

# Modafinil as an Adjunctive Treatment of Sedation, Negative Symptoms, and Cognition in Schizophrenia: A Critical Review

Carlos Saavedra-Velez, M.D.; Anna Yusim, M.D.;  
Deepti Anbarasan, B.S.; and Jean-Pierre Lindenmayer, M.D.

**Objective:** Given recent reports about the off-label use of modafinil as an adjuvant for the treatment of antipsychotic-associated sedation in schizophrenia patients and the recent interest in its putative cognitive-enhancing effects in this population, we present a systematic review of available data on trials of modafinil as an adjuvant in the treatment of cognitive deficits, negative symptoms, and antipsychotic-induced fatigue, and its tolerability.

**Data Sources:** PubMed was searched for trials published in English up to January 2008 evaluating modafinil's effects on fatigue, negative symptoms, and cognition in schizophrenia with combinations of the following terms: *schizophrenia*, *modafinil*, *cognition*, *negative symptoms*, and *fatigue*.

**Study Selection:** Six trials were identified: 2 randomized, prospective, double-blind placebo-controlled trials; 3 randomized, prospective, double-blind placebo-controlled crossover trials; and 1 open-label pilot study. Case series and case reports were excluded in the data analysis, except to identify potential adverse reactions to modafinil.

**Data Extraction:** Studies were examined for number of subjects, trial duration, design, dosing, and outcomes with respect to sedation, negative symptoms, cognitive function, and tolerability.

**Results:** One of 4 reviewed studies found a significant effect of modafinil as an alerting agent for antipsychotic-induced fatigue and sedation. Neither of 2 reviewed studies found modafinil to improve negative symptoms of schizophrenia. Three of 6 reviewed studies showed that modafinil may improve short-term memory, attention, and the ability to shift mental sets. Two neuroimaging studies identified functional correlates in areas associated with working memory functions. The main adverse effect was found to be a small risk of psychosis exacerbation, which was seen in 5 of 83 patients (6.0%) in the active treatment groups as compared to 2 of 70 patients (2.9%) in the placebo groups.

**Conclusions:** While the available data suggest that modafinil is generally well tolerated and may have some efficacy in the treatment of antipsychotic-induced sedation and cognitive domains, the small sample sizes, contradictory results,

and methodological differences between trials, especially with respect to cognitive testing, make it difficult to draw firm conclusions about the overall effectiveness of modafinil as an adjunct in the treatment of schizophrenia. Well-powered, prospective, randomized placebo-controlled trials using the MATRICS battery concomitantly with functional outcome measures are necessary to elucidate modafinil's efficacy and effectiveness as an adjunctive treatment for sedation, negative symptoms, and cognitive deficits in schizophrenia. Hence, before prescribing modafinil to a schizophrenia patient, the possible risks and benefits of each particular case should be evaluated.

(*J Clin Psychiatry* 2008;69:000–000)

© Copyright 2008 Physicians Postgraduate Press, Inc.

Received Dec. 6, 2007; accepted July 2, 2008. From the Department of Psychiatry, New York University Medical Center (Drs. Saavedra-Velez, Yusim, and Lindenmayer); New York University School of Medicine (Ms. Anbarasan); and the Psychopharmacology Research Unit–Nathan S. Kline Institute for Psychiatric Research, Manhattan Psychiatric Center (Dr. Lindenmayer), New York, N.Y.

Dr. Lindenmayer has received grant/research support from Eli Lilly, Janssen, Johnson & Johnson, Bristol-Myers Squibb, AstraZeneca, Pfizer, Organon, and Azur and has served as a consultant to Eli Lilly and Johnson & Johnson. Drs. Saavedra-Velez and Yusim and Ms. Anbarasan report no financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Jean-Pierre Lindenmayer, M.D., Psychopharmacology Research Unit–Nathan S. Kline Institute for Psychiatric Research, Manhattan Psychiatric Center, Wards Island, New York, NY 10035 (e-mail: lindenmayer@NKI.rfmh.org).

