The Efficacy of Modafinil as a Cognitive Enhancer

A Systematic Review and Meta-Analysis

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Abstract:

Background: Animal models and human studies have identified the potential of modafinil as a cognitive enhancing agent, independent of its effects on promoting wakefulness in sleep-deprived samples. Given that single-dose applications of other putative memory enhancers (eg, D-cycloserine, yohimbine, and methylene blue) have shown success in enhancing clinical outcomes for anxiety-related disorders, we conducted a meta-analytic review examining the potential for single-dose effects for modafinil on cognitive functioning in non–sleep-deprived adults.

Methods: A total of 19 placebo-controlled trials that examined the effects of single-dose modafinil versus placebo on the cognitive domains of attention, executive functioning, memory, or processing speed were identified, allowing for the calculation of 67 cognitive domain–specific effect sizes.

Results: The overall positive effect of modafinil over placebo across all cognitive domains was small and significant ($g = 0.10$; 95% confidence interval, 0.05–0.15; $P < 0.001$). No significant differences between cognitive domains were found. Likewise, no significant moderation was found for modafinil dose (100 mg vs 200 mg) or for the populations studied (psychiatric vs nonpsychiatric).

Conclusions: In conclusion, the available evidence indicates only limited potential for modafinil to act as a cognitive enhancer outside sleep-deprived populations.

Key Words: cognitive enhancer, modafinil, cognitive functioning, memory functions

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Translational research has introduced the potential of using cognitive enhancers to promote therapeutic learning from cognitive-behavior therapy (CBT).[1] After the success of D-cycloserine for enhancing exposure-based CBT and promising early effects for methylene blue and yohimbine, there has been consideration of other agents that may be administered in single doses before therapy sessions to enhance retention of therapeutic learning from those sessions.[2–5]

Modafinil is Food and Drug Administration approved as a wakefulness-promoting agent for narcolepsy and related sleep disorders.[6] It also has broad-based effects on neurotransmitter systems, including primary effects on dopamine and norepinephrine, and secondary effects on glutamate, GABA, and serotonin, among other effects.[7] A general potential for cognitive enhancement has been revealed in both animal models and in human studies as is common for stimulants, but modafinil's mechanism of action is divergent enough from that of amphetamine,[a] for example, that a different profile or magnitude of cognitive effects can be anticipated.[7–9] For example, evaluation of low-dose modafinil in animal models suggests that it can enhance hippocampal-dependent memory tasks (eg, Shuman et al.[10]), although findings are not consistent between studies.[7] Similarly, in the human literature, modafinil offers significant benefit for promoting wakefulness, reducing fatigue, and improving sleep-related cognitive impairments (eg, Flindall et al,[11] Sugden et al,[12] Repantis et al,[13] and Kelley et al[14]), but effects on cognition in those who are not sleep deprived have been inconsistent.[7,13,14] Indeed, the cognitive-enhancement literature had been marked by positive effects on different cognitive functions across studies, with limited replication of findings for effects in specific cognitive domains,[7] raising concerns about the reliability of cognitive enhancement effects in healthy, non–sleep-deprived samples. Notably absent from the literature have been any recent comprehensive quantitative reviews of the efficacy of modafinil as a cognitive enhancer across relevant cognitive domains, so that positive effects for a cognitive domain observed in one study are evaluated relative to the same cognitive domain in other studies. Previous meta-analytic comparisons have been completed.[13,14] The largest of these indicated that attention but not memory was significantly enhanced by modafinil in non–sleep-deprived individuals,[13] yet there has been a substantial increase in the number of studies (12) since this meta-analysis was completed. Furthermore, Repantis and associates[13] did not include studies of psychiatric samples in their meta-analytic review.

