anxiety disorder, 100% vs. 25% for obsessive–compulsive disorder, 50% vs. 40% for panic disorder and 33% vs. 13% for social phobia [53].
Psychotherapy versus sham psychotherapy

Primary outcomes

While electrodermal biofeedback did not help DPRD participants increase skin conductance response (an hypothesized index of emotional responsiveness), real-time biofeedback resulted in lower state (but not trait) scores on the Cambridge Depersonalization Scale [early vs. late mean scores and standard deviations in the real-time biofeedback group: 36.0 (16.9) vs. 29.9 (18.9), p=.01; compared to 30.5 (14.7) vs. 31.8 (14.9), p=.63, scores obtained from patients exposed to sham biofeedback. Biofeedback had no effect on DES, BDI or BDI scores, compared to sham biofeedback.

Meta-analysis

Due to the clinically diverse nature of each trial, studies could not be meta-analyzed i.e. each study used a different intervention.

Discussion

To the best of our knowledge, this is the first systematic literature review on the treatment of depersonalization-derealization disorder. Although no meta-analysis was possible, the data does not provide support for the efficacy of any pharmacotherapy or psychotherapy in DPRD.

Data on lamotrigine is inconsistent with one trial indicating that lamotrigine was not significantly superior to placebo as a sole medication for DPRD, and one trial showing a statistically significant difference in improvement (i.e., 50% reduction in the CDS) compared with that in the placebo group [54]. Further
work on the potential mechanisms of action whereby anticonvulsants may act
to improve depersonalization-derealization symptoms may be informative. In
addition, larger studies may be useful in order to determine whether particular
subgroups of these patients are responsive to anticonvulsant treatment.

Fluoxetine was not demonstrated to be efficacious in treating primary
depersonalization. However, it showed improvement in depersonalization by
the CGI–I score alone and depersonalization was more likely to improve if
comorbid anxiety disorder improved [53]. The lack of responsiveness of
depersonalization to fluoxetine perhaps suggests that DRPD is not bio-
chemically closely related to anxiety or mood disorders (e.g., [10]), but is
rather best classified as a distinct dissociative disorder. The relationship of
depersonalization to anxiety and depression remains unclear. However, it is
conceivable that severe emotional states such as intense depression or
anxiety, are also powerful stressors that may trigger depersonalization in
individuals with an underlying vulnerability, and that in some cases the
depersonalization may become chronic and autonomous of the precipitating
stressor [60].

Nevertheless, findings that depersonalization can be induced by a known
serotonin receptor agonist such as meta-chlorophenylpiperazine [61], and by
drugs believed to be serotonin agonists such as cannabis [13], lysergic acid
diethylamide, and “ecstasy” [62] suggest that serotonergic mechanisms could
be important in depersonalization. Serotonin reuptake blockers (SSRIs) were
reported to be associated with positive treatment outcome among eight
patients with DPRD and a co-occurrence of obsessive-compulsive and panic disorders [62]. Furthermore, in a double-blind crossover trial of SSRI consisting of 8 weeks of desipramine and 8 weeks of clomipramine, there was limited evidence for the value of clomipramine compared to desipramine. While one subject responded to desipramine. Three of seven subjects that commenced clomipramine discontinued the trial early, while still on a low dose, as they were unable to tolerate the adverse effects. Of the remaining four subjects, there were two responders. One responder was subsequently followed in open maintenance treatment with clomipramine for four years, and her depersonalization symptoms remained in almost complete remission, with relapses upon each attempt to adjust or change medication. Thus, while randomized controlled trials have not yet supported the role of SSRI in depersonalization-derealization disorder, further work in this area may well be justified.

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. Use of evoked potential mapping, Blanke et al. [63] demonstrated bilateral temporo-parietal junction (TPJ) activation where healthy volunteers imagined themselves in a position and visual perspective generally reported by people experiencing spontaneous “out of body experiences” similar to those experienced in DPRD. In view of this, the effects of inhibitory low-frequency rTMS administered to TPJ were tested in 12 DPRD patients in an open-label cross-over trial. Four patients dropped out after the
first phase as they did not feel any benefit from the treatment, four patients were classified as full responders and two patients as partial responders. Response rate after cross-over was still 50%, with the same responders as at the end of phase one [56].

One reviewed trial had several limitations that should be considered when assessing its reported negative outcomes. In the biofeedback study [59] half the patients were on various medications, which can affect autonomic response; however, both conditions had similar proportions of medicated and non-medicated patients, and statistical analysis did not find medication status 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. 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.

