Modafinil Augmentation Therapy in Unipolar and Bipolar Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Alexander J. Goss, BA, MSc; Muzaffer Kaser, MD, MPhil; Sergi G. Costafreda, MD, PhD; Barbara J. Sahakian, PhD; and Cynthia H. Y. Fu, MD, PhD

ABSTRACT

Objective: Current pharmacologic treatments for a depressive episode in unipolar major depressive disorder (MDD) and bipolar depression are limited by low rates of remission. Residual symptoms include a persistent low mood and neurovegetative symptoms such as fatigue. The objective of this study was to examine the efficacy and tolerability of augmentation of first-line therapies with the novel stimulant-like agent modafinil in MDD and bipolar depression.

Data Sources: MEDLINE/PubMed, PsycINFO, 1980–April 2013 were searched using the following terms: (*modafinil* or *armodafinil*) and (*depressi** or *depressed* or *major depressive disorder* or *major depression* or *unipolar* or *bipolar* or *dysthymi**). Inclusion criteria were as follows: randomized controlled trial (RCT) design, sample comprising adult patients (18–65 years) with unipolar or bipolar depression, diagnosis according to *DSM-IV*, *ICD-10*, or other well-recognized criteria, modafinil or armodafinil given as augmentation therapy in at least 1 arm of the trial, and publication in English in a peer-reviewed journal.

Study Selection: Double-blind, randomized, placebo-controlled clinical trials of adjunctive treatment with modafinil or armodafinil of standard treatment for depressive episodes in MDD and bipolar depression were selected.

Data Extraction: Two independent appraisers assessed the eligibility of the trials. A random-effects meta-analysis with DerSimonian-Laird method was used. Moderator effects were evaluated by meta-regression.

Results: Data from 6 RCTs, with a total of 910 patients with MDD or bipolar depression, consisting of 4 MDD RCTs (n = 568) and 2 bipolar depression RCTs (n = 342) were analyzed. The meta-analysis revealed significant effects of modafinil on improvements in overall depression scores (point estimate = −0.35; 95% CI, −0.61 to −0.10) and remission rates (odds ratio = 1.61; 95% CI, 1.04 to 2.49). The treatment effects were evident in both MDD and bipolar depression, with no difference between disorders. Modafinil showed a significant positive effect on fatigue symptoms (95% CI, −0.42 to −0.05). The adverse events were no different from placebo.

Conclusions: Modafinil is an effective augmentation strategy for acute depressive episodes, including for symptoms of fatigue, in both unipolar and bipolar disorders.

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Corresponding author: *Cynthia H. Y. Fu, MD, PhD, School of Psychology, University of East London, Stratford Campus, Water Lane, London E15 4LZ UK (c.fu@uel.ac.uk).*

Depression is the leading cause of disability worldwide in terms of years lost due to illness.[1] Among the key neurovegetative features of depression are fatigue, lack of energy, sleep disturbances, and loss of concentration.[2–4] According to survey data, about three-quarters of patients experience fatigue or lack of energy and sleep disturbances.[2–4] In addition to being primary features of depressive episodes, these symptoms may also occur as adverse side effects of antidepressants and mood stabilizers.[5,6] Furthermore, they can also persist as residual symptoms despite adequate pharmacotherapy and clinical remission.[7]

Nonresponse and partial response to antidepressants remain problematic, with approximately one-third of depressed patients failing to achieve symptomatic remission.[8] For example, hypersomnia has been reported as a residual depressive symptom in up to 15% of patients no longer meeting full criteria for major depressive disorder (MDD).[9] In a recent study,[10] 25% of patients with bipolar disorder in an acute depressive episode reported hypersomnia during the interepisode. These residual symptoms are known to predict relapse of major affective episodes in both MDD[11] and bipolar depression.[12]