The purpose of the current meta-analysis was to address inconsistent findings in the literature on modafinil's effect on cognition by providing an updated quantitative analysis of the overall and specific benefits of modafinil augmentation of cognition in non–sleep-deprived participants. We limited our analyses to single-dose applications to provide an index of the type of cognitive enhancement that may be achieved if modafinil is administered before psychosocial treatment sessions as a strategy for augmenting attention to, retention of, or the consideration/utilization of therapeutic information. Indeed, given that current pharmacological strategies for cognitive enhancement of CBT have been targeted to exposure-based treatment,[1] there is the question of whether modafinil may have broader-based cognition enhancing effects appropriate to other applications of CBT outside exposure paradigms (eg, the treatment of depression[15]). Accordingly, this meta-analysis was targeted toward examining the efficacy of such single-dose effects on cognition in individuals who were not sleep deprived. We evaluated modafinil effects on specific cognitive domains—attention, executive functioning, memory, and processing speed—as well as overall effects across domains. Furthermore, given limited evidence for more reliable cognitive benefits with 100 mg modafinil compared with 200 mg modafinil in non–sleep-deprived healthy adults, we evaluated whether dose moderated the degree of cognitive enhancement.[14]

[a] Modafinil and amphetamine are not labeled to be used to enhance cognition in healthy adults.

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Similarly, given the application of modafinil in psychiatric populations,[16,17] we evaluated whether cognitive effects were moderated by the sample studied.

MATERIALS AND METHODS

Search Strategy

A literature search was conducted on PubMed and PsycINFO databases to identify studies for inclusion that were published up to July 18, 2016. A Boolean search term ((modafinil[Title/Abstract] AND cognitive[Title/Abstract]) OR (modafinil[Title/Abstract] AND memory[Title/Abstract]) OR (modafinil[Title/Abstract] AND neuroenhancement[Title/ Abstract]) OR (modafinil[Title/Abstract] AND neuropsychological[Title/ Abstract])) was used. This method served to include any articles that had the term "modafinil" in addition to either of the terms "cognitive," "memory," "neuroenhancement," or "neuropsychological" in the title or the abstract, while also removing duplicates. These same search terms were used to identify studies for inclusion that were posted on ClinicalTrials.gov, a national registry of clinical trials, through August 2016. We specifically searched for studies that were categorized as "completed," "studies with results," and "interventional studies." In addition, the reference sections of relevant systematic reviews and meta-analyses were also examined for additional studies.[14,18] Two authors independently conducted the literature search.

Study Selection

Studies obtained from the search were selected if they met the following inclusion criteria: (1) studies investigating modafinil-induced cognitive enhancement among humans in either healthy or psychiatric populations; (2) studies written in English; (3) peer-reviewed articles; (4) placebo-controlled studies containing a randomization protocol; and (5) studies that included at least one outcome from the cognitive domains of attention, executive functioning, memory, and processing speed.

Studies meeting any of the following criteria were excluded: (1) studies of populations with sleep disorders, neurocognitive disorders, brain injuries, or other medical conditions (eg, cancer and HIV); (2) studies of sleep-deprived patients (eg, studies examining atypical sleep regimens, such as studies with shift workers or using experimentally induced insomnia); (3) studies that included chronic dosing of modafinil; (4) studies in which cognitive training was provided before drug administration; (5) studies in which transcranial magnetic stimulation was used; (6) studies in which modafinil was combined with another substance (eg, nicotine); and (7) studies that included only atypical cognitive outcome (ie, a test not listed in the glossary of common neuropsychological tests compendiums; eg, Lezak et al[19]).

Data Abstraction

Articles meeting the inclusion/exclusion criteria were identified. Data were abstracted by 2 authors (A.K., S.O.) and independently checked for accuracy by a third author (M.A.K.).

For computing effect sizes, means and SDs were used. For all but one study, only poststudy pill administration data were provided and abstracted. For one study, prestudy and poststudy pill administration data, as well as pre/postdata correlations, were available and abstracted.[20] In cases where insufficient data were presented (lack of statistics to generate effect size), multiple attempts were made to contact the authors of the study.