**M**odafinil is a wake-promoting drug approved by the U.S. Food and Drug Administration for the treatment of narcolepsy and shift work sleep disorder, and as an adjunct treatment for obstructive sleep apnea/hypoapnea syndrome.<sup>1</sup> Modafinil's specific pharmacologic mechanism of action and selective cortical arousal properties remain a source of speculation,<sup>2,3</sup> although it is believed to work on a number of brain regions, including the paraventricular and suprachiasmatic nuclei, anterior hypothalamus, amygdala, and tuberomammillary nucleus.<sup>4</sup> Clinical studies point to modafinil as a unique and highly selective  $\alpha_1$ -adrenergic agonist,<sup>5</sup> which may enhance glutamate and inhibit  $\gamma$ -aminobutyric acid (GABA).<sup>6,7</sup> Modafinil also activates hypocretin-releasing

neurons in the lateral hypothalamus,<sup>8</sup> which in turn cause glutaminergic nerve firing in the hippocampal arousal circuits and histamine release in the tuberomammillary nucleus.<sup>9</sup>

Modafinil has been shown to improve fatigue and sedation in a variety of off-label conditions, including neurologic disorders, antipsychotic-induced sedation, and major depression.<sup>10–14</sup> Its stimulant-like properties suggest potential efficacy in the management of amphetamine and cocaine withdrawal symptoms, such as dysphoria, hypersomnolence, and attentional deficits.<sup>15,16</sup> While there are few systematic data available on the prevalence of the use of modafinil in the United States for the indications discussed in this article, we found that in our 340-bed psychiatric hospital, a total of 11 patients were prescribed it over a period of 6 months.

Modafinil appears to be well tolerated and has limited liability for abuse.<sup>17,18</sup> Studies in healthy volunteers, cocaine users, and attention-deficit/hyperactivity disorder (ADHD) patients have found little evidence of dependence and fewer side effects with modafinil than with placebo.<sup>19</sup> Clinical observations of modafinil misuse in a postmarketing review concluded that the potential for large-scale abuse was limited.<sup>20</sup> However, the potential for abuse is not negligible among students and athletes due to modafinil's perceived performance-enhancing effects.<sup>21</sup>

Recently, modafinil has gained attention as an off-label adjuvant for the treatment of antipsychotic-induced sedation, negative symptoms, and cognitive deficits in schizophrenia patients. The traditional stimulants, methylphenidate and amphetamines, have been previously studied in this same context.<sup>22–24</sup> Although there have been no large-scale prospective studies on the use of traditional stimulants for counteracting sedation, negative symptoms, or cognitive problems in schizophrenia, several small studies have shown no significant effects on the above parameters, have shown exacerbated psychotic symptoms, and/or have been inconclusive. A 2-week double-blind crossover study with 8 schizophrenic inpatients showed no enhanced efficacy of methylphenidate treatment on the above parameters relative to placebo for patients taking a stabilized neuroleptic dose.<sup>25</sup> Bilder et al.<sup>26</sup> previously examined the cognitive consequences and interactions of methylphenidate challenge and antipsychotic treatment in a sample of chronic schizophrenic patients. He identified an “inverse U” relationship between dopaminergic neurotransmission and oral word production, whereby intermediate levels of dopaminergic agonism correlated to maximal word production. In another study, patients infused with methylphenidate at 2 phases—acute onset of schizophrenia and after stabilization—showed an increase in redundancy errors and perseverations in the stabilized phase and increased disorganization in both phases.<sup>27</sup> In contrast to methylphenidate, amphetamines have been shown to

have some reduction in negative symptoms such as apathy and lack of energy in the intermediate term,<sup>28</sup> as well as improvement on the Wisconsin Card Sorting Test in a group of patients previously stabilized during treatment with haloperidol.<sup>29</sup> However, the improvement in negative symptoms is often counteracted by the exacerbation of positive symptoms, such as delusions and hallucinations. In summary, the effectiveness of traditional stimulants in reducing negative symptoms, sedation, and cognitive impairment in schizophrenia is inconclusive at best. These effects cannot be generalized to modafinil, which may work through different physiologic mechanisms.