One potential candidate for augmenting current first-line therapies for depression is the novel stimulant-like agent modafinil, which is US Food and Drug Administration (FDA)–approved for treating excessive sleepiness in narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[13] Modafinil is a racemic mixture of *R*- and *S*-enantiomers, while the isolated *R*-enantiomer, armodafinil, has a longer half-life and is also available with identical FDA approval.[14] The exact mechanisms underlying the action of modafinil are complex and yet to be fully elucidated. It is known to directly bind to, and inhibit, both the dopamine transporter and norepinephrine transporter, thus elevating extracellular levels of dopamine and norepinephrine in a similar manner to conventional amphetamine-like psychostimulants.[15] Modafinil, though, has a relatively localized rather than widespread brain activation, a diminished side effect profile, and a lower potential for abuse.[15] Unlike those of conventional stimulants, the wake-promoting effects of modafinil have been largely attributed to increased hypothalamic histamine release, which has a central role in the regulation of arousal and circadian rhythms.[16] Modafinil also raises orexinergic, serotonergic, and glutamatergic activity[15] and decreases the release of γ-aminobutyric acid.[17] These effects are thought to be secondary to the elevated catecholamine levels and increased activation of α-adrenergic, D_1, and D_2 receptors.[15] The multimodal actions may be responsible for its diverse effects, in which orexinergic and histaminergic actions

improve alertness in patients with sleep disturbance, while noradrenergic mechanisms may be associated with the cognitive-enhancing effects observed in non–sleep-deprived healthy individuals.[18]

Modafinil has received much interest over the past 2 decades as a potential treatment for depressive disorders. The first report by Menza and colleagues[19] showed beneficial effects of modafinil augmentation therapy for treatment-resistant patients with MDD or bipolar depression who had residual fatigue. These findings have prompted a large number of studies investigating the efficacy and safety of modafinil augmentation therapy for depression, which have yielded inconsistent results. A 2008 Cochrane review,[20] which was based on only 2 randomized controlled trials (RCTs), concluded that the evidence to date did not support the use of modafinil in the treatment of MDD. Since then, further research has been conducted, and researchers have also investigated the adjunctive use of modafinil in the treatment of an acute depressive episode in bipolar disorder. Hence, the purpose of the present study was to perform a systematic review and to conduct a meta-analysis of the effectiveness of modafinil and armodafinil augmentation therapy for MDD and bipolar depression.

METHOD

A literature search was conducted to identify RCTs on the efficacy of adjunctive modafinil/armodafinil therapy for unipolar (MDD) and bipolar depression. The following search terms were entered into MEDLINE/PubMed and PsycINFO: (*modafinil* or *armodafinil*) and (*depressi** or *depressed* or *major depressive disorder* or *major depression* or *unipolar* or *bipolar* or *dysthymi**). The search included publications from 1980–April 2013. This yielded 201 results in PubMed and 169 results in PsycINFO. Eighty-nine papers were duplicated in both databases and therefore subtracted from the total, resulting in 281 publications. A further search of reference lists of the included studies and relevant reviews did not generate additional suitable publications for inclusion.

Studies were selected according to the following inclusion criteria: RCT design; sample comprising adult patients (18–65 years) with unipolar or bipolar depression; diagnosis according to *DSM-IV*, *ICD-10*, or other well-recognized criteria; modafinil or armodafinil given as augmentation therapy in at least 1 arm of the trial; and publication in English in a peer-reviewed journal. Exclusion criteria were trials for patients with illnesses other than unipolar or bipolar depression and use of a nonpharmacologic therapy.

For quantitative analysis, random-effects meta-analysis with the DerSimonian-Laird method was used. Heterogeneity was assessed with I^2, and the level of heterogeneity was reported in every analysis. The primary endpoint of the quantitative analysis was the efficacy of modafinil treatment on total mood measures at the final visit. The effect of the diagnosis and baseline depression severity as moderators of the effect of modafinil treatment was evaluated by meta-regression. Secondary efficacy endpoints included remission rates at final assessment, early effects (at week 1), and effects at the final visit on specific symptoms (sleepiness and fatigability) of modafinil versus placebo. Furthermore, safety and tolerability measures were investigated. Hedges *g* estimate was used as the measure of standardized mean difference. As a guide, Hedges *g* can be interpreted as effect sizes with cutoffs of 0.2 = small, 0.5 = medium, and 0.8 = large. Results were deemed significant within 95% confidence intervals (CIs).