The directions of effect sizes were coded as positive if they reflected a beneficial change or better cognitive performance after modafinil compared with placebo administration. Effect directions were coded as negative if they reflected a deleterious change or poorer cognitive performance after modafinil compared with placebo administration. Direction determinations were made based on information provided in individual articles and standard scoring guidelines for cognitive tests.[19,21]

Data regarding the cognitive domains assessed (attention, executive functioning, memory, or processing speed), modafinil dose (100 or 200 mg), and population type (psychiatric or nonpsychiatric) were abstracted to be used in moderator analyses. Decisions about categorization were made based on standard guidelines and test descriptions.[19,21] A list of individual cognitive tests by domain can be found in Table 1. Study samples were categorized as either psychiatric or nonpsychiatric. Samples were deemed to be "psychiatric" when authors specified that a patient population was recruited. Unselected and healthy samples were considered "nonpsychiatric." There was an insufficient number of studies conducted on any given psychiatric diagnosis to conduct moderator analyses by diagnosis type. Moderator analyses were only conducted when a total of 8 or more comparisons and at least 3 comparisons for any particular moderator grouping were available to contribute to the analyses. Separate effect sizes for each moderator group were computed using mixed-effects

TABLE 1. Cognitive Domains and Neuropsychological Tests

Domain	Test
Attention	Continuous Performance Test-II
	d2 Test of Attention
	Digit Cancellation
	Paced Auditory Serial Addition Task
	Rapid Visual Information Processing (CANTAB)
	Trail Making Test A
Executive function	Biber Cognitive Estimation Test
	Controlled Oral Word Association Test—Category Fluency
	Controlled Oral Word Association Test—Letter Fluency
	Intra-Extra Dimensional Set Shift (CANTAB)
	One Touch Stockings of Cambridge
	One Touch Tower of London (CANTAB)
	Raven's Advanced Progressive Matrices II
	Stop Signal Task (CANTAB)
	Stroop Interference/Inhibition
	Trail Making Test B
Memory	Delayed Matching to Sample (CANTAB)
	Digit Span
	Hopkins Verbal Learning Test-Revised
	Letter Number Sequencing (WAIS-III)
	Logical Memory
	Paired Associates Learning (CANTAB)
	Pattern Recognition Memory (CANTAB)
	Spatial Span (CANTAB)
	Spatial Working Memory (CANTAB)
Processing speed	Digit Symbol Coding (WAIS-III)
	Digit Symbol Substitution
	Stroop Congruent/Naming
	Symbol Copying

CANTAB indicates Cambridge Neuropsychological Test Automated Battery; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition.

analysis, and the Cochran Q test of heterogeneity was examined to determine significance between moderator groups.

Data Analytic Strategy

Effect Size Analyses

Analyses were conducted using the Comprehensive Meta-Analysis software program (Version 3). Random-effects models were used. Random-effects models assume that studies in a meta-analysis are taken from populations with varying effect sizes. This contrasts with fixed-effects models, which assume that studies are sampled from populations with the same effect size. Random-effects models are recommended over fixed-effects models to assess social science data given the likely heterogeneous population effect sizes.[22] Hedge g (corrected effect size) and its 95% confidence interval (CI) were used as an indicator of effect size. Hedge g provides a measure of how much the experimental group differs from the control group and is a commonly used effect size metric in meta-analyses. Effects were interpreted as small (0.2), medium (0.5), or large (0.8).[23] Hedge g is recommended over another commonly used effect size metric, Cohen d, in cases when individual study sample sizes are small, which was the case for some studies included in the current meta-analysis. The I^2 statistic[24] was used to examine heterogeneity and quantify inconsistency across studies. The I^2 statistic represents the percentage of variability in effect estimates that is due to heterogeneity rather than a result of sampling error (chance), with I^2 statistics greater than 30% representing moderate heterogeneity. In instances where heterogeneity is high, conducting a meta-analysis and reporting an average effect may not be appropriate.