Despite modafinil's off-label use in schizophrenia patients, there are only a limited number of controlled studies examining its efficacy in treating sedation, negative symptoms, and cognitive deficits, as well as evaluating its tolerability in this population. In this article, we critically review the available data on modafinil's use as an adjuvant treatment in schizophrenia. We focus on the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) guidelines, which aim to systematize and optimize the search for an effective cognitive-enhancing agent by establishing specific standards for future studies.<sup>30</sup> We also review data available on this agent's safety profile, given the theoretical risk of stimulating agents to exacerbate psychosis.

## METHOD

PubMed was searched for trials published in English up to January 2008 studying modafinil's effects on fatigue, negative symptoms, and cognition in schizophrenia patients with a combination of the following terms: *schizophrenia, modafinil, cognition, negative symptoms, and fatigue*. Six trials were identified: 2 randomized, prospective, double-blind placebo-controlled trials; 3 randomized, prospective, double-blind, placebo-controlled crossover trials; and 1 open-label pilot study (Table 1). Case series and case reports were excluded in the data analysis, except to identify potential adverse reactions to modafinil. Studies were examined for number of subjects, length of trial, design, modafinil dosing, and outcomes with a focus on sedation, cognitive functioning, negative symptoms, and adverse effects. Methodological limitations of the studies are discussed.

## RESULTS

### Sedation

Sedation is a common and uncomfortable side effect of many antipsychotic medications. Sedation has been found to be the second most frequently reported adverse event associated with antipsychotic use contributing to negative perceptions, poor outcomes, and medication noncompliance.<sup>37</sup> In the inpatient setting, antipsychotic-induced

**Table 1. Characteristics of the 6 Trials Examining Modafinil as Adjunctive Treatment in Schizophrenia**

Characteristic	Pierre et al 2007 <sup>31</sup>	Sevy et al 2005 <sup>32</sup>	Hunter et al 2006 <sup>33</sup>	Spence et al 2005 <sup>34</sup>	Turner et al 2004 <sup>35</sup>	Rosenthal and Bryant 2004 <sup>36</sup>
Design	Randomized double-blind placebo-controlled trial	Randomized double-blind placebo-controlled trial	Randomized double-blind placebo-controlled crossover trial	Randomized double-blind placebo-controlled crossover trial	Randomized double-blind placebo-controlled crossover trial	Open-label pilot study
Subjects	10 subjects: modafinil, N = 10; placebo, N = 10	13 subjects: modafinil, N = 13; placebo, N = 11	12 males: modafinil, N = 12; placebo, N = 12	17 subjects: modafinil, N = 17; placebo, N = 17	20 subjects: modafinil, N = 20; placebo, N = 20	11 subjects: modafinil, N = 11
Length	8 wk	8 wk	2 sessions, 2 wk apart	2 sessions, 1 wk apart	2 sessions, at least 1 wk apart	4 wk
Dosage	100 mg in first wk; 200 mg in wk 2-8, if tolerated	100 mg in first 2 wk; 200 mg in last 6 wk	100 mg × 1 session	100 mg × 1 session	200 mg	100 mg in days 1-14; increased to 200 mg in days 15-28, if tolerated
Adverse events	Psychosis exacerbation (N = 1 in modafinil group and N = 2 in placebo group), edema (N = 1), tinnitus (N = 1), bitter taste (N = 1)	Psychosis exacerbation (N = 1)	None reported	Psychosis exacerbation (N = 1)	None reported	Hallucinations (N = 2), dry mouth (N = 2)

sedation is associated with diminished participation in therapeutic groups and delayed psychosocial rehabilitation. In the outpatient setting, patients' persistent somnolence and fatigue prevent them from meeting interpersonal and occupational demands. It is therefore important to minimize sedation, which in turn may lead to better compliance with antipsychotic medication and better overall psychosocial functioning.

