Efficacy of pharmacotherapy against core traits of borderline personality disorder: meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that drug treatments can have modest positive effects on some core traits of patients with borderline personality disorder. The poor reporting of review methods and differences between the studies make it difficult to assess the reliability of these conclusions.

Authors' objectives
To evaluate the effects of pharmacotherapy on core traits in patients with borderline personality disorder (BPD).

Searching
MEDLINE (from 1966), EMBASE (from 1980), PsycLIT (from 1974) and the Cochrane CENTRAL Register were searched up to June 2006; the search terms were reported. In addition, the references of retrieved studies were screened. Abstracts and unpublished studies were excluded.

Study selection
Placebo-controlled randomised controlled trials (RCTs) that evaluated the effects of pharmacotherapy on core traits in patients of either sex with BPD were eligible for inclusion. BPD could be diagnosed using any criteria and studies could include patients with BPD and patients with other personality disorders. The primary review outcomes were affective instability and anger, impulsivity and aggression, interpersonal relationships, suicidality and global functioning. The secondary review outcome was the percentage of patients leaving the study early. Preferred rating scales were listed but other rating scales were also included.

The included studies evaluated antipsychotics (aripiprazole, haloperidol, olanzapine, risperidone and thiotixene), antidepressants (amitriptyline, ethyl-eicosapentaenoic acid, fluoxetine, fluvoxamine and phenelzine) and mood stabilisers (carbamazepine, divalproex sodium, lamotrigine and topiramate). In some studies the patients received concomitant psychotherapy. In most of the studies, patients were diagnosed with BPD using the American Psychiatric Association's DSM-IV criteria or the International Classification of Diseases (ICD-10) criteria. The majority of studies were conducted in out-patient settings. Just over half of the studies (11 out of 20) only included patients with BPD. Half of the studies excluded actively suicidal patients. The duration of the studies ranged from 4 to 24 weeks (median 8).

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using the Jadad scale, which considers the reporting and handling of randomisation, blinding and handling of withdrawals. The maximum possible score was 5 points.

The authors did not state how the validity assessment was performed.

Data extraction
For each study, means and standard deviations of scores at end point or the last visit before end point were extracted, or estimated. Standardised mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for each outcome of interest. Acceptability of treatments was assessed using the relative risk (RR) of drop-out. Authors were contacted for missing data. The numbers of patients who dropped out early were also extracted and used to calculate RRs with 95% CIs. For crossover studies, only data from the first phase were used.

Two reviewers independently extracted the data onto a standardised form. Any disagreements were resolved through consensus with a third reviewer.
Methods of synthesis
Fixed-effect and random-effects models were used to calculate pooled SMDs and RRs with 95% CIs. Statistical heterogeneity was assessed using the $\chi^2$ statistic. Pre-specified sensitivity analyses were conducted by analysing studies that only included patients with BPD and by excluding studies in which more than 50% of the patients dropped out early. Post hoc sensitivity analysis was performed by including or excluding individual drug treatments. Publication bias was assessed using the Begg and Egger test.

Results of the review
Twenty RCTs (n=818) were included. These studies provided 22 drug-placebo comparisons. All of the studies were described as double-blind. Treatment groups ranged in size from 4 to 49 patients. The Jadad scores ranged from 2 to 4 (mean 2.9). Three studies reported drop-out rates of greater than 50%.

Instability and anger: there was no statistically significant difference between antipsychotics and placebo (2 studies). Compared with placebo, significant reductions were found in patients allocated to antidepressants (SMD -0.55, 95% CI: -0.92, -0.17; based on 4 studies) and mood stabilisers (SMD -1.74, 95%CI: -2.76, -0.73; based on 6 studies); significant heterogeneity was found (p=0.091 and p<0.0001, respectively).

Impulsivity and aggression: there were no statistically significant differences between antidepressants and placebo (6 studies) or between mood stabilisers and placebo (3 studies). Antipsychotics were associated with a significant reduction in impulsivity and aggression (SMD -0.31 (95% CI: -0.63, -0.003; based on 3 studies). No significant heterogeneity was found for any of these analyses.

Interpersonal relationships: there were no statistically significant differences between antidepressants and placebo (1 study) or between mood stabilisers and placebo (2 studies). Antipsychotics were associated with a significant reduction compared with placebo (SMD -0.31, 95% CI: -0.63, -0.003; based on 3 studies); no significant heterogeneity was found.

Suicidality: there were no statistically significant differences between antidepressants and placebo (1 study), between mood stabilisers and placebo (1 study), or between antipsychotics and placebo (1 study).

Global functioning: there were no statistically significant differences between antidepressants and placebo (4 studies) or between mood stabilisers and placebo (1 study). Antipsychotics were associated with a significant reduction compared with control (SMD -0.56, 95% CI: -1.00, -0.11; based on 7 studies); significant heterogeneity was found (p=0.002).

Drop-outs: there were no statistically significant differences between antipsychotics and placebo (43% versus 35%, p=0.57; 6 studies), between antidepressants and placebo (20% versus 16%, p=0.65; 5 studies), or between mood stabilisers and placebo (33.3% versus 33%, p= 0.49; 6 studies).

The results of sensitivity analyses were also reported.

Authors' conclusions
Pharmacotherapy can have modest positive effects on some core traits of patients with BPD.

CRD commentary
The review question was stated clearly. Several relevant sources were searched and no evidence of publication bias was found. However, it is not clear if attempts were made to minimise publication and language bias. Appropriate methods were used to minimise reviewer error and bias during the data extraction, but since the methods used to select studies and assess validity were not described, it is not known whether similar efforts were made to reduce reviewer error and bias at these stages. Only RCTs were included and validity-related criteria were apparently extracted, but results were not reported which makes it difficult to judge the reliability of the results. Appropriate methods were used for the meta-analyses, heterogeneity was assessed, and various predefined subgroup analyses were conducted. The evidence appears to support the authors' conclusions, but the lack of reporting of study quality means it is difficult to comment on the strength of the evidence underpinning the authors' conclusions.
Implications of the review for practice and research
Practice: The authors stated that physicians should try to base treatment decisions on the best available evidence.

Research: The authors stated that future trials should define a priori outcome measures that differentiate between state symptoms of acute decompensation from specific core traits in patients with BPD.

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