The Potential Procognitive Effects of Modafinil in Major Depressive Disorder: A Systematic Review

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ABSTRACT

Objective: To assess the efficacy of modafinil, a wakefulness-promoting drug, in major depressive disorder (MDD), with a specific focus on the putative procognitive effects of modafinil.

Data Sources: A database search of MEDLINE, PsycINFO, and Embase was conducted. No date limits were applied (the end date of the search was October 26, 2018), and only articles in English were included. The following search terms were used: *modafinil*, *depression*, *depress**, *major depressive disorder*, *cognition*, *cognitive dysfunction*, and *cogniti**.

Study Selection: Studies included were placebo-controlled or open-label trials of modafinil in MDD populations. Participants had to be diagnosed with MDD via *DSM-IV* or *DSM-5* criteria, and no other interventions other than standard antidepressant treatment could be used in the trial. Overall, 540 articles were screened, 22 full-text research articles for inclusion criteria were assessed, and 12 studies were included in this review.

Data Extraction: Two independent reviewers extracted data and assessed the quality of publications.

Results: Modafinil was associated with improvements in executive functioning after 4 weeks of open-label adjunctive treatment in currently depressed participants. Furthermore, in a placebo-controlled study of remitted MDD participants, modafinil led to rapid improvements in episodic and working memory after a single dose. There were contradictory findings on the subjective effects of modafinil on concentration.

Conclusions: Modafinil shows preliminary evidence of alleviating specific cognitive symptoms in MDD patients, especially in the short term. However, more research using placebo-controlled longitudinal designs is needed to assess the benefits of modafinil, as there are very few studies addressing modafinil and cognition in MDD.

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Depressive disorders are the leading cause of disability worldwide, with more than 300 million people living with depression.[1] Fatigue and sleepiness are common symptoms experienced by individuals with major depressive disorder (MDD), and many people continue to experience these symptoms after their depressive symptoms have subsided.[2] Fatigue and sleepiness are associated with greater depressive severity and poorer functional outcome[3,4] and are thought to be associated with MDD pathology as well as being side effects of standard antidepressant medications.[2] Individuals with depression also demonstrate significant deficits in the cognitive domains of executive functioning, memory, and attention compared to healthy controls.[5] Furthermore, these cognitive deficits often persist after remission of mood symptoms.[5] Depression can have significant negative effects on one's ability to function normally, both socially and at work.[6,7] Cognitive symptoms are a major contributor to this reduced functional ability.

Very few antidepressant trials have made cognitive function a primary or secondary endpoint for monotherapy. Currently, 4 antidepressants have been shown to improve cognition in depression. Vortioxetine, a serotonin modulator, improved learning, memory, attention, executive function, and processing speed in MDD populations.[8,9] Vortioxetine is the only antidepressant medication currently recognized by the US Food and Drug Administration (FDA) as an antidepressant with potential procognitive effects.[10] Second, there are several reports that duloxetine, a selective serotonin-norepinephrine reuptake inhibitor (SNRI), improves episodic and working memory in depressed patients significantly more than escitalopram (a selective serotonin reuptake inhibitor [SSRI])[11] and improves composite cognition significantly more than placebo in elderly MDD populations.[12] Duloxetine also improved psychomotor function and mental processing speed in a 12-week open-label trial.[13] Third, treatment with desvenlafaxine was associated with improvements in global cognition, processing speed, executive function, psychomotor speed, complex attention, and cognitive flexibility after 8 weeks.[14] Finally, after treatment with bupropion, participants experienced improvements in visual memory, mental processing speed,[15] verbal and nonverbal learning and memory,[16] and overall global cognition.[17]

Adjunctive agents have also been examined for their potential procognitive effects. Multiple trials[18] have

Clinical Points

- Cognitive impairment is a common symptom of major depressive disorder (MDD), yet few studies have assessed medications to relieve it.
- If a patient with MDD reports difficulties in cognition during or after a depressive episode, adjunctive modafinil may be considered.
- However, modafinil may improve only specific cognitive domains, and more research on its efficacy is needed.

studied psychostimulants, including dextroamphetamine, lisdexamfetamine, and methylphenidate, for this purpose. However, only lisdexamfetamine has shown limited efficacy.[18] One study[19] found that lisdexamfetamine improves executive function in partially or fully remitted MDD patients. The FDA, however, cautions against the use of lisdexamfetamine with antidepressants that affect serotonergic neurotransmitter systems, as this combination can increase risk for development of serotonin syndrome.[20] Other non-antidepressant treatments that show some potential procognitive effects in depressed populations include donepezil, an acetylcholinesterase inhibitor[21–23]; erythropoietin (EPO), a hormone involved in the production of red blood cells[24,25]; and *S*-adenosylmethionine (SAMe), an important molecule for cellular metabolism.[26] Two studies[21,22] found that geriatric patients with MDD and comorbid cognitive disorders treated with a donepezil adjuvant experienced a short-term improvement in memory and executive function, while another study[23] found no cognitive improvement. Donepezil was associated with high rates of depression relapse[27] and other adverse events.[23] EPO improved memory and executive function when given in a single high dose[24] and improved verbal learning and memory when given repeatedly in lower doses to MDD patients.[25] EPO, however, requires cautious use as it increases risk of hypertension and blood clotting.[27] Finally, SAMe improved patient-reported recall abilities in depressed populations in one clinical trial.[26]