Clinical Points

- Modafinil augmentation shows a significant beneficial effect to antidepressant medications in unipolar and bipolar patients in an acute depressive episode.
- The fatigue symptoms associated with depression show an improvement with adjunctive modafinil treatment.

RESULTS

The literature search identified 6 studies that met the inclusion and exclusion criteria. MDD was the only form of unipolar depression addressed among the studies, and all 6 RCTs were double-blind. Four studies[5,21–23] involving a total of 568 patients with unipolar MDD evaluated the efficacy and safety of modafinil augmentation of antidepressant therapy, and 2 studies[13,24] involving a total of 342 patients with bipolar depression evaluated the efficacy and safety of modafinil augmentation of mood stabilizers with or without concomitant antidepressant treatment (Table 1).

Primary Endpoint Analysis

Effects of modafinil on depression severity. Percentage reduction in mood scores (Hamilton Depression Rating Scale [HDRS] or Inventory of Depressive Symptomatology [IDS]) at the end of the study relative to baseline was used as a standardized measure for the pooled studies. There was a significant improvement in depression scores following modafinil treatment as compared to placebo across all studies (point estimate = −0.35; 95% CI, −0.61 to −0.10) (Figure 1). However, the amount of heterogeneity was substantial ($I^2 = 67.39\%$, $Q_5 = 15.33$, $P = .009$). As Abolfazli et al[21] was an outlier, a sensitivity analysis was conducted excluding this study. Even with the exclusion of Abolfazli et al,[21] modafinil was associated with a significant reduction in depression scores (95% CI, −0.36 to −0.09; $P < .001$) (Table 2), and heterogeneity was not significant ($I^2 = 0\%$, $Q_4 = 1.71$, $P = .789$), indicating the agreement across the remaining 5 studies.

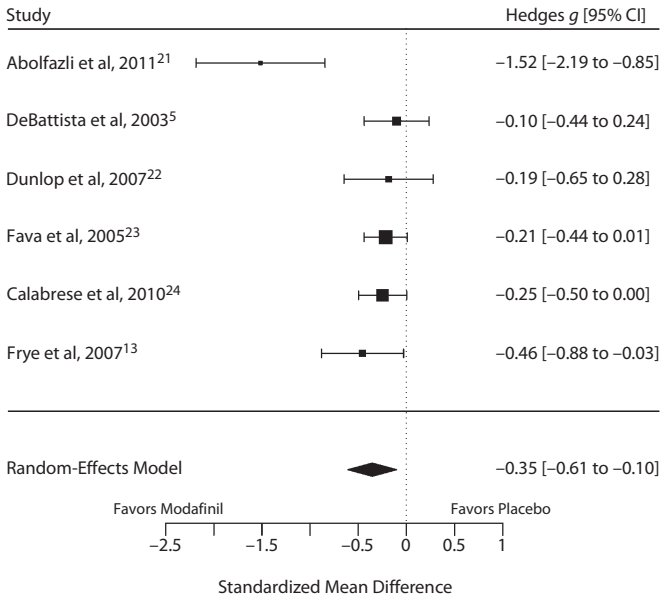
The analysis of the 4 studies in unipolar depression suggested a positive effect of modafinil on depression scores, which approached significance (Hedges $g = -0.41$; 95% CI, −0.84 to 0.01; $P = .056$). After exclusion of the outlier study,[21] the results were statistically significant for a positive effect of modafinil treatment on final depression scores in unipolar depression (Hedges $g = -0.18$; 95% CI, −0.35 to −0.01; $P = .040$) (Figure 2). Similarly, the meta-analysis of

Table 1. Summary of Studies of Modafinil Augmentation in Unipolar and Bipolar Depression