For studies using between-subject designs that contained multiple subgroups of participants (eg, a subgroup that received 100 mg of modafinil and a subgroup that received 200 mg of modafinil, compared with one placebo group), each subgroup was treated as a separate sample, data from the placebo group were used twice, and the sample size of the placebo group was halved for each entry. For studies using within-subject designs (ie, crossover studies) that contained multiple subgroups (eg, a subgroup of healthy participants and a subgroup of alcohol-dependent participants), each subgroup was treated as a separate sample and data from the modafinil and control phases for each subgroup were used. Thus, a study with 2 subgroups contributed twice as many effect sizes to the meta-analysis as a study with 1 subgroup. If multiple neuropsychological tests were used to assess a given cognitive domain within 1 subgroup, data for all tests presented in the article were abstracted, an effect size for each test was calculated, and the average of these effect sizes was used toward the meta-analysis. Thus, only one effect size per cognitive domain per subgroup contributed to the meta-analysis. This ensured that individual studies did not overly contribute to the overall effect size simply because they used more tests to assess a given cognitive domain.

For within-subject designs (ie, crossover studies), a paired data format that included means and SDs from both phases (ie, control phase, modafinil phase) of the study was used. Data from the 2 phases of crossover studies are inevitably correlated as the same participants complete each phase; thus, the calculation of effect sizes for such studies requires the correlation statistic for the data from the 2 phases (ie, pre-post correlation). Given that articles did not report pre-post correlations for their data, pre-post correlations were estimated to be $r = 0.6$. This value was chosen because it falls between published recommendations for imputation of pre-post correlations ($r = 0.7$, $r = 0.5$).[23–25] Per recommendations, sensitivity analyses were conducted using values of $r = 0.5$ and $r = 0.7$.[24]

Publication Bias

Funnel plots were examined for asymmetry. A funnel plot is a scatterplot of effect sizes against a measure of study precision, in this case SE, with the mean effect size as the midline of the plot.[24] In a situation where publication bias is not present, a funnel plot would appear symmetrical. There would be as many effects to the right of the mean effect size as to the left of the mean effect size, and this would be true toward to the top and bottom of the funnel (with small and large SEs). In a situation where publication bias is likely present, a funnel plot would appear asymmetrical. If, for example, many negative studies with small sample sizes (and therefore large SEs) were not published, there would be fewer studies in the bottom left corner of the funnel plot than the bottom right of the funnel plot, and the funnel plot would appear asymmetrical. Because visual inspection of funnel plots does not provide any information on what the effect size would be without publication bias, the Trim and Fill method[26] was also used for significant effects from primary analyses. The Trim and Fill method aims to correct for funnel plot asymmetry by removing (ie, trimming) smaller studies causing asymmetry, using the trimmed funnel plot to estimate the true center of the funnel (mean effect size), and then replacing the omitted studies and their missing "counterparts" around the center (ie, filling) to make the plot symmetrical. This results in an adjusted intervention effect that is derived by performing the meta-analysis including the filled studies. This adjusted effect approximates the effect size corrected for possible publication bias.

Risk of Bias

In addition to bias due to studies not being published, bias can also occur as a result of poorly conducted studies entering the meta-analysis. Although the inclusion/exclusion criteria somewhat prevent this, it is also necessary to examine the quality of the included studies closely, so that this may be considered alongside the results of the meta-analysis. Two independent raters (A.K., M. A.K.) assessed the quality and risk of bias of individual studies included in the meta-analysis using the Cochrane Collaboration's tool for assessing risk of bias.[27] Disagreements on ratings were resolved through discussion with the last author (M.W.O.). The Cochrane Collaboration tool for assessing risk of bias was developed to replace quality scales and checklists, which have been shown to be inconsistent and inadequate for randomized controlled trials.[28,29] The tool provides a method of qualitatively assessing selection bias, performance bias, detection bias, attrition bias, and reporting bias, through examining the following domains of each study: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other sources of bias. Criteria for each domain are provided allowing one to make a judgment of low risk of bias, high risk of bias, or unknown risk of bias for each domain. More information on this tool and detailed guidelines for assessing each domain are provided by the Cochrane Collaboration.