One drug that has shown potential as a procognitive adjunctive agent is modafinil. Modafinil is a wakefulness-promoting agent that is currently indicated for the treatment of narcolepsy, obstructive sleep apnea, and shift-work sleep disorder.[28] The precise mechanism of action of modafinil is currently unknown; however, modafinil is thought to act on the dopaminergic and GABAergic systems.[28] In vitro and in vivo studies found modafinil acts as a dopamine reuptake inhibitor and increases the turnover rate of 5-hydroxytryptamine (5-HT) and enhances 5-HT_2 receptor activity, affecting the GABAergic system.[28] Modafinil is generally well-tolerated by users, including MDD populations. The most common side effects (> 5% of users) include headache (reported in 34% of users), nausea (11%), back pain (6%), diarrhea (6%), nervousness (7%), and rhinitis (7%).[28] In MDD populations, similar side effects are reported, as well as anxiety (6%–32%), insomnia (11%–31.8%), and dizziness (7%).[29,30] Compared to psychostimulants, modafinil is better tolerated and has less potential for abuse and addiction.[31]

Several investigators have assessed the efficacy of modafinil in depressed populations.[32,33] Modafinil has been shown to reduce impairments of episodic and working memory and executive function in individuals with MDD.[34,35] Additionally, there is evidence that modafinil decreases overall depressive symptoms[2,33,36,37] and symptoms of fatigue and daytime sleepiness[34,35,38] in individuals with MDD. In healthy populations, modafinil improved cognition on a variety of domains, including reaction time, logical reasoning, attention, learning, working memory, planning, and decision making.[39–43] However, a few studies[44,45] failed to identify any effect of modafinil on cognition in healthy subjects. The authors of a previous systematic review[46] focused on modafinil's effects on depression scores, fatigue, and sleepiness when prescribed as an adjuvant for unipolar and bipolar depression. However, to our knowledge, there have been no systematic reviews assessing the effects of modafinil on cognition in depressed populations. Here, we examine the efficacy of modafinil specifically in treating cognitive impairments associated with MDD. Furthermore, as a secondary objective, we assess the efficacy of modafinil in treating fatigue, daytime sleepiness, and mood symptoms in MDD populations.

METHODS

Search Methods

A comprehensive search of 3 databases—MEDLINE, PsycINFO, and Embase—through Ovid was conducted using the following search terms: *modafinil*, *depression*, *depress**, *major depressive disorder*, *cognition*, *cognitive dysfunction*, and *cogniti**. Clinicaltrials.gov was also searched, using the search terms *depression* and *modafinil*. The end date of the search was October 26, 2018. Two authors (S.R.V. and V.B.) independently conducted an initial screening and assessment for eligibility of the results. Discrepancies were discussed and resolved by consensus. Additional research articles were identified from alternative sources, including the reference section of extracted articles.

Inclusion Criteria

Placebo-controlled and open-label trials in human participants who met prespecified *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition *(DSM-IV)* or Fifth Edition (*DSM-5*), criteria for MDD were included. No additional interventions could be used in the study design (eg, manipulations of environment, other drugs taken in conjunction with modafinil) besides standard pharmacologic antidepressants and psychotherapy. Studies were excluded if some or all of the participants met criteria for comorbid psychiatric disorders such as attention-deficit/hyperactivity disorder, posttraumatic stress disorder, or substance use disorder; we did not exclude individuals with comorbid anxiety disorders as they are commonly comorbid

Table 1. GRADE Criteria Checklist

GRADE Item[a]	Results
Selection bias: Was random sequence generation used?	RCT: yes Open-label: NA
Performance bias: Was there blinding of participants?	RCT: yes Open-label: no
Detection bias: Was there blinding of outcome assessment?	RCT: unclear Open-label: unclear
Reporting bias: Were more than 80% of participants enrolled in trials included in the analysis?	Did not meet criteria: Ninan et al 2004[37] (79%) Rasmussen et al 2005[51] (not reported) Dunlop et al 2007[49] (70%) Kaser et al 2017[34] (not reported)
Selective reporting: Were data reported consistently for the outcome of interest?	RCT: yes Open-label: yes
Did the trials end as scheduled?	Did not meet criteria: Dunlop et al 2007[49]

[a]GRADE criteria checklist items from Guyatt et al[47] and Meader et al.[48]
Abbreviations: GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; NA = not applicable; RCT = randomized controlled trial.

with MDD. Finally, articles had to be written in English. There was no restriction on the year of publication or age constraint. Due to the limited number of articles on this topic, cognition was not required to be a study outcome and there were no constraints on what cognition measures could be used.