The small number of controlled trials included in this review reflects the scarcity of research on the treatment of depersonalization-derealization disorder. Additional research on the efficacy of various treatments, including lamotrigine therapy, with larger samples is warranted. Inconsistent outcomes on different measures following fluoxetine treatment, and the improvement of depersonalization symptoms in some patients with comorbid anxiety disorder, contribute to an argument that further research on the potential role of SSRIs in DPRD is reasonable. Controlled trials of cognitive-behavior therapy and
third generation psychotherapies (e.g., mindfulness therapy) may also be warranted given that anxiety and depersonalisation are thought to be related [40].

Conclusion
There is insufficient evidence to support the efficacy of any particular pharmacotherapy or psychotherapy in DPRD. Further exploration of the value of lamotrigine, serotonin selective reuptake inhibitors and other interventions in larger trials may be useful. Indeed, a great deal of further research on the pathogenesis and treatment of depersonalization-derealization disorder is required.

Competing interests
Eli Somer has no known conflicts of interest.
Taryn Amos-Williams has no known conflicts of interest.
Dan Stein has received research grants and/or consultancy honoraria from Astrazeneca, Eli-Lilly, GlaxoSmithKline, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, and Wyeth. He has participated in a number of ongoing trials, and has presented data from some of these trials on behalf of the sponsoring companies.

Author's contribution
Eli Somer was responsible for screening studies for inclusion and writing the methodology, the results and the interpretive components of the review (discussion and conclusion). Taryn Amos-Williams was responsible for
compiling the original protocol. Eli Somer and Taryn Amos-Williams extracted data from the RCTs. Dan Stein provided assistance as a content expert and coordinator, provided feedback on draft versions of the protocol and review and was responsible for responding to editorial comments. Eli Somer stands as guarantor of this review.

Sources of funding
None of the authors received any funding for this study.
References


<table>
<thead>
<tr>
<th>Study ID</th>
<th>Funding</th>
<th>Country</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Weeks (sessions)</th>
<th>Total randomized</th>
<th>Mean age of sample</th>
<th>% female in sample</th>
<th>Diagnostics &amp; baseline screening</th>
<th>Primary measures</th>
<th>Secondary measures</th>
<th>Drop-outs</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliyev 2011</td>
<td>none</td>
<td>Azerbaijan</td>
<td>Lamotrigine</td>
<td>Placebo</td>
<td>12</td>
<td>80</td>
<td>37.7</td>
<td>0</td>
<td>CDS</td>
<td>CDS</td>
<td>Improvement</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Sierra 2003</td>
<td>UK</td>
<td>UK</td>
<td>Lamotrigine</td>
<td>Placebo</td>
<td>12</td>
<td>14</td>
<td>35.2</td>
<td>DSM-IV</td>
<td>PSE</td>
<td>CDS</td>
<td>DES</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Simeo 2004</td>
<td>NIMH</td>
<td>USA</td>
<td>Fluoxetine (provided by Eli Lilly)</td>
<td>Placebo</td>
<td>10</td>
<td>54</td>
<td>36</td>
<td>39</td>
<td>SCID-D Semi-structured clinical interview</td>
<td>CGI-I</td>
<td>DES-DEP</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Schoenberg 2012</td>
<td>Medical Research Council Pilkington Pilozzo Charitable Trust</td>
<td>UK</td>
<td>Electro-dermal biofeedback</td>
<td>Sham electro-dermal biofeedback</td>
<td>4 (8)</td>
<td>32</td>
<td>35</td>
<td>25</td>
<td>SCID-D</td>
<td>CDS DES BAI BDI</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1 Randomized controlled trials included in the review (n = 4)
### Table 2 Risk of bias in selected studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliyev 2011</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
<td>yes</td>
<td>unclear</td>
<td>no</td>
</tr>
<tr>
<td>Sierra 2003</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
<td>yes</td>
</tr>
<tr>
<td>Simeon 2004</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Psychotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoenberg 2012</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

1: allocation sequence adequately generated; 2: allocation adequately concealed; 3: knowledge of allocation adequately prevented; 4: incomplete outcome adequately addressed; 5: free of selective outcome reporting; 6: free of other problems
Identification
Records identified through database searching: n=1296

Screening
Title screening: n=1059

Abstract screening: n=718

Eligibility
Full-text articles assessed for eligibility: n=29

Included
Studies included in qualitative synthesis: n=4

Records excluded: n=237
Reason: Duplicates

Records excluded: n=341
Reason: Not Depersonalization/derealization

Records excluded: n=689
Reason: Not treatment articles or no outcome provided

Full-text articles excluded: n=25
Reasons: Retrospective studies and open trials