CRD summary
The review concluded that pirlindole was comparable to its comparators in terms of efficacy and significantly better at reducing anxiety. The author's conclusions are in line with the evidence presented, but the limited number of studies included in some analyses and limitations in trial quality and the review process mean these results should be interpreted with caution.

Authors' objectives
To determine the efficacy and frequency of adverse events of pirlindole compared with active comparators for the treatment of adults with major depression.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1966 to August 2010 without language restrictions. Search terms were reported. A manual search of the Grupo Tecnimede website was performed. Abstracts of conference proceedings were excluded.

Study selection
Randomised controlled trials (RCTs) in adults with bipolar disorder that compared pirlindole with placebo or an active control for the treatment of major depression or depressive episodes were eligible for inclusion. Eligible active controls included monoamine oxidase inhibitors, tricyclic antidepressants, tetracyclic antidepressants and selective serotonin reuptake inhibitors. Trials were required to report efficacy and adverse events profiles.

Pirlindole doses ranged from 150mg to 450mg. Active comparators included desipramine (150mg), amitriptyline (150-300mg), imipramine (150mg), maprotiline (150mg), moclobemide (360-600mg), mianserin (60-90mg) and fluoxetine (20mg). In two trials the comparator was placebo. Most participants were in-patients with major depression. The primary outcome was clinical improvement. A range of efficacy measures were reported; the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) were used to assess the primary endpoints in most trials. Where stated, mean age of participants ranged from 35 to 51 years and 16% to 83% of the participants were women.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale of randomisation, blinding and follow-up of withdrawals and dropouts. A total score was awarded for each study (up to a maximum of 5 points). Any discrepancies were resolved through consensus.

Data extraction
Two reviewers independently extracted the mean HDRS and HARS, percentage of patients who improved by 50% on HDRS and HARS and the number of participants who reported adverse events. Mean differences and odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated. Any disagreements were resolved through discussion.

Methods of synthesis
Weighted mean differences (WMDs) and odds ratios, with 95% CIs, were pooled using a fixed-effect model (no heterogeneity found) or a random-effects model (statistical heterogeneity was found). Statistical heterogeneity was assessed using the Q test (p<0.1 considered significant). Trials were excluded from the meta-analysis where the comparator was placebo. Trials with methodological limitations were excluded from the meta-analysis.

Results of the review
Thirteen RCTs were included in the review (892 participants). Nine RCTs (776 participants) were included in the meta-analyses; all of these compared pirlindole with an active comparator. Follow-up ranged from 21 days to 180 days. Twelve trials reported randomisation. The proportion of dropouts ranged from 5% to 40%. Mean Jadad score was 3.7 (range 2 to 5).

Pirlindole had a greater improvement on the HARS (WMD 0.26, 95% CI 0.03 to 0.48; three RCTs) compared with active controls. No statistically significant between-group differences were found for improvement on the HDRS (six RCTs) and the proportion of patients whose clinical condition improved by 50% as assessed by the HDRS and HARS (two RCTs). No significant statistical heterogeneity was found.

Adverse events were reported in seven RCTs (580 participants). The most frequently reported adverse events with pirlindole were dry mouth and sleep disturbances. No significant between-group differences were found between pirlindole and active comparators for the percentage of patients with any adverse event. No serious adverse events with pirlindole were reported.

**Authors’ conclusions**
The results indicated that pirlindole was comparable to its comparators in terms of efficacy and significantly better at reducing anxiety, but the overall quality of the included studies suggested that research was needed to confirm these results.

**CRD commentary**
The review question was supported by inclusion criteria. The search included relevant databases and some attempt was made to locate unpublished trials. There were no language restrictions, which minimised the risk of language bias. Publication bias was not assessed. Appropriate methods were used to minimise reviewer error and bias for data extraction and validity assessment; whether similar procedures were taken for study selection was not clear.

The quality of the included studies was assessed using a standardised measure, although some important criteria (such as allocation concealment) were not included. The authors acknowledged limitations of the review, including the quality of the included trials. Studies were pooled by meta-analyses and heterogeneity was assessed.

The review was funded by and one author was an employee of Grupo Tecnimede (manufacturer of pirlindole).

The author’s conclusions are in line with the evidence presented, but given the small number of studies included in some of the analyses and methodological limitations in the trials themselves and in the review process itself, these should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors suggested that further trials with more rigorous methodologies and larger populations as well as more recently introduced comparators were needed.

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