Quality of Assessment

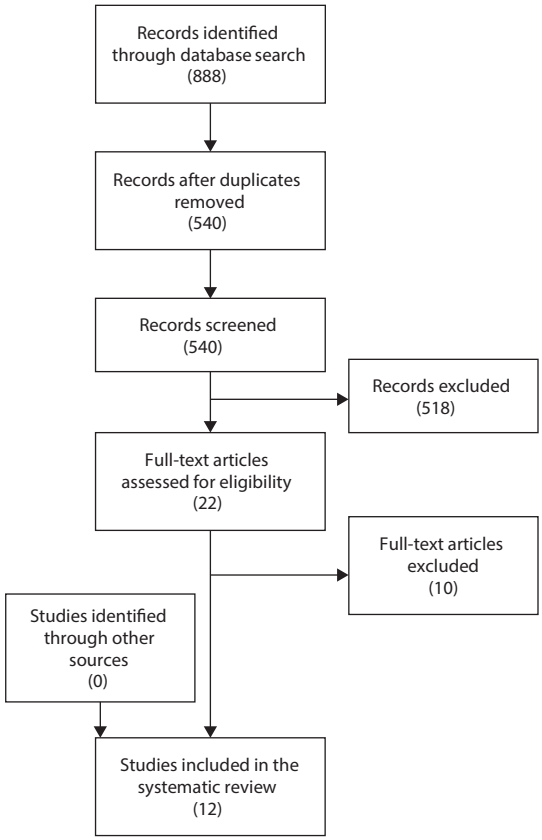
All studies were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) checklist.[47,48] All placebo-controlled studies had a low potential for selection and performance biases because they all used a double-blinded treatment randomization protocol. In the open-label studies, all participants received the same treatment, which minimized selection bias, although performance bias could not be excluded. Similarly, without details of how raters were blinded to treatment, we could not discuss detection bias.

A minimum of 70% of participants who were enrolled in the respective studies completed the trial; although the GRADE criteria specify 80% as appropriate, we deemed 70% an acceptable rate based on the population being studied. We identified reports of both significant and nonsignificant findings, demonstrating a low selective reporting bias. One study[49] ended prematurely due to a serious adverse event. Table 1 summarizes the included studies in terms of GRADE criteria.

RESULTS

Of 540 reports identified through the database search (including conference abstracts), 22 articles were assessed for eligibility and 12 studies were included in the systematic review (see Figure 1). Studies were excluded for reasons such as the study cohort had other comorbid psychiatric illnesses or the article was based on case studies. The search results also included trials of armodafinil, the *R*-enantiomer of modafinil, but no studies in depressed populations were identified.

Figure 1. PRISMA Flow Diagram of Studies Screened and Assessed for the Review



Description of Studies

Of the 12 studies published between 2003 and 2017, 4 were double-blind placebo-controlled, 6 were open-label, and 2 had both open-label and blinded components (ie, placebo-controlled design followed by open-label extension study or vice versa). A summary of these studies is presented in Table 2 (randomized controlled) and Table 3 (open-label). Sample size for individual trials varied from 20 to 311 participants. Three studies[30,32,50] had sample sizes greater than 100 individuals, and another 3[33,34,49] had between 50 and 100. The remaining 6 studies[29,35–37,51,52] had a smaller sample size, ie, less than 50. Figure 2 outlines the sample sizes by study. Study duration ranged from 1 day to 12 weeks. Only 2 studies[34,35] directly measured cognition.

Demographic and clinical characteristics. Participants tended to be "middle-aged" (mean age ranging from 32 to 51 years) and female (range, 38%–88%). Depression severity ranged across studies from remitted to severe depression. In all but 1 study,[33] modafinil was an adjuvant to antidepressant medication. In these studies, selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants (range, 57%–100% of participants). In fact, 7 of the studies[29,30,32,36,37,49,52] required participants

Table 2. Summary of Randomized Controlled Trials[a]

	DeBattista et al[50]	Fava et al[32]	Vaishnavi et al[33] Phase 2
Year	2003	2005	2006
N (enrolled)	136	311	50
Age, mean, y	45	42	39
Female, %	70%	71%	86%
Study duration	6 wk	8 wk	12 wk
Diagnosis	Current MDD ($HDRS_{21}$ = 14–28)	• Current MDD ($HDRS_{31}$ = 14–26) • Fatigue (FSS ≥ 4) • Sleepiness (ESS ≥ 10)	• Current MDD with atypical features ($HDRS_{29}$ ≥ 18 with atypical features) • Illness severity rated as markedly ill or worse (CGI-S ≥ 4)
Concomitant antidepressant therapy	Stable antidepressant with partial response for ≥ 6 weeks (majority on SSRI)	SSRI (fluoxetine, paroxetine, or sertraline) with partial response for ≥ 8 week, stable monotherapy for ≥ 4 weeks	None permitted
Modafinil, mg/d	100–400	200	200–400
Outcome measures	• Fatigue (FSS) • Sleepiness (ESS) • Depressive symptoms (HDRS) • Psychomotor retardation (HDRS retardation subscale) • Clinical condition/illness severity (CGI-S) • Change in illness severity (CGI-I) • Health-related quality of life (SF-36)	• Fatigue (FSS, BFI) • Sleepiness (ESS) • Depressive symptoms (HDRS, MADRS) • Clinical condition/illness severity (CGI-S) • Change in illness severity (CGI-I)	• Depressive symptoms (HDRS) • Fatigue (FSS, BFI) • Sleepiness (ESS) • Psychopathology (SCL-90) • Atypical depression features (ADDS) • Clinical condition/illness severity (CGI-S) • Symptom severity (SOSS)
Findings	• Greater reduction in fatigue in modafinil group vs placebo at wk 2, but not wk 6 • Greater reduction in sleepiness in modafinil group vs placebo at wk 1, but not wk 6 • No difference in depressive symptoms between groups • No difference in overall clinical condition between groups • No difference between groups in mental or physical health-related quality of life	• Modafinil improved clinical condition vs placebo at all time points • Improvements in fatigue and sleepiness with modafinil vs placebo at wk 1 (effect size, d = 0.24 and d = 0.05, respectively) but not wk 8 or final visit • Decrease in worst level of fatigue in past 24 h with modafinil vs placebo at wk 8 and final visit (effect size, d = 0.13 and d = 0.10, respectively) • No difference in depressive severity after treatment with modafinil vs placebo • Individuals with baseline HDRS ≥ 14 taking modafinil had greater reduction on sleepiness (ESS; effect size, d = 0.05) and depressive severity (on $HDRS_{17}$ only) at final visit vs placebo • Modafinil group experienced weight loss (effect size, d = 0.002)	• No difference between modafinil and placebo group for depressive symptoms, fatigue, sleepiness, atypical depression symptoms, or clinical condition • Improvement in anxiety (SCL-90 anxiety subscale) found in modafinil group vs placebo • Modafinil group experienced weight loss (effect size, d = 0.03) and BMI decrease vs placebo
Adverse events (most common)	• Headache • Nervousness	• Nausea • Feeling "jittery"	None found to be more common in modafinil group
Limitations	• Participants did not have to report fatigue or sleepiness for inclusion • Cognition not measured	• Fixed dose of modafinil • Did not measure cognition	• Possible carryover effects of drug to placebo • Did not measure cognition