RESULTS

Search Results

Using the search strategy described previously, 370 unique articles were initially identified. Abstracts and full texts were reviewed, and 296 articles were excluded because of not meeting specific inclusion/exclusion criteria. During data extraction, an additional 55 articles were excluded. Specific reasons for exclusion are outlined in the consort diagram (Supplementary Fig. S1, Supplementary Digital Content 1, http://links.lww.com/JCP/A593).

Domain	Hedges's *g*	Standard Error	Lower limit	Upper limit	p-Value	Hedges's *g* and 95% CI
Attention	0.062	0.062	-0.059	0.184	0.315	
Executive Functioning	0.096	0.045	0.008	0.184	0.033	
Memory	0.070	0.047	-0.023	0.163	0.138	
Processing Speed	0.201	0.064	0.075	0.327	0.002	

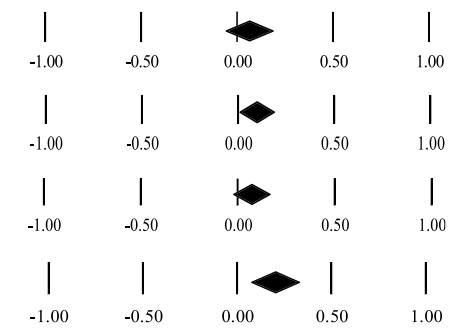

FIGURE 1. Summary of effects of modafinil over placebo on domains of attention, executive functioning, memory, and processing speed.

Ultimately, 19 articles met the inclusion/exclusion criteria and contributed to the analyses. Within the 19 articles, 26 subgroups were identified. Within the 26 subgroups, 406 comparisons of specific neuropsychological tests were used to calculate 67 cognitive domain–specific effect sizes.

Study Characteristics

The analyses comprised data from 767 participants. Seven studies used between-subject designs, and 12 studies used within-subject designs. For studies that used between-subject designs, all but 1 study confirmed that participants did not differ at baseline on verbal intelligence.[20] Esposito et al[20] administered the same cognitive test before and after modafinil/placebo administration and confirmed that the modafinil and placebo groups did not differ in scores on the cognitive test before drug administration. Within-subject designs randomized the order of modafinil and placebo administration across participants and typically used a washout period between drug administrations.

Most subgroups within studies were administered a 200-mg dose of modafinil (n = 18). Six subgroups were administered a 100-mg dose, one a 300-mg dose, and one a 400-mg dose. Most subgroups comprised nonpsychiatric populations (n = 19). Of the subgroups that comprised psychiatric populations (n = 7), 3 examined alcohol- or drug-dependent patients, 2 examined patients with psychosis, 1 examined patients with attention-deficit/hyperactivity disorder, and 1 examined patients with trichotillomania. Further details on specific studies can be found in Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JCP/A594.[30–45] The sample sizes reported from hereafter reflect number of comparisons (ie, cognitive domain–specific effect sizes) unless stated otherwise.

Quantitative Data Synthesis

Main Effects

The overall effect of modafinil over placebo across all cognitive domains and comparisons was small and significant ($g = 0.10$; 95% CI, 0.05–0.15; $P < 0.001$, n = 67). In further examining the significance and size of effects separately by cognitive domain, all effects were small (Fig. 1). The aggregate effects for the domains of executive functioning and processing speed were found to be significant (executive functioning: $g = 0.10$ [95% CI, 0.01–0.18; $P < 0.05$, n = 23], Supplementary Fig. S2, Supplemental Digital Content 3, http://links.lww.com/JCP/A595; processing speed: $g = 0.20$ [95% CI, 0.07–0.33; $P < 0.01$, n = 9], Supplementary Fig. S3, Supplemental Digital Content 4, http://links.lww.com/JCP/A596), whereas those for attention and memory were not (attention: $g = 0.06$ [95% CI, −0.06 to 0.18; $P = 0.32$, n = 16], Supplementary Fig. S4, Supplemental Digital Content 5, http://links.lww.com/JCP/A597; memory: $g = 0.07$ [95% CI, −0.02 to 0.16; $P = 0.14$, n = 19], Supplementary Fig. S5, Supplemental Digital Content 6, http://links.lww.com/JCP/A598). Statistical heterogeneity was low (overall, $I^2 = 0\%$; attention, $I^2 = 0\%$; executive functioning, $I^2 = 2\%$; memory, $I^2 = 0\%$; processing speed, $I^2 = 0\%$), nor were there any significant differences in aggregate effect sizes between any 2 specific cognitive domains (P values > 0.10). Sensitivity analyses using pre-post correlations of $r = 0.5$ and $r = 0.7$ for within-subject design studies did not change the overall or domain specific effects outlined previously. Post hoc analyses eliminating tests with possible ceiling effects produced comparable results.[b]

