Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials

Goss AJ, Kaser M, Costafreda SG, Sahakian BJ, Fu CH

CRD summary
This review concluded that the evidence supported use of adjunctive modafinil for the safe treatment of depression and fatigue in patients with unipolar or bipolar depression. The evidence base was small, heterogeneous and of unclear quality. It was unclear how the results translated into clinical benefit. The limitations and uncertainties suggest that the authors’ conclusions may not be reliable.

Authors' objectives
To assess the efficacy and tolerability of first-line treatment with modafinil for unipolar and bipolar depression.

Searching
MEDLINE/PubMed and PsycINFO were searched between 1980 and April 2013 for English-language peer-reviewed articles. Search terms were reported. Reference lists of included studies and relevant reviews were screened manually.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared the efficacy of adjunctive modafinil/armodafinil treatment versus placebo in adults (aged 18 to 65 years). Eligible participants had to have been diagnosed with unipolar (major depressive disorder) or bipolar depression according to DSM-IV, ICD-10 or other well-recognised criteria. The outcome of interest was the effect of modafinil on depression severity at the final visit. Secondary outcomes included remission and response rates at final assessment (as defined in the review), early effects (at one week), effects on specific symptoms (sleepiness and fatigue) and safety and tolerability.

Included trials assessed modafinil 100 to 400 mg/day for six or eight weeks or armodafinil 150 mg/day for eight weeks. Additional treatments to modafinil/armodafinil included antidepressants or mood stabilizers with or without concomitant antidepressants. Baseline depression severity varied across trials (as reported in the review). Depression severity was assessed using the Hamilton Depression Rating Scale or Inventory of Depressive Symptomatology.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
The authors did not state that they assessed trial quality but stated that trials had to be double blind.

Data extraction
Outcome data were extracted to calculate mean differences from baseline to the end of the study, or odds ratios (OR) along with their 95% confidence intervals. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
A DerSimonian-Laird random-effects model was used to pool outcome data to calculate standardised mean differences (Hedge's g) or pooled odds ratios, along with their 95% confidence intervals. Hedge's g with an effect size cut-off of 0.2 indicated a small treatment effect, 0.5 a medium treatment effect and 0.8 a large treatment effect. The number needed to treat (NNT) to avoid one event was calculated.

Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were performed by depression diagnosis. Sensitivity analysis was conducted where trials showed very different results.

Meta-regression was performed to assess the effects of diagnosis and baseline depression severity on treatment effect.

Results of the review
Six RCTs (910 patients, range 46 to 311) were included in the review.
Depression severity: Modafinil treatment statistically significantly improved depression scores compared to placebo (Hedge's g -0.35, 95% CI -0.61 to -0.10; six RCTs). However, there was evidence of substantial statistical heterogeneity (I²=67%). Sensitivity analysis excluding one trial did not significantly alter the results, but did explain the statistical heterogeneity (I²=0%).

Subgroup analyses showed that modafinil improved depression scores in patients with unipolar depression but this was not quite statistically significant (Hedge's g -0.41, 95% CI -0.84 to 0.01; four RCTs). However, the improvement became statistically significant when the one trial that showed very different results was removed. Modafinil statistically significantly improved depression scores in patients with bipolar depression (Hedge's g -0.30, 95% CI -0.52 to -0.09; two RCTs).

Secondary outcomes: Modafinil statistically significantly increased rate of remission compared to placebo (OR 1.61, 95% CI 1.04 to 2.49; NNT 10; five RCTs; I²=32%). Response rates were similar between participants who received modafinil or placebo (five RCTs). Modafinil appeared to be generally safe and well tolerated. Modafinil had a statistically significant benefit on fatigue scores compared to placebo (Hedge's g -0.15, 95% CI -0.28 to -0.02; six RCTs) but had no significant effect on sleepiness.

Compared to placebo, modafinil had a statistically significant early treatment beneficial effect on total depression scores at one week (four RCTs) and on fatigue (two RCTs) and sleepiness (three RCTs). There were no differences between modafinil and placebo on sad mood scores (results were partly reported in the review).

Results for meta-regression analyses were reported in the review.

Authors' conclusions
The evidence supports the use of adjunctive modafinil for the safe treatment of depression and fatigue in patients with unipolar or bipolar depression.

CRD commentary
The review question and supporting inclusion criteria were clearly stated. The literature search was limited to two electronic databases and was restricted by language and publication status so potentially relevant evidence may have been missed. Study selection was performed in duplicate and this reduced potential for reviewer error and bias; it was unclear whether this was also the case for data extraction. The authors did not state that they assessed trial quality, other than all trials were double blinded.

There were clinical and methodological differences across trials in terms of inclusion criteria, modafinil/armodafinil doses and type of additional treatment. Treatment duration was short-term across all trials and sample sizes were small. Extraction of outcome data was not clearly reported but it appeared that appropriate methods were used to pool data and investigate statistical heterogeneity. The authors acknowledged the considerable heterogeneity between trials and that the addition of further trials may affect the results. It was unclear how much of the findings were the result of the additional modafinil/armodafinil or due to the primary treatments administered. It was unclear how the statistically significant results translated into clinical significance, given that the confidence intervals suggested that the effects were only just statistically significant.

The evidence base was small and had unclear methodological quality and significant variability in terms of patient and trial characteristics. Given the limitations and uncertainties surrounding the evidence, the authors' conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that evidence of early effectiveness of modafinil on depressive symptoms, fatigue and sleepiness may possibly have beneficial implications for treatment compliance and work functioning.

Research: The authors stated that future research was warranted, should include more methodologically similar trials of longer treatment duration and should investigate the effects of modafinil on cognitive domains in depression. Trials should directly compare adjunctive modafinil and armodafinil for both unipolar and bipolar depression.

Funding
Individual authors were supported by a Cambridge-IDB International Scholarship, National Institute for Health Research, South London and Maudsley Biomedical Research Unit in Dementia, Wellcome Trust, and the Medical Research Council.

Bibliographic details

PubMedID
24330897

DOI
10.4088/JCP.13r08560

Original Paper URL
http://article.psychiatrist.com/dao_1-login.asp?ID=10008467

Indexing Status
Subject indexing assigned by NLM

MeSH
Antidepressive Agents /adverse effects /therapeutic use; Antimanic Agents /adverse effects /therapeutic use; Benzhydryl Compounds /adverse effects /therapeutic use; Bipolar Disorder /diagnosis /drug therapy /psychology; Depressive Disorder, Major /diagnosis /drug therapy /psychology; Drug Therapy, Combination; Humans; Personality Inventory /statistics & numerical data; Psychometrics; Randomized Controlled Trials as Topic; Wakefulness-Promoting Agents /adverse effects /therapeutic use

AccessionNumber
12014000562

Date bibliographic record published
13/01/2014

Date abstract record published
01/08/2014

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.