Study	Depression Type	Sample Size	Inclusion Criteria	Primary Treatment	Augmentation Therapy	Study Duration
DeBattista et al (2003)[5]	Unipolar	n = 69 modafinil n = 69 placebo	HDRS-21 score of 14–28 ≥ 6 wk of antidepressant treatment	Antidepressants (majority SSRIs)	Modafinil (100–400 mg/d)	6 wk
Fava et al (2005)[23]	Unipolar	n = 158 modafinil n = 153 placebo	HDRS-31 score of 14–26 ESS score ≥ 10 FSS score ≥ 4 ≥ 8 wk of SSRI at minimally effective dose ≥ 4 wk of stable SSRI monotherapy	SSRIs (fluoxetine ≥ 20 mg/d, paroxetine ≥ 20 mg/d, sertraline ≥ 100 mg/d)	Modafinil (200 mg/d)	8 wk
Dunlop et al (2007)[22]	Unipolar	n = 37 modafinil n = 36 placebo	MADRS score ≥ 15 ESS score ≥ 10 FSS score ≥ 4 No antidepressant 14 d before baseline (28 d for fluoxetine)	SSRIs (sertraline 100 mg/d, paroxetine 20 mg/d, citalopram 20 mg/d, escitalopram 10 mg/d, fluoxetine 20 mg/d)	Modafinil (200 mg/d)	6 wk
Frye et al (2007)[13]	Bipolar I or II depression	n = 41 modafinil n = 44 placebo	IDS score ≥ 16 ≥ 2 wk stable medication	Mood stabilizer with or without antidepressant	Modafinil (200 mg/d)	6 wk
Calabrese et al (2010)[24]	Bipolar I depression	n = 128 armodafinil n = 129 placebo	QIDS-SR16 score ≥ 13 CGI-BP score ≥ 4 YMRS score ≤ 10 with 0 or 1 on items 1–3 ≥ 8 wk of mood stabilizer	Lithium (≤ 0.6 mEq/L plasma), olanzapine (≤ 5 mg/d), valproic acid (≤ 50 μg/mL)	Armodafinil (150 mg/d)	8 wk
Abolfazli et al (2011)[21]	Unipolar	n = 23 modafinil n = 23 placebo	HDRS-17 score ≥ 18 with ≥ 2 on item 1 (depressed mood) No psychotropic medications 4 wk before study entry	Fluoxetine (40 mg/d)	Modafinil (400 mg/d)	6 wk

Abbreviations: CGI-BP = Clinical Global Impression—Bipolar; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; HDRS = Hamilton Depression Rating Scale; IDS = Inventory of Depressive Symptomatology; MADRS = Montgomery-Asberg Depression Rating Scale; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology, Self-Report; YMRS = Young Mania Rating Scale.

Figure 1. Meta-Analysis of Effects of Modafinil Augmentation on Depression in Major Depressive Disorder and Bipolar Disorder[a]



[a]The forest plot illustrates the effects of modafinil augmentation on total depression scores between patients and controls at the end of each study in the combined analysis of major depressive disorder and bipolar disorder. The right column presents the standardized mean difference in total depression score at end of each study (Hedges *g* and 95% confidence intervals). The random-effects model showed a significant beneficial summary effect of modafinil on final depression scores in both unipolar (major depressive disorder) and bipolar depression.

bipolar depression studies indicated a significant positive effect of modafinil on the end-of-trial depression IDS scores (Hedges $g = -0.30$; 95% CI, −0.52 to −0.09; $P = .006$) (Figure 2).

The effect of depression severity at baseline on the therapeutic effects of modafinil approached statistical significance (6 studies, test of moderator, $Q_1 = 3.60$, $P = .0577$) in a meta-regression analysis. Patients with more severe levels of depression showed larger gains from modafinil augmentation. However, there was no moderator effect of diagnosis type (MDD vs bipolar depression) on the reduction in depression severity following modafinil treatment as compared to placebo (6 studies, $Q_1 = 0.03$, $P = .8674$). Accordingly, the secondary analyses were based on pooled unipolar and bipolar data.

Secondary Endpoints Analysis

Remission and response rates. Remission was defined as an HDRS score ≤ 7 in unipolar depression studies and an IDS score ≤ 11 in bipolar depression. Five of the 6 studies reported remission rates (except DeBattista et al[5]). There was a significantly increased rate of remission with modafinil augmentation over placebo at the final visit (odds ratio [OR] = 1.61; 95% CI, 1.04 to 2.49; $P = .035$; heterogeneity, $I^2 = 32.29\%$, $Q_4 = 5.91$, $P = .206$). On the basis of this summary estimate, the number needed to treat with modafinil to obtain an additional achievement of remission is 10 patients.

