Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review
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CRD summary
There was an overall beneficial clinical effect of pindolol augmentation to antidepressive treatment in adults with depressive disorders, most clearly up to four weeks of treatment. The conduct of this review was generally good and the conclusions seemed reliable, although some results maybe underestimated due to a difficulty in obtaining outcome data from some trials.

Authors' objectives
To investigate whether pindolol enhances the efficacy of antidepressant treatment at sequential time points up to six weeks in adults with depressive disorders.

Searching
The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (included searches of MEDLINE, EMBASE, CINAHL, PsycLIT, PSYNDEX and LILACS from 1990 to April 2007) was searched. Search terms were reported. The Cochrane Library, reference lists of included articles and major textbooks and papers that covered affective disorders were searched. Authors in the field and drug companies were contacted.

Study selection
Prospective randomised controlled trials (RCTs) in patients who suffered from a depressive disorder according to explicit criteria (which included unipolar and bipolar depressive disorders) that compared pindolol against placebo in combination with selective serotonin reuptake inhibitors (SSRIs) were eligible for inclusion. Trials needed to report clinical response up to six weeks (a binary outcome indicated more than 50% reduction in a depression scale score).

Participants in the included studies were aged from 18 to 65 or 70 years; one study only included those aged over 25. Participants were non-psychotic or bipolar outpatients or psychotic or bipolar in-patients. Study duration was between 10 and 42 days. Pindolol doses were either 2.5mg three times daily or 5mg twice daily given in combination with either an unnamed SSRI, fluoxetine 20mg, paroxetine 20mg or up to 150mg of fluvoxamine.

The authors did not report how studies were selected for the review.

Assessment of study quality
Study quality was assessed using Cochrane Collaboration criteria for randomisation procedure, allocation concealment, double-blinding and reporting of withdrawals. Authors were contacted for further information where necessary.

The assessment was performed by two reviewers independently. Disagreements were resolved by consensus.

Data extraction
Results for clinical response (more than 50% reduction in depressive symptoms) were extracted and used to calculate odds ratios (OR) together with 95% confidence intervals (CI). Last observation carried forward was used to account for patient withdrawals and these were treated as non-responders in the analyses. Outcomes were extracted at weekly intervals for up to six weeks.

Data were extracted by two reviewers independently. Disagreements were resolved by consensus.

Methods of synthesis
Results were pooled using fixed-effect models. Heterogeneity was assessed using the Q statistic (p<0.1 was considered
significant) and $I^2$. Sources of heterogeneity were explored. Random-effects models were used as sensitivity analyses. Separate analyses were performed for results at each week up to six weeks. A time-to-event analysis using a discrete logistic model was undertaken using the cumulative responses at each time point. Where significant heterogeneity was found, the effect of study level characteristics was explored.

**Results of the review**

Eleven reports of 10 trials (n=889) were included. All trials were judged to have adequate randomisation and allocation concealment. Trials that reported withdrawals 11% of pindolol and 13% of placebo patients withdrew.

Pooled odds ratios were: week one 2.39 (95% CI 1.40 to 4.06, $I^2$=32.6%; nine trials); week two 2.39 (95% CI 1.74 to 3.29, $I^2$=42.3%; 10 trials); week three 1.94 (95% CI 1.46 to 2.58, $I^2$=81.7%; nine trials) and week four 1.59 (95% CI 1.16 to 2.18, $I^2$=42.2%; eight trials). These were in favour of pindolol. There were no statistically significant differences between pindolol and placebo at weeks five or six. Random-effects models produced similar results. A similar benefit for pindolol was seen in the time to response analysis (hazard ratio 1.26, 95% CI 1.01 to 1.58) compared with placebo.

Possible reasons for heterogeneity (such as differences between refractory and non-refractory patients, severity of illness at baseline, type and dose of SSRI and pindolol dose) were discussed.

**Authors' conclusions**

This review concluded that there was an overall beneficial clinical effect of pindolol augmentation, most clearly up to four weeks of treatment.

**CRD commentary**

This review had clear inclusion criteria for study design, interventions, participants and outcomes. The search covered a number of databases and searched for unpublished literature. It was unclear whether there were language restrictions, so language bias could not be ruled out. Data were extracted and quality assessed by two reviewers independently; was not reported whether the same method was used to select the studies for the review. The quality assessment was appropriate and the evidence was considered to be mostly good quality. Methods of meta-analysis were appropriate and included sensitivity analyses. The authors discussed possible reasons for any observed heterogeneity; very high heterogeneity was seen for the three week result.

The conduct of this review was generally good and the conclusions seemed reliable, although some results may have been underestimated due to a difficulty in obtaining outcome data from some trials.

**Implications of the review for practice and research**

**Practice**: The authors stated that there was modest support for augmentation of newly started serotonergic antidepressant treatment with pindolol, especially if fast onset was important. This needed to be weighted against potential adverse effects.

**Research**: The authors stated that further larger trials and access to continuous data that were unavailable in the trials in this review were needed to confirm or refute these findings. Further studies should examine the time of onset of the effects of pindolol and use more homogenous patient populations regarding illness severity, refractory syndrome and naivety to treatment.

**Funding**

Not stated.

**Bibliographic details**

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.