(continued)

Table 2 (continued).

	Dunlop et al[49] Phase 1	Abolfazli et al[29]	Kaser et al[34]
Year	2007	2011	2017
N (enrolled)	72	46	60
Age, mean, y	44	33	45
Female, %	56%	52%	62%
Study duration	6 wk	6 wk	<1 d
Diagnosis	• Current MDD (MADRS ≥ 15) • Fatigue (FSS ≥ 4) • Sleepiness (ESS ≥ 10)	Current MDD (HDRS-17 ≥ 18)	Remitted MDD (MADRS < 12) for ≥ 2 mo
Concomitant antidepressant therapy	SSRI (started at baseline with modafinil)	Fluoxetine (started at baseline with modafinil)	Could be on antidepressant medication, but not required
Modafinil, mg/d	200	200	200
Outcome measures	• Depressive symptoms (MADRS, HDRS) • Fatigue (FSS, BFI) • Sleepiness (ESS) • Clinical condition/illness severity (CGI-S) • Change in illness severity (CGI-I) • Quality of life (Q-LES-Q, SF-36) • Subjective ratings of sad mood, anxiety, low energy, lack of motivation, and difficulty thinking (VAS)	• Depressive symptoms (HDRS) • Fatigue (HDRS subscale)	• Anxiety (STAI) • Depressive severity (MADRS) • Premorbid IQ (NART) • Psychosocial function (GAF) • Work functioning (LEAPS) • Cognition (computerized neurocognitive battery; RVIP, SOC, SWM, and PAL) • Fatigue (FSS) • Feelings (VAS)
Findings	• No reduction in sleepiness or fatigue in modafinil group vs placebo • Greater improvement on HDRS hypersomnia items in modafinil group vs placebo • No difference in depressive severity between modafinil and placebo • Change in $HDRS_{31}$ score was greater for modafinil vs placebo from wk 4 to wk 5 • Modafinil group reported lower levels of sad mood, low energy, and lack of motivation vs placebo after 1 wk (effect size, $d = 0.20$, $d = 0.22$, and $d = 0.26$, respectively) • No difference in self- reported levels of concentration over time between modafinil and placebo	• Greater reduction in depressive symptoms in modafinil group vs placebo after 6 wk (effect size, $d = 0.75$) • Greater percent of participants in the modafinil group responded and remitted (50% reduction in HDRS and HDRS ≤ 7, respectively) • Greater reduction in fatigue in modafinil group vs placebo (effect size, $d = 1.85$)	• Modafinil had no effect on fatigue • Modafinil improved episodic memory performance vs placebo (effect size, $d = 0.01$) • Modafinil improved performance on the hardest tests of working memory vs placebo (effect size, $d = 0.006$) • No effect of modafinil on planning performance or attention • Depressive severity was related to longer response latency on attention task • Association between baseline cognition and cognition after treatment/placebo
Adverse events (most common)	No significant difference between modafinil and placebo	No difference in frequency of side effects between modafinil and placebo	No difference in frequency of side effects between modafinil and placebo
Limitations	• Fixed dose of modafinil • Did not measure cognition (did assess subjective ability to think/concentration)	• Fixed dose of modafinil • Did not measure cognition	Did not measure long- term effects of modafinil on cognition

[a]Cohen *d* effect size was calculated by the authors when data were available in the included articles.

Abbreviations: ADDS = Atypical Depression Diagnostic Scale, BFI = Brief Fatigue Inventory, BMI = body mass index, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, GAF = Global Assessment of Functioning, HDRS = Hamilton Depression Rating Scale, LEAPS = Lam Employment Absence and Productivity Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, NART = National Adult Reading Test, PAL = Paired Associates Learning, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, RVIP = rapid visual information processing, SCL-90 = Symptom Checklist-90, SF-36 = 36-Item Short Form Health Survey, SOC = Stockings of Cambridge, SOSS = Severity of Symptoms Scale, SSRI = selective serotonin reuptake inhibitor, STAI = State-Trait Anxiety Inventory, SWM = spatial working memory, VAS = visual analog scale.