Four of the 6 aforementioned studies of modafinil as an adjuvant treatment in schizophrenia have examined its effect on antipsychotic-induced sedation and fatigue. In an 8-week double-blind placebo-controlled study including 24 outpatients with DSM-IV diagnosis of schizophrenia or schizoaffective disorder, subjects were randomly assigned to either 200 mg adjunctive modafinil (N = 13) or placebo (N = 11) after being treated with the same dose of antipsychotic medication for at least 1 month prior to randomization.<sup>32</sup> Subjects improved in Fatigue Severity Scale (FSS) scores throughout the trial period, but there was no significant difference between the modafinil and the placebo groups. The investigators suggest that the lack of significant difference between the groups could be due to the placebo group having a higher baseline FSS score ( $50.6 \pm 7.5$ ) than the modafinil group ( $39.7 \pm 4.6$ ), leading to a regression toward the mean and greater improvement in the placebo group. The authors point out that the FSS was administered at random times during the day and not 2 to 4 hours after drug administration, which is the average time for modafinil to achieve its peak plasma concentration and maximal cognitive effect.<sup>38</sup> This methodological issue could have further accounted for the lack of significant difference between the groups. Because of the small number of subjects, the authors were unable to compare the effects of modafinil between patients taking different classes of psychotropic medications. In a more recent randomized placebo-controlled trial, modafinil-treated patients reported greater reductions in mean hours of daytime and nighttime sleep, but this change did not reach statistical significance.<sup>31</sup>

A double-blind, placebo-controlled crossover trial of modafinil 200 mg in 20 patients with schizophrenia also failed to show a significant benefit of modafinil over placebo in the treatment of antipsychotic-induced fatigue.<sup>35</sup> Fatigue was evaluated using a subjective analog scale consisting of 100 mm lines with opposite emotions at each end, which included alert/drowsy, fuzzy/clear-headed, lethargic/energetic, and mentally slow/quick-witted. There were no statistically significant effects of the study drug in any of the subjective measures. The results contrasted with the findings of a similar study by the same group in healthy volunteers, which reported increased alertness and energy in the modafinil group. The authors hypothesized that the lack of difference in the subjective scale reports in the schizophrenic patients could have been due to the patients' lack of insight into

their changing mood, insufficient modafinil dose, and/or short study duration.

The only study to find a significant effect of modafinil on fatigue was a 4-week open-label pilot study with 11 schizophrenia subjects.<sup>36</sup> This study compared the patients' FSS score at baseline with their scores at weeks 1 through 4 after they received up to 200 mg of modafinil. There was a significant change in FSS scores at week 3, which coincided with the increase of the modafinil dose from 100 mg to 200 mg in 7 of the patients. The authors suggest that the lack of change in fatigue at the end of the first 2 weeks could have been due to the low dose, while the lack of change at week 4 could have been due to the emergence of tolerance to the medication. The open-label nature of the study makes it difficult to draw definitive conclusions about the results because the patients' subjective reports of fatigue may have been influenced by their knowing the medication they were taking. Given the methodological issues inherent in the above studies, it is difficult to come to a conclusion about how effective modafinil is in the treatment of antipsychotic-induced sedation on the basis of the current data. From these reports, the effects of modafinil on sedation are inconclusive.

### Negative Symptoms

Negative symptoms of schizophrenia refer to reductions in psychological, emotional, and cognitive functioning. They consist of affective flattening (and consequent loss of facial expression, eye contact, expressive gestures, and/or vocal intonations), alogia (impoverished thinking or speech), and avolition (loss of motivation, diminished drive, and apathy). Negative symptoms are a core feature of schizophrenia, and even though they may overlap with neurocognitive deficits, they are considered as separate components of the illness as per the National Institute of Mental Health–MATRICS consensus statement.<sup>39</sup> The relationship of negative symptoms to neurocognitive deficits in schizophrenia varies depending on the domain of cognitive impairment. Negative symptoms have face validity as treatment targets as they represent loss of normal function. Despite the substantial morbidity associated with negative symptoms, there is no effective treatment for these symptoms as atypical antipsychotics have recently been shown not to be as effective for negative symptoms as initially expected.<sup>40</sup> Since the negative symptoms of schizophrenia may be related to dopaminergic hypofunction in the prefrontal cortex,<sup>41,42</sup> drugs that increase dopaminergic activity should theoretically decrease negative symptoms. Thus, focus has turned to other agents, such as modafinil, in hopes of improved efficacy.