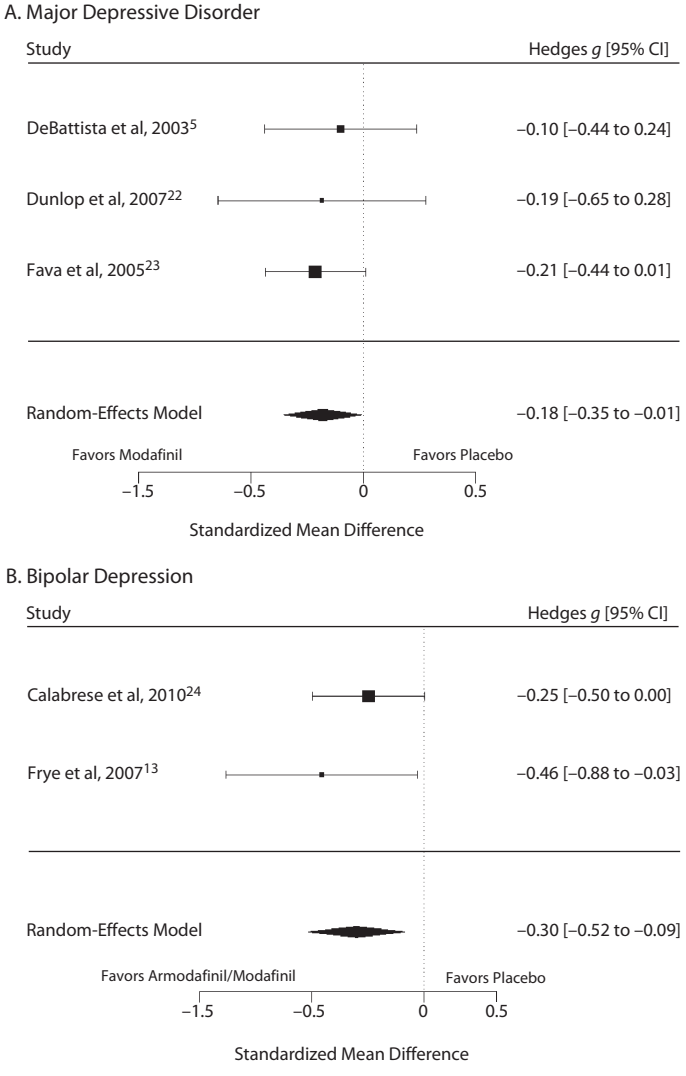
Response was defined as a 50% reduction in depression severity score in all studies except Fava et al,[23] in which

Table 2. Efficacy on Mood Scores at Final Visit

Studies	Effect Size Estimate (Hedges *g*)	95% CI	Test for Overall Effect (*z* value)	*P*	Heterogeneity (I^2)	Test for Heterogeneity		
						Q	*df*	*P*
All studies (MDD and bipolar depression)	−0.3543	−0.6071 to −0.1016	−2.7483	.006	67.39%	15.3311	5	.009
All studies except outlier[a]	−0.2278	−0.3627 to −0.0928	−3.3078	.0009	0%	1.7112	4	.7887
MDD studies	−0.4125	−0.8358 to 0.0107	−1.9102	.0561	79.42%	14.5796	3	.0022
MDD studies except outlier[a]	−0.1807	−0.3536 to −0.0079	−2.0492	.0404	0%	0.3026	2	.8596
Bipolar depression studies	−0.3012	−0.5172 to −0.0852	−2.7333	.0063	0%	0.6801	1	.4096

[a]Outlier study: Abolfazli et al.[21]
Abbreviation: MDD = major depressive disorder.