Moderators

Modafinil Dosage

Across all cognitive domains, no significant differences were found in effect sizes between comparisons from subgroups given 100 mg of modafinil ($g = 0.14$, $P = 0.15$, n = 17) and comparisons from subgroups given 200 mg of modafinil ($g = 0.10$, $P < 0.001$, n = 45; $Q = 0.21$, $df = 1$, $P = 0.65$). Furthermore, no effect of dose was found within any specific cognitive domain (P values > 0.55).

Population Type

Across all cognitive domains, no significant differences were found in effect sizes between comparisons from psychiatric samples ($g = 0.07$, $P = 0.11$, n = 17) and comparisons from nonpsychiatric samples ($g = 0.11$, $P < 0.001$, n = 50; $Q = 0.62$, $df = 1$,

[b]Post hoc analyses were conducted after excluding tests that prior authors[18] have suggested may have ceiling effects (ie, the Delayed Matching to Sample, Pattern Recognition Memory, Rapid Visual Information Processing, and Spatial Working Memory tasks from the Cambridge Neuropsychological Test Automated Battery) as well as specific outcomes for which authors noted potential ceiling effects in their articles (ie, Paired Associates Learning task in Müller et al[34]). Excluding these outcomes did not change the size or significance of the overall ($g = 0.11$; 95% CI, 0.06–0.17; $P < 0.001$, n = 59) or individual domain effect sizes: attention ($g = 0.14$; 95% CI, −0.05 to 0.32; $P = 0.15$, n = 9), executive functioning ($g = 0.10$; 95% CI, 0.01–0.18; $P < 0.05$, n = 23), memory ($g = 0.09$; 95% CI, −0.01 to 0.18; $P = 0.08$, n = 18), and processing speed ($g = 0.20$; 95% CI, 0.07–0.33; $P < 0.01$, n = 9).

$P = 0.43$). Furthermore, no effect of population type was found within any specific cognitive domain (P values > 0.31).

Publication Bias

Funnel plots for the effects of modafinil on cognition across all outcomes and across specific domains (Supplementary Figs. S6–S10, Supplemental Digital Content 7, http://links.lww.com/JCP/A599) were inspected. The funnel plots for the overall (ie, all 67 comparisons) and executive functioning effects were slightly asymmetrical with more positive than negative effects. The funnel plots for attention, memory, and processing speed appeared to be symmetrical. Trim and Fill analysis for the overall effect resulted in imputed effects to the left of the mean. However, the adjusted effect size and CIs were not dramatically different from our original estimates ($g = 0.07$; 95% CI, 0.02–0.12), suggestive of minimal impact of publication bias on this overall outcome. Trim and Fill analysis for executive functioning also resulted in imputed effects to the left of the mean. In this case, the adjusted effect size and CIs were quite different from our original estimates ($g = 0.02$; 95% CI, −0.10 to 0.14), suggestive of possible publication bias specific to this domain. Trim and Fill analysis for processing speed did not result in any imputed effects and thus no adjusted effect size. These findings suggest that publication bias may be slightly impacting results, but not to the degree to impact the size and significance of the overall effect.

Risk of Bias

A visual summary of the risk of bias assessment, as recommended by the Cochrane Collaboration, can be found in Supplementary Figure S11, Supplemental Digital Content 8, http://links.lww.com/JCP/A600.[27] We interpret this figure as depicting mostly low or unclear risk of bias. Ratings of unclear risk of bias were largely due to authors not reporting their method of allocation and not registering their protocols online, making it difficult to assess allocation concealment, blinding of participants and personnel, and selective outcome reporting.