A recent randomized double-blind placebo-controlled trial measured Scale for the Assessment of Negative Symptoms (SANS) scores at baseline and at 8 weeks for patients taking either modafinil (N = 10) or placebo

(N = 10).<sup>31</sup> Both total SANS and SANS subscale scores improved modestly in both groups, but there was no significant difference between groups, which is similar to the results of another 8-week randomized double-blind placebo-controlled trial that also used the SANS to look at the effect of modafinil on negative symptoms.<sup>32</sup> To date, none of the studies examining modafinil's effect on negative symptoms in schizophrenia have yielded statistically significant results.

Given a certain degree of overlap between depressive symptoms and negative symptoms of schizophrenia, the efficacy of modafinil for the treatment of depression is of particular interest. A 6-week placebo-controlled study of 118 patients with major depressive disorder showed short-term but not long-term improvements in fatigue and daytime sleepiness in the modafinil group relative to placebo.<sup>43</sup> In contrast, a multicenter placebo controlled clinical trial evaluating the use of modafinil as an adjunctive therapy for depression in partial selective serotonin reuptake inhibitor responders showed no significant difference in fatigue, sleepiness, or depression, but did show a significant benefit on the Clinical Global Impressions-Improvement (CGI-I) scale. In addition, a 6-week placebo-controlled trial in depressed patients diagnosed with bipolar disorder, showed significantly greater response and remission rates with modafinil augmentation as compared to placebo by week 2 until study endpoint.<sup>44</sup> It appears, then, that modafinil may have a role as an augmentation agent in unipolar and bipolar depression, but no demonstrated effects on negative symptoms in patients with schizophrenia.

### Cognition

Clinical studies have highlighted the importance of cognitive dysfunction as another core psychopathologic feature in schizophrenia, and not simply a consequence of positive and/or negative symptoms or the side effects of antipsychotic medication.<sup>45–47</sup> Cognitive impairment associated with schizophrenia is the main predictor of social, vocational, and health-related functional outcomes.<sup>30,32,37,38</sup> Atypical antipsychotics are not as efficacious in the treatment of cognitive symptoms as previously thought.<sup>48</sup> Despite adequate trials with various atypical antipsychotics, patients continue to show marked cognitive deficits.<sup>49</sup> Since cognitive functions are better indicators of functional outcome in schizophrenia than either positive or negative symptoms, interest has also focused on modafinil's putative utility as a cognitive enhancing agent in this patient population.

Improvements in cognition have been observed in healthy volunteers after taking modafinil at a dose of 100 to 200 mg<sup>19</sup> and in ADHD patients after taking a dose of 200 mg.<sup>20</sup> In an open-label study, schizophrenia patients had a significant increase in their scores on the letter-number sequencing subtest of the Wechsler Adult

Intelligence Scale-Third Edition during treatment with 100 mg to 200 mg of modafinil at week 4 of treatment.<sup>36</sup> In a double-blind randomized placebo-controlled crossover study, Turner et al.<sup>35</sup> found that schizophrenia patients who took modafinil 200 mg 2 hours before cognitive testing performed better in forward and backward trials of the digit span test and in the 3 dimensional attention set shifting task (Intra-Dimensional Extra-Dimensional [IDED]). Specifically, they demonstrated improved completion of the extra-dimensional shift task and made fewer errors in the intra-dimensional reversal stage. Interestingly, no improvement was seen in this task when using the same dose in healthy volunteers<sup>19</sup> and ADHD patients.<sup>20</sup> Schizophrenia patients did not perform better on the stop-signal task during treatment with modafinil 200 mg, while healthy volunteers showed improvement on this task at the same dose, supporting the idea that the drug has different effects depending on the brain's specific neurochemical and functional characteristics. Schizophrenia patients taking modafinil also required fewer attempts to achieve the right answer in the "One-Touch" Tower of London spatial planning task, which consists of planning a sequence of moves to achieve a specific arrangement of colored balls without moving the balls. This difference in performance showed a trend toward significance, which was related to an increase in latency performing the task, which itself was significant. Some of the beneficial effects of modafinil seem to be based on increasing the amount of time that patients take to react to a given task, thereby allowing them to more adequately process all the information needed to meet the task's demands. Taken together, these results suggest that modafinil appears to have some beneficial effects on short-term memory, attention, and the ability to shift mental sets in patients with schizophrenia.