Table 3. Summary of Open-Label Trials[a]

	DeBattista et al[35]	Ninan et al[37]	Schwartz et al[36]
Year	2004	2004	2004
N (enrolled)	35	29	20
Age, mean, y	48	36	45
Female, %	58%	72%	55%
Study duration	4 wk	6 wk	3 wk
Diagnosis	• Current MDD ($HDRS_{17} > 16$) • Complaints of hypersomnia, fatigue, daytime somnolence, or impaired daytime alertness	• Current MDD (SIGH-D ≥ 15) • Fatigue (FSS ≥ 4)	• Current MDD • Reported sedation arising from use of SSRIs
Concomitant antidepressant therapy	Stable antidepressant with partial response for ≥ 4 wk	• Started SSRI (fluoxetine or paroxetine) at baseline • Free of antidepressants for 4 wk prior	SSRI (monotherapy)
Modafinil, mg/d	100–400	100–200	50–400
Outcome measures	• Depressive symptoms (HDRS, BDI) • Clinical condition/illness severity (CGI-S) • Fatigue (FSI, VAS-F) • Cognition (neurocognitive battery; Stroop Interference, WAIS-III Letter Number sequencing, WAIS-III Digit Span Forward and Backward, Trailmaking A and B)	• Depressive symptoms (SIGH-D, HDRS) • Cognition (SIGH-D) • Reverse "vegetative" symptoms (SIGH-D) • Fatigue (FSS, VAS) • Sleepiness (ESS) • Motivation (VAS) • Concentration (VAS) • Health-related quality of life (SF-36)	• Depressive symptoms (HDRS) • Sleepiness (ESS) • Fatigue (FSS) • Health-related quality of life (SF-12)
Findings	• Improvement in depressive symptoms (HDRS and BDI) from baseline to week 2 specifically in the domains of energy, fatigability, effort, and tiredness; improvements maintained at wk 4 • No significant change in psychomotor retardation after treatment • Decrease in fatigue from baseline to wk 2 (VAS-F and FSI); improvement maintained at wk 4 • Improvement in clinical condition from baseline to wk 2; improvement maintained at wk 4 • Improvement in executive function (Stroop test) observed over the 4-wk period • No improvements in other neurocognitive domains	• Significant reduction in depressive symptoms (SIGH-D and HDRS) occurred by wk 1, and for every subsequent wk • Response was achieved by 79% and remission by 58% after 6 wk • Significant reduction in fatigue and sleepiness occurred by wk 1, and for every subsequent wk • Improved self-reported mood, anxiety, energy/fatigue, motivation, concentration, and sleepiness found at all time points • Significant improvement in health-related quality of life	• Improvement in depressive symptoms after 1 wk; improvement maintained at all subsequent time points • 71% Response rate (≥ 50% reduction in HDRS score) • Improvement in wakefulness after 1 wk; improvement maintained at all subsequent time points • Reduced levels of fatigue observed by wk 2; improvement maintained at all subsequent time points • Improvements in health related quality of life observed at wk 3 and final visit (effect size, $d = 0.11$)
Adverse events (most common)	Not reported	• Headache • Nausea	• Dry mouth • Insomnia
Limitations	• Measured cognition, but did not include cognitive impairment as inclusion criteria • Possible carryover effects from other antidepressants • Open-label	• Open-label • Cognition not measured (however, subjective concentration was)	• Open-label • Selective entry criteria (only SSRI-related fatigue) • Did not measure cognition

(continued)

Table 3 (continued).

	Rasmussen et al[51]	Thase et al[30] (Fava et al[32] 2005 extension study)	Konuk et al[52]
Year	2005	2006	2006
N (enrolled)	21	250	25
Age, mean, y	51	43	32
Female, %	62%	71%	38%
Study duration	Until psychiatrist deemed condition stabilized	12 wk	6 wk
Diagnosis	• Current MDD • Hypersomnia	• Current MDD ($HDRS_{31}$ = 14–26) • Fatigue (FSS ≥ 4) • Sleepiness (ESS ≥ 10)	• Current MDD ($HDRS_{17}$ > 12) • Fatigue (FSS ≥ 4)
Concomitant antidepressant therapy	Any other antidepressant therapy/therapies with partial response over past several months	SSRI (fluoxetine, paroxetine, or sertraline) with partial response for ≥ 8 week, stable monotherapy for ≥ 4 weeks (before starting Fava et al 2005[32])	SSRI (began ≥ 12 wk before study)
Modafinil, mg/d	100–400	100–400	100–200
Outcome measures	• Psychopathology (SCL-92) • Depressive symptoms (MDI) • Hypersomnia (SCL-92 hypersomnia scale)	• Fatigue (FSS, BFI) • Sleepiness (ESS) • Depressive symptoms (HDRS, MADRS) • Clinical condition/illness severity (CGI-S) • Change in illness severity (CGI-I)	• Depressive symptoms (HDRS) • Fatigue (FSS) • Sleepiness (ESS)
Findings	• 43% response rate (≥ 50% reduction in MDI score) • 43% remission rate (MDI ≤ 13) • Nonresponders scored significantly higher on measures of "concentration difficulties" and "restlessness" than responders (effect size, d = 0.68 and d = 0.28, respectively) • Depressed mood, lack of interest, and lack of energy were more improved in the responder group compared to nonresponders (effect size, d = 1.04, d = 1.05, and d = 2.4, respectively) • Note: responders were less severely depressed at baseline (effect size, d = 0.86) • Nonresponders showed greater psychopathology than responders (especially somatization, obsessive-compulsive symptoms, and psychoticism) (effect size, d = 2.6) • All participants • Experienced > 50% reduction in hypersomnia	• 70% of participants showed a clinical improvement of "much improved" or "very much improved" • Improvement in sleepiness and fatigue observed at each time point, compared with baseline • Decrease in depressive symptoms observed at each time point, compared with baseline • Improvements on all outcome measures were minimum 2 times greater among former non-responders vs responders (Fava et al 2005[32] study)	• Improvement in depressive symptoms from baseline to wk 2; improvement maintained at wk 6 • Improvements in sleepiness and fatigue from baseline to wk 2; improvements maintained at wk 6 • 76.4% responded by the end of the study (> 50% decrease on HDRS) and 64.7% remitted (HDRS < 7)
Adverse events (most common)	Slight headache at beginning of trial	• Headache • Nausea • Dizziness	• Headache • Tremulousness • Nausea
Limitations	• Open-label • Baseline questionnaires were completed retrospectively • Did not measure cognition (did measure concentration difficulties)	• Open-label • Did not measure cognition	• Open-label • Did not measure cognition