Figure 2. Meta-Analysis of Effects of Modafinil Augmentation in (A) Major Depressive Disorder With Exclusion of an Outlier Study[a] and (B) Bipolar Depression[b]



[a]Outlier study: Abolfazli et al.[21]
[b]The forest plot illustrates the effects of modafinil augmentation on total depression scores between patients and controls at the end of each study in (A) major depressive disorder with exclusion of an outlier study[21] and (B) bipolar disorder. The right column presents the standardized mean difference in total depression score at end of each study (Hedges *g* and 95% confidence intervals). The random-effects model showed significant beneficial summary effects of modafinil on final depression scores in unipolar (major depressive disorder) as well as in bipolar depression separately.

response was defined as "much or very much improved" on the Clinical Global Impressions-Improvement scale, and 1 study[5] in which response rates were not reported. There were no significant differences in the response rates following modafinil augmentation relative to placebo (OR = 1.62; 95% CI, 0.96 to 2.75; $P = .071$; heterogeneity, $I^2 = 53.75\%$, $Q_4 = 8.65$, $P = .070$).

Interestingly, we found a significant early treatment effect in which modafinil showed a positive effect on total depression score at week 1 relative to placebo (4 studies, except Frye et al[13] and Abolfazli et al[21]: 95% CI, −0.33 to −0.045; $P = .009$). Specific effects on sad mood scores at the final visit showed no differences between modafinil and placebo (3 studies[21,22,24]: 95% CI, −0.99 to 0.17; $P = .169$).

Effects on fatigue and sleepiness. Effects on fatigue were analyzed across all 6 studies, while the effects on sleepiness included 5 studies (except Abolfazli et al[21]). There were significant effects of modafinil on fatigue at the final visit (95% CI, −0.28 to −0.02; $P = .023$) (Figure 3), but there were no significant effects on sleepiness (95% CI, −0.45 to 0.11; $P = .240$). Early treatment effects were also investigated where available, indicating an early improvement following 1 week of modafinil augmentation in both fatigue (2 studies[5,23]: 95% CI, −0.42 to −0.05; $P = .012$) and sleepiness (3 studies[5,22,23]: 95% CI, −0.57 to −0.09; $P = .006$).

Safety and tolerability. No significant effects were found to indicate any differences between modafinil and placebo augmentation in frequency of dropout rates; serious adverse events; frequency of headache, insomnia, or emergent suicidal ideation; or frequency of emergent mania/hypomania (all $P > .2$).

DISCUSSION

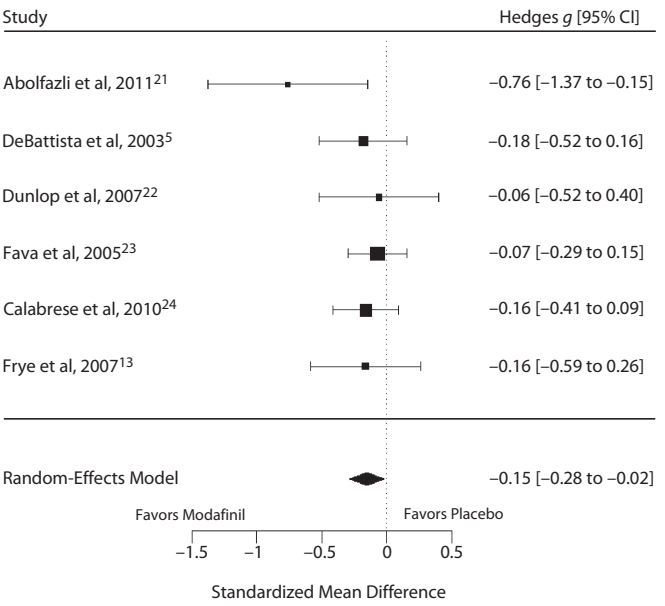
The present meta-analysis of RCT studies supports the use of modafinil augmentation therapy in the treatment of depression. Augmentation with modafinil was associated with a significantly greater improvement in depression scores. In particular, a greater severity of depression was associated with a greater improvement with modafinil augmentation, which was not evident in some of the individual studies. Moreover, the effect of modafinil was independent of whether the depressive episode was part of a unipolar or bipolar disorder.