The mechanism for modafinil's putative cognitive enhancing effect is unclear. In a neuroimaging study of brain activation during a working memory task, 10 of 17 patients taking modafinil 100 mg showed increased activation of the anterior cingulate gyrus as compared to patients not taking modafinil.<sup>34</sup> Of the 10 patients with increased activation, only 6 showed improved performance in the working memory task. Six of the original 17 patients showed a decrease in signal in the anterior cingulate cortex associated with modafinil, which in turn was associated with impaired performance. In this study, modafinil was significantly related to an increase in anterior cingulate gyrus activation (10 of 17 patients), but not to an improvement in performance in the working memory task (6 of 10 patients). Of note, the dose of modafinil utilized in this study was only 100 mg, which was less than the 200 mg used in the Pierre et al.,<sup>31</sup> Sevy et al.,<sup>32</sup> and Turner et al.<sup>35</sup> randomized placebo-controlled trials. The heterogeneous response of subjects to modafinil again suggests that modafinil has different effects depending on the brain's unique biological properties, accounting for

improved performance in cognitive tasks in some patients but not others. In another imaging study of schizophrenia patients, modafinil 100 mg increased dorsolateral prefrontal cortex activation during purposeful modulation of motor activity in time (a cognitive task), which correlated with improved task performance in patients whose prefrontal function was impaired at baseline.<sup>33</sup> Modafinil may therefore increase brain activation in brain areas generally thought to be associated with working memory functions.

Despite these promising findings, 3 studies have shown no effect of modafinil on cognition in schizophrenia patients. Sevy et al.,<sup>32</sup> who examined the effects of modafinil 200 mg on attention, working memory, executive functioning, immediate recall, and delayed recall, found no significant differences between the modafinil group and placebo. However, patients in this study were not consistently tested 2–4 hours after receiving the drug, which is the average time for modafinil to achieve its peak plasma concentration and when maximal cognitive effects are expected. In a recent study looking at the use of modafinil 200 mg for the treatment of negative symptoms in schizophrenia, the investigators also examined secondary outcome measures of performance on the California Verbal Learning Test (CVLT), Degraded Stimulus-Continuous Performance Test (DS-CPT), and Trail Making Test B.<sup>31</sup> They found no significant differences between the control and treatment group, although they did find significant clinical global improvement at the study endpoint in the modafinil group. The challenge with interpreting these discrepant results is that the studies focused on different aspects of cognition and only overlapped in their measures of attention and working memory. Four studies evaluated working memory and 3 included attention. In addition, different measures were used when assessing the same areas of cognition, resulting in a lack of outcome measures consistency.

The effect sizes of the effects of modafinil on cognitive functions have ranged from 0.27 (Digit Span backward) to 0.55 for the 3 dimensional attention set shifting task (IDED). This compares favorably to effect sizes found in treatment trials with atypical antipsychotics. The heterogeneity of cognitive measures has been addressed by the MATRICS initiative, which advocates for the consistent use of a well-accepted and validated test battery that covers 5 domains of cognitive deficits commonly found in patients with schizophrenia (Table 2). Thus, future trials examining the effects of modafinil on cognition should use the MATRICS guidelines to achieve consistency and elucidate its specific pattern of cognitive and functional effects.