(continued)

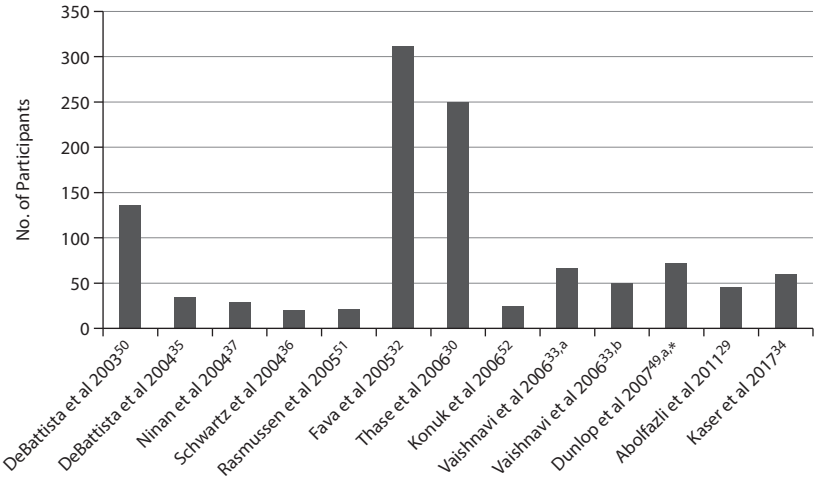
Table 3 (continued).

	Vaishnavi et al[33] Phase 1	Dunlop et al[49] Phase 2
Year	2006	2007
N (enrolled)	66	Not provided
Age, mean, y	40	44
Female, %	88%	56%
Study duration	12 wk	4 wk
Diagnosis	• Current MDD with atypical features ($HDRS_{29} \geq 18$ with atypical features • Illness severity rated as markedly ill or worse (CGI-S ≥ 4)	• Current MDD (MADRS ≥ 15) • Fatigue (FSS ≥ 4) • Sleepiness (ESS ≥ 10)
Concomitant antidepressant therapy	None permitted	SSRI (started at baseline with modafinil)
Modafinil, mg/d	200–400	100–300
Outcome measures	• Depressive symptoms (HDRS) • Fatigue (FSS, BFI) • Sleepiness (ESS) • Psychopathology (SCL-90) • Atypical depression features (ADDS) • Clinical condition/illness severity (CGI-S) • Symptom severity (SOSS)	• Depressive symptoms (MADRS, HDRS) • Fatigue (FSS, BFI) • Sleepiness (ESS) • Clinical condition/illness severity (CGI-S) • Change in illness severity (CGI-I) • Quality of life (Q-LES-Q, SF-36) • Subjective ratings of sad mood, anxiety, low energy, lack of motivation, and difficulty thinking (VAS)
Findings	• Improvement in depressive symptoms (effect size, $d = 0.32$) • Improvements in psychopathology symptoms (effect size, $d = 1.82$)	Premature discontinuation due to serious adverse event
Adverse events (most common)	Nausea, bad taste in mouth, palpitations, thirst	Phase 2: suicidal ideation (n = 2)
Limitations	• Possible carryover effects of drug to placebo • Did not measure cognition	• Premature discontinuation • Fixed dose of modafinil • Did not measure cognition (did assess subjective ability to think/concentration)

[a]Cohen *d* effect size was calculated by the authors when data were available in the included articles.

Abbreviations: ADDS = Atypical Depression Diagnostic Scale, BDI = Beck Depression Inventory, BFI = Brief Fatigue Inventory, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, ESS = Epworth Sleepiness Scale, FSI = Fatigue Symptom Inventory, FSS = Fatigue Severity Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MDI = Major Depression Inventory, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SCL-90 = Symptom Checklist-90, SCL-92 = Symptom Checklist-92, SF-12 = 12-Item Short Form Health Survey, SF-36 = 36-Item Short Form Health Survey, SIGH-D = Structured Interview Guide for the Hamilton Depression Rating Scale, SOSS = Severity of Symptoms Scale, SSRI = selective serotonin reuptake inhibitor, VAS = visual analog scale, VAS-F = visual analog scale–fatigue, WAIS-III = Wechsler Adult Intelligence Scale–Third Edition.