The therapeutic benefit of modafinil was also evident in improved remission rates, in which the number needed to treat to achieve an additional remission was 10 patients. Remission is the primary goal of acute antidepressant treatment, yet it is not achieved in one-third of depressed patients receiving current treatment methods,[8] and residual depressive symptoms are predictive of relapse of an acute depressive episode.[11,12] Adjunctive modafinil therapy shows some evidence in improving the rates of remission and in turn helping to prevent the occurrence of a relapse. Of interest is that the positive effects of modafinil augmentation were observable at the first week of treatment, which may contribute to treatment compliance at the early stages.

Fatigue and sleepiness are among the leading causes of antidepressant discontinuation.[25] Modafinil augmentation improved levels of fatigue at the final visit, though not measures of sleepiness. The difference in these phenomenologically close domains may be an effect of methodological variances. For example, the subscale for fatigue employed by Abolfazli et al[21] consisted of item 7 (work and activities) from the 17-item HDRS, which may not have provided a reliable measure of fatigue alone. As a methodological point, some of the depression severity scales have shortcomings with regard to symptoms such as hypersomnia and concentration, which is relevant in evaluating the effect of an activating therapy such as modafinil. The 17-item HDRS includes 3 items relating to reduced sleep, and the Montgomery-Asberg Depression Rating Scale includes items addressing lassitude and concentration difficulties, but none on hypersomnia. The 31-item HDRS version does include 3 items on hypersomnia, and it was used in 1 study, Dunlop et al,[22] who reported a positive effect of modafinil on all 3 item scores. As the recently suggested research domain criteria of the National Institute of Mental Health[26,27] encourage research on underlying neural circuitry dysfunctions in psychiatric disorders, modafinil might provide a valuable research tool for understanding the neurochemical substrates of the arousal/regulatory systems research domain.

Of note is that DeBattista et al[5] and Fava et al[23] evaluated the effects of modafinil augmentation therapy on residual fatigue and sleepiness following antidepressant treatment, while Abolfazli et al[21] and Dunlop et al[22] coadministered adjunctive modafinil from the start of pharmacologic treatment. Modafinil augmentation was associated with improvements in both sleepiness and fatigue at the first-week assessment, although these results were based on limited data. On the whole, these results are largely in accordance with evidence from open-label studies[28,29] and a retrospective analysis of pooled data[30] suggesting that modafinil helps to reduce fatigue and sleepiness symptoms in MDD patients. While such potential benefits were not observed in improved discontinuation rates in the modafinil treatment arms, they may be responsible for some of the improved outcomes that were observed. Furthermore, the findings indicate an early onset of beneficial effects, which may improve compliance.

Figure 3. Meta-Analysis of Effects of Modafinil Augmentation on Fatigue Scores[a]



[a]The forest plot shows the effects of modafinil augmentation on fatigue scores at the end of each study in unipolar (major depressive disorder) and bipolar depression. The right column presents the standardized mean difference at end of each study (Hedges *g* and 95% confidence intervals). The random-effects model showed a significant beneficial summary effect of modafinil on final fatigue scores.

In terms of possible adverse effects, the findings indicate that modafinil augmentation therapy is generally safe and well tolerated. Although there were no overall differences from placebo, incidences reported in the individual studies are worth mentioning. Dunlop et al[22] reported 2 incidents of suicidal ideation development in the modafinil group as compared to none in the placebo group. In this study, modafinil was coadministered with antidepressant therapy from the start of treatment, and the authors highlighted the potential danger of energizing depressed patients before there is an improvement in their mood.[22] Calabrese et al[24] reported an increased incidence of hypomania in the modafinil group (2%) compared to placebo (1%), but there were no overall differences in hypomanic/manic symptoms according to standardized scores.

Conventional stimulants have also been prescribed to augment antidepressant treatment.[20] A few studies have reported efficacy; however, these have been case series[31] or open-label studies.[32] A systematic review[33] of controlled trials with psychostimulants indicated that placebo-controlled trials with methylphenidate (3 studies) and *d*-amphetamine (3 studies) did not demonstrate beneficial effects in clinical measures of depression. On the other hand, 1 controlled study[34] with adjunctive methylphenidate use did report positive effects on fatigue and apathy. To our knowledge, no study to date has compared the effects of modafinil augmentation with those of conventional stimulants in depression. In terms of adverse effects, modafinil has advantages over methylphenidate and amphetamine in the

long term, although no significant severe side effects (eg, cardiac effects, psychotic symptoms) have been reported with the short-term use of conventional stimulants.[33] From an evidence-based point of view, the present review lends support to the use of adjunctive modafinil in patients with depression, while the same level of evidence is not available for conventional stimulants due to the absence of pooled data or a meta-analysis.