### Tolerability

Given modafinil's stimulating properties and the theoretical risk of psychosis exacerbation in schizophrenia

Table 2. Cognitive Tests in the MATRICS Battery Compared to Those Used in the Trials of Modafinil as Adjunctive Treatment in Schizophrenia

Cognitive Function	MATRICES	Pierre et al <sup>31</sup>	Sevy et al <sup>32</sup>	Hunter et al <sup>33</sup>	Spence et al <sup>34</sup>	Turner et al <sup>35</sup>	Rosenthal and Bryant <sup>36</sup>
Speed of processing	1. Category fluency 2. BACS symbol-coding 3. Trail Making Test A	Trail Making Test B					
Attention/vigilance	CPT-IP	DS-CPT	1. Vigilance: CPT-IP 2. Concentration: Letter Number Span			IDED	WAIS-III- LNS
Working memory	1. Verbal: University of Maryland- Letter Number Span 2. Nonverbal: WMS-III spatial span		1. Spatial: Occulomotor Delayed Response test 2. Nonverbal: DelayedMatch to Sample Task		"The 2-back" standard working memory task	1. SWM task 2. SSP task 3. NTOL	WAIS-III- LNS
Verbal learning	HVLT-Revised	CVLT					
Visual learning	BVMT-Revised						
Reasoning and problem solving	NAB-mazes						
Social cognition	MSCEIT-managing emotions						
Executive functioning				SAINT task		COWAT	

Abbreviations: BACS = Brief Assessment of Cognition; BVMT = Brief Visuospatial Memory Test; COWAT = Controlled Oral Word Association Test; CPT-IP = Continuous Performance Test, Identical Pairs version; CVLT = California Verbal Learning Test; DS-CPT = Degraded Stimulus-Continuous Performance Test; HVLT = Hopkins Verbal Learning Test; IDED = Intra-Dimensional/Extra-Dimensional; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; NAB = Neuropsychological Assessment Battery; NTOL = "One-Touch" Tower of London spatial planning task; SAINT = Sheffield Activity IN Time; SSP = Spatial Span; SWM = Spatial Working Memory; WAIS-III-LNS = Wechsler Adult Intelligence Scale, Third Edition-letter number sequencing subtest; WMS-III = Wechsler Memory Test III.

patients, it is important to evaluate the incidence of adverse events in this patient population. In 4 of the 6 studies reviewed, there were reports of psychosis exacerbation in 1 or more of the subjects. In the Sevy et al.<sup>32</sup> trial, 1 patient had worsening psychosis and hallucinations during the first week of treatment with modafinil 100 mg. In the Pierre et al.<sup>31</sup> trial, 3 patients had psychotic exacerbations, 2 of whom were in the placebo group and 1 of whom was in the modafinil group (at an unspecified dose between 100 and 200 mg), leading to their discontinuation. In the Rosenthal and Bryant study,<sup>36</sup> 1 patient taking modafinil 100 mg left the open-label trial because of worsening of auditory hallucinations that progressed from moderate to severe. The investigators attributed the exacerbation of hallucinations to inadequate antipsychotic treatment, but the contribution of modafinil cannot be ruled out. Another patient in this study also reported worsening hallucinations but did not leave the study. In the neuroimaging trial by Spence et al.<sup>34</sup> 1 patient who received modafinil 100 mg left the study 4 days after the first scanning session because of an acute psychosis exacerbation. In the same study, 3 of the starting 24 subjects dropped out during the first 2 weeks due to loss of contact (N = 1, modafinil group), incarceration (N = 1, modafinil

group) and choice of another treatment (N = 1, placebo group). In the 6 studies cited in this review, 5 of the 83 patients (6.0%) in the modafinil groups reported psychotic exacerbations as compared to 2 of the 70 patients (2.9%) in the placebo groups, suggesting that modafinil may indeed exacerbate psychosis in select patients.