Figure 2. Number of Participants by Study



[a]Phase 1 study.
[b]Phase 2 study.
*Phase 2 N not included due to premature study discontinuation.

to be taking an SSRI as an inclusion criterion. Doses of modafinil ranged from 50 to 400 mg/d, with the daily dose most commonly 200 mg. No other patterns (ie, regarding depression severity, duration, or recurrence) were identified.

Randomized Control Trials

Cognition. In the single-dose study[34] of modafinil, remitted MDD participants improved significantly in episodic memory and on the most difficult tests of working memory. However, modafinil did not have an effect on planning performance or attention.[34] Another study[49] found that after 6 weeks of modafinil treatment, there was no difference in self-reported "improved concentration" between the modafinil group and the placebo group.

Fatigue and daytime sleepiness. In 4 studies,[32,33,49,50] while daytime sleepiness and fatigue improved from baseline, the modafinil group did not experience significantly greater improvement at the end of the study compared with placebo. In 2 reports[32,50] in which fatigue and sleepiness were evaluated, there was a significant improvement in fatigue and sleepiness after 1–2 weeks of modafinil treatment compared to placebo, but this difference was no longer significant at the final visit. In contrast, Abolfazli and colleagues[29] reported a sustained and significant improvement in fatigue symptoms in the modafinil group. Finally, in another study,[37] modafinil participants also self-reported significantly greater improvements in "energy" and "wakefulness" at final visit.

Depressive symptoms. In 4[32,33,49,50] of 5 placebo-controlled studies that measured change in depressive severity over time, improvement in depressive symptoms for the modafinil group was not significantly greater than for placebo. In the fifth trial,[29] there was a greater reduction in mood symptoms after 6 weeks of treatment and a greater percentage of responders and remitters in the modafinil group versus placebo.

Open-Label Trials

Cognition. After 4 weeks of modafinil treatment, participants experienced an overall improvement in executive function,[35] measured using the Stroop Interference Test.[53] There was no improvement in any other neurocognitive domains (working memory, visual attention, and task-switching).[35] Elsewhere,[37] participants reported feelings of improved concentration after 1 week of modafinil treatment and at final visit. Similarly, in a separate trial,[51] those who achieved an antidepressant response during modafinil treatment reported significantly fewer concentration difficulties after treatment.

Fatigue and daytime sleepiness. Both fatigue and daytime sleepiness responded favorably to modafinil within 1–2 weeks, and this improvement was maintained at final visit.[30,35–37,52] In 1 study,[51] participants experienced a greater than 50% reduction in hypersomnia symptoms after being adequately treated with modafinil. Finally, participants self-reported significantly greater "energy" and "wakefulness" after taking modafinil.[37]

Depressive symptoms. Modafinil was also associated with rapid improvement in depressive symptoms. Improvements were seen after 1–2 weeks of treatment, and these improvements were maintained at final visit (4 to 12 weeks).[30,33,35–37,52] In 1 study,[51] 43% of previous antidepressant nonresponders achieved remission (Major Depression Inventory score ≤ 13).

Safety Findings

Modafinil was generally well tolerated by users. The most frequently reported adverse events across studies were headache and nervousness. Only 1 serious adverse event was reported from all the studies: a participant experienced significant suicidal ideation requiring hospitalization, leading to early termination of the study.[49] Post hoc analysis

of the suicide item on either the Hamilton Depression Rating Scale or Montgomery-Asberg Depression Rating Scale showed no significant difference between the modafinil and placebo groups in terms of change in suicidal intent.[49]

DISCUSSION

This systematic review examined the effects of modafinil on cognition; only 2 studies were found that directly assessed cognition. One of these studies was a 4 week study,[35] while the other was a single-dose study.[34] Therefore, we did not deem a meta-analysis feasible for the purpose of this review.

Modafinil was associated with improvement in executive functioning over 4 weeks in an open-label, small-scale study.[35] When short-term, rapid effects were measured, modafinil was associated with significant improvements in episodic and working memory in remitted participants versus placebo.[34] However, these effects were small (Cohen $d = 0.01$ and 0.006, respectively), and several other cognitive domains were measured, including planning, attention, and task-switching, which did not show improvement after single-dose or long-term modafinil treatment. Modafinil may, therefore, play a role in improving only certain cognitive functions, specifically memory and executive function. Interestingly, 1 small-scale study[54] (which did not reach inclusion criteria for this report) that assessed the effect of modafinil as adjuvant for antidepressants found that treatment with modafinil was associated with significant improvements in global functioning. Only 1 study[34] that directly assessed cognition included in this review used a placebo-controlled design, and it was a single-dose study. Furthermore, all placebo-controlled trials assessing modafinil and cognition in healthy populations[39,41–45] used a single-dose or short-term (2 to 10 days) study design as well. Therefore, the long-term effects of modafinil on cognition, in both depressed and nondepressed samples, remain unclear. Future research should focus on assessing prolonged effects on modafinil on cognition using a placebo-controlled design. While subjective concentration improved in both studies using subjective measures of cognition, the difference was not significant from placebo, suggesting this improvement may be due to placebo effects.

It is also of note that the 2 studies assessing cognition used different cognitive batteries. In future studies, key domains such as memory, executive function, attention, information processing, and psychomotor speed could be assessed using validated scales such as the Cambridge Neuropsychological Test Automated Battery[55] or the CNS Vital Signs Neurocognitive Battery.[56] These scales have been used by multiple previous studies[11,13–15,17] that assessed cognition with other antidepressants.