There were several limitations in the present review. First, it was not possible to include all the studies for each measure due to the limited replication by studies. Second, there was considerable heterogeneity between individual RCTs, including variations in inclusion criteria, depression type (MDD vs bipolar depression), drug type (modafinil vs armodafinil), dosage used (100–400 mg/d), joint initiation of modafinil with the antidepressants[21] versus addition of modafinil to the ongoing antidepressant treatment,[5] sample size, and study duration. As only 1 study[24] used armodafinil, the findings may be confounded by a higher proportion of modafinil use among the included RCTs. There was a high rate of heterogeneity in the effect on depression, which was largely due to an outlier study.[21] Even after exclusion of this study, which showed significant effects of modafinil on depression, the cumulative effect of favoring modafinil persisted. Although the effect size was small (point estimate = −0.23), the agreement between studies increased markedly (0% heterogeneity). It should be noted that the sample in the Abolfazli et al[21] study was the smallest and had the highest average baseline depression scores. Moreover, all the trials broadly agree on the effect size of the benefit, which is from a small to moderate effect, as shown in their overlapping confidence intervals, with the exception of Abolfazli et al,[21] which showed a large effect size. As the present meta-analysis is based on 6 studies (total sample = 910 patients), the addition of a few more trials may affect the results. However, it is clear from Figure 1 that there was a significant degree of homogeneity across studies with regard to the efficacy of modafinil, because all of the studies favored modafinil versus placebo in the primary outcome, although individually the majority were not statistically significant. In this situation, a meta-analysis can be most useful by aggregating the power of individual studies.

The costs of depression to the economy are substantial.[35] Adjunctive modafinil treatment could help reduce absenteeism and presenteeism at work. In addition, modafinil has been shown to improve task-related motivation in healthy people,[18] which may be beneficial for patients returning to work. Future research is warranted and should include RCTs that are more uniform in their drug dosing, are longer in duration, and include both adjunctive modafinil and armodafinil treatment for both MDD and bipolar depression in order to compare these drugs directly in both disorders. Longer trials would also help to elucidate the potential long-term benefits of these augmentation treatments. Lastly, modafinil has been shown to have procognitive effects in healthy volunteers[18] and in patients with depression.[36] Previous data suggested that depressed patients suffer from both "hot" and "cold" cognition deficits,[37] in which "hot" cognition refers to processes involving emotional or reward-related stimuli, while "cold" cognition refers to cognitive abilities such as planning, memory, and mental flexibility. These deficits are associated with distinct neural effects[38] that show diagnostic specificity for depression.[39,40] Thus, further research investigating the effects of modafinil on cognitive domain in depression is warranted.

In summary, the findings of the present systematic review and meta-analysis support the use of adjunctive modafinil for the safe treatment of depression and fatigue in patients with MDD or bipolar depression. In particular, evidence of early effectiveness of modafinil on depressive symptoms, fatigue, and sleepiness may possibly have beneficial implications for treatment compliance and work functioning.

Drug names: armodafinil (Nuvigil), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lithium (Lithobid and others), methylphenidate (Focalin, Daytrana, and others), modafinil (Provigil), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), valproic acid (Depakene, Stavzor, and others).

Author affiliations: School of Medicine (Mr Goss) and Department of Old Age Psychiatry, Institute of Psychiatry (Dr Costafreda), King's College London, London, United Kingdom; Bahcesehir University, Istanbul, Turkey (Dr Kaser); Department of Psychiatry and MRC/Wellcome Trust Behavioral and Clinical Neuroscience Institute, University of Cambridge, Cambridge, United Kingdom (Drs Kaser and Sahakian); and School of Psychology, University of East London, United Kingdom (Dr Fu).

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