DISCUSSION

Modafinil earned an early reputation as a potential cognitive enhancer, and the variable results documented in the literature have helped maintain this perception.[7,18,46] However, when the magnitude of modafinil effects is tallied across studies, with attention to results for specific domains of cognitive functioning, the available evidence indicates that single-dose modafinil has only limited efficacy for cognitive enhancement when applied outside sleep-deprived populations. Specifically, in this meta-analysis, we documented a small but significant effect size ($g = 0.10$; 95% CI, 0.05–0.15) as indicated by 67 domain-specific effects across 19 placebo-controlled trials. We did not find substantial evidence of bias for this estimate. Furthermore, effect size estimates were fairly consistent across each of the cognitive domains examined—attention, $g = 0.06$; executive functioning, $g = 0.10$; memory, $g = 0.07$; and processing speed, $g = 0.20$—with no significant differences between domains. Relative to the most comprehensive prior meta-analysis conducted in this area,[13] the consideration of a larger literature led to the loss of significance of single-dose modafinil effects on attention, but emergence of significant small effects for executive functioning and processing speed; effects on memory remained nonsignificant. Also, early reports of an advantage for 100 mg versus 200 mg of modafinil were not confirmed in our tests of moderation.[14] By way of comparison, the magnitude of single-dose modafinil effects across cognitive domains was in the same range as those estimated for acute exercise ($g = 0.11$).[47]

We did not find evidence that modafinil has stronger effects in psychiatric relative to nonpsychiatric samples, although the research evidence is limited to the studies of patients with alcohol or drug dependence, psychosis, attention-deficit/hyperactivity disorder, or trichotillomania that make up the current literature for single-dose evaluations of modafinil efficacy for cognitive enhancement. Mood benefits have been documented for daily dosing of modafinil as an augmentation strategy for treating major depression (eg, Goss et al[48]), but notably, we were unable to find published studies of single-dose applications of modafinil in major depression or anxiety disorder populations. Accordingly, we cannot rule out the potential for differential cognitive effects of single-dose modafinil in depressed or anxious samples, for example, where fatigue, sleep disturbances, and memory impairments are common.[49,50]

Our study findings are specific to single-dose applications of modafinil given to non–sleep-deprived samples and do not comment on the effects of modafinil in promoting wakefulness and attenuating some of the cognitive deficits associated with sleep deprivation (eg, Flindall et al[11] and Repantis et al[13]). We evaluated single-dose applications of modafinil in relation to the growing literature on the pharmacological enhancement of therapeutic learning from CBT.[1,2] Our current effect size estimates for modafinil do not hold specific promise for its application to the enhancement of single-session learning formats, as is relevant to the application of modafinil to enhancing the learning in a single therapy session. Nonetheless, this conclusion needs to be considered in relation to at least 3 caveats. First, it is possible that modafinil may have differential effects on emotional memory tasks relevant to therapy; affectively charged memory tasks were not assessed in any study used in the meta-analysis. Second, we were unable to evaluate the effects of modafinil on extinction learning, an area of specific efficacy for the other putative memory enhancers evaluated with exposure-based CBT.[2,5] Third, we tested the effects of modafinil for specific cognitive tasks evaluated in laboratory settings; it is possible that modafinil may have different effects on prolonged or complex actions involved in real-life problem solving (eg,[51]).

In conclusion, qualitative reviews of the cognitive effects of modafinil indicated a number of studies with positive findings for select cognitive domains among a battery of tests, which were nonetheless inconsistently supported between studies of non–sleep-deprived samples.[7] The current quantitative review underscores the degree of this inconsistency. Despite the prominence of select positive findings in the literature, when the same domains of cognition are evaluated across a large number of studies, estimates of the efficacy of modafinil are in the small range.

**Articles included in current meta-analysis.*

AUTHOR DISCLOSURE INFORMATION

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