Modafinil rapidly improved fatigue and sleepiness across studies in 1 to 2 weeks. This effect was small in the study by Fava et al[32] (Cohen $d = 0.24$ for fatigue and $d = 0.05$ for sleepiness); however, no other studies provided effect size data. Furthermore, modafinil increased subjective energy and wakefulness compared to baseline and significantly more than placebo.[36,37,49] Again, this effect size was small (Cohen $d = 0.22$) in the 1 study[49] that provided effect size data. In the meta-analysis by Goss et al,[46] modafinil was shown to have a positive effect on fatigue, but not sleepiness, relative to control; however, that study was looking at both unipolar and bipolar depression. The majority of placebo-controlled studies did find that, while this improvement was maintained, there was no difference in fatigue and wakefulness between modafinil and placebo in the long-term. This lack of difference may be due to placebo effects that led to improvements in fatigue or sleepiness. Furthermore, the majority of studies included participants, in both the placebo and treatment groups, who were taking antidepressants. These medications may have had effects on fatigue and sleepiness, confounding the results. Due to the latency period of most antidepressants to take effect, their effects on fatigue and sleepiness may not have appeared until week 1 or 2. However, while it is still unclear if modafinil provides long-term relief of fatigue and sleepiness, it appears to be an effective treatment in the short term. Thus, future studies could examine if modafinil could help fill in the time gap for standard antidepressant treatment, which typically has a time lag of a few weeks for therapeutic response.[50] Interestingly, all of the studies[34,35,37,49] that found a positive effect of modafinil on cognition, using objective or subjective measures, also found a positive effect on sleepiness and fatigue symptoms. Several studies[57–60] have reported that fatigue and sleepiness are related to cognitive impairment. Further, individuals who reported less concentration difficulties after modafinil treatment also experienced improvements in mood symptoms,[51] and low mood is related to cognitive impairment.[61–64] Further research should focus on delineating from modafinil the effects of sleepiness, fatigue, and low mood on cognition, for which path analysis could be helpful. Furthermore, studying remitted MDD patients with residual cognitive impairments may also be useful for delineating the effects of mood, for which no studies were available.

In one of the original studies looking at modafinil in MDD patients (which was a case series, and therefore not included in our results), Menza and colleagues[65] found that all 7 patients who had partial response or nonresponse to standard antidepressants achieved full or partial remission from depressive symptoms within approximately 1–2 weeks. The clinical trials explored in this review corroborated these results, finding modafinil to be associated with an improvement in depressive symptoms. However, this improvement was not significantly different from placebo, except in 1 small-scale study[29] that found a Cohen d effect size of 0.75. This lack of significant improvement is consistent with the 2013 meta-analysis by Goss et al,[46] who found that, while modafinil appeared to have a positive effect on depressive symptoms, the difference between modafinil and placebo did not reach significance ($P = .056$). It is also important to note that all but 1 study[33] required participants to be taking standard antidepressants during the treatment trial, raising the possibility that the improvements in mood may have been due to antidepressants rather

than to modafinil. Furthermore, the trial[33] that did not allow participants to take antidepressants found no effect of modafinil on depressive symptoms when compared to placebo.

Modafinil was deemed a safe and well-tolerated drug in all of the studies included in this systematic review. Previous studies[18,19,66,67] have suggested that psychostimulants be used as adjuvant antidepressants for cognitive impairment. However, psychostimulants have a risk of addiction and abuse[31] and can rarely cause treatment-emergent affective switch into mania.[68] Given the lack of positive results among studies assessing the procognitive effects of psychostimulants in depression, modafinil could be an alternative treatment choice with its benign side-effect profile and alternative mechanism of action.

There were limitations to the studies included in our systematic review. First, the majority of these studies were open-label, and all conclusions made in this systematic review must be considered in this light. A lack of treatment blinding can lead to inflation of results due to both patient and experimenter bias. Therefore, we cannot rule out a possible placebo effect in the majority of included studies. Second, there was a wide range of participant sample sizes across studies. Third, effect size data were not provided in the majority of studies; when the data were available for cognition, the effect sizes were small. This small effect suggests that the modafinil may not provide a meaningful benefit to cognition even if users respond to this medication. Fourth, there was heterogeneity among the dosing procedures used in these studies. Some studies allowed for physician judgment when deciding on the dose for patients (typically ranging from 100 to 400 mg/d), while others set a fixed dose of 200 mg/d. Setting a fixed dose may prevent the drug from exerting its full effect, as participants may be taking too low a dose. However, 200 mg has been suggested as an effective and safe dose of modafinil, and higher doses have been associated with a greater risk of side effects.[28] Finally, most participants across studies were taking antidepressants, most commonly SSRIs, and modafinil might be more efficacious and better tolerated when used with other specific classes of antidepressants.

In conclusion, modafinil appears to be a well-tolerated drug with potential benefits as an adjuvant to standard antidepressant treatment, specifically for fast-acting relief of fatigue and sleepiness. There is some evidence that modafinil may be effective in improving specific cognitive domains in individuals with depression, specifically executive functioning, episodic memory, and working memory. However, very few studies have assessed cognition with modafinil, and no placebo-controlled studies have assessed the long-term effects of modafinil on cognition. Due to the current lack of effective treatments for cognitive impairment in depression, more trials assessing procognitive treatments for depression, such as modafinil, are needed.

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