Individual case studies were reviewed to identify documented reports of adverse events following the use of modafinil. During premarketing trials conducted by the manufacturer of modafinil, there was 1 reported case of a healthy male volunteer developing psychotic symptoms after taking multiple doses of modafinil 600 mg.<sup>50</sup> Mariani and Hart<sup>51</sup> describe one incident of modafinil precipitating psychosis in a patient with no known history of psychiatric disorders in the setting of sleep disruptions meant to simulate shift-work schedules. The authors noted that the risk of modafinil precipitating psychosis may be increased in individuals who are subjected to sleep disruptions and stress such as that caused by abrupt changes in work schedules.<sup>51</sup> Narendran et al.<sup>52</sup> described a case of exacerbated psychosis in a patient with undifferentiated schizophrenia who was treated with modafinil for clozapine-related sedation. This case led the authors to speculate that modafinil's mechanism of inhibiting

GABA release may exacerbate the already-depressed GABAergic inhibition associated with N-methyl-D-aspartate glutamate receptor hypofunction in schizophrenia. Modafinil has also been implicated in the induction of mania.<sup>53–55</sup> Given the small number of subjects in these reports and the fact that the greater majority of patients tolerated modafinil well, studies with larger sample sizes are needed to further elucidate modafinil's tolerability and adverse effect profile.

## CONCLUSION

Systematic reviews aim to summarize large amounts of information in a critical and transparent manner. Synthesizing data using meta-analytic techniques increases power to identify differences in effects, and combining data from several studies increases the accuracy of estimates. Because of the limitations discussed above, in particular the difference in outcome measures between the studies, no meta-analyses could be performed and the results from each study stand alone.

One of the 4 reviewed studies found a significant effect of modafinil as an alerting agent for antipsychotic-induced fatigue and sedation. Neither of the 2 reviewed studies found modafinil to improve negative symptoms of schizophrenia. Three of the 6 reviewed studies showed that modafinil may have some clinically-relevant effects in improving short-term memory, attention, and the ability to shift mental sets. Two neuroimaging studies identified functional changes in areas associated with working memory functions. The main adverse effect was found to be a small risk of psychosis exacerbation, which was seen in 5 of 83 patients (6.0%) in the active treatment groups as compared to 2 of 70 patients (2.9%) in the placebo groups.

Methodological limitations of the 6 studies reviewed here include small sample sizes, differences in subjects (one group may have been more impaired than the other, as was the case in the Turner et al.<sup>35</sup> study), short trial duration (the longest studies were 8 weeks long), variable dosing between trials, lack of accounting for effects of other medications on modafinil efficacy, and the use of different outcome measures, particularly with respect to cognition. The only trial to show efficacy in the treatment of antipsychotic-induced sedation was the open-label trial by Bryant and Rosenthal.<sup>36</sup> The open-label nature of the study makes it difficult to draw definitive conclusions about the results. In the Sevy et al.<sup>32</sup> trial, which showed no significant improvements in fatigue with modafinil relative to placebo, the authors suggested that the timing of the test relative to dose or the duration of modafinil action may have been responsible for the negative result. This may indeed be the case, but if improvements in cognition or sedation are only seen at peak drug levels, modafinil's effects on these measures may be short lived

and therefore not clinically meaningful. Rosenthal and Bryant,<sup>36</sup> whose study showed fatigue reduction with modafinil (relative to placebo) at 3 hours but not at 2 hours or 4 hours, suggest that the lack of improvement in fatigue at the end of the first 2 weeks may have been due to the low dose (100 mg vs. 200 mg), while the lack of change at week 4 may have been due to the emergence of tolerance to the medication. These findings again bring the clinical utility of modafinil into question. If effects of modafinil are only seen at peak drug levels or before tolerance develops, they will not be useful to patients in the longer term.

Since this review focuses on modafinil's adjunctive efficacy in schizophrenia treatment, it would be important to know how modafinil interacts with different types of antipsychotics. This information was not available in some of the reports, and, when available, the numbers were too small (active groups ranged from 10 to a maximum of 20 subjects) to conduct a meaningful statistical analysis. It would be equally important to review the subjects' polypharmacy regimens of non-antipsychotic medications that could further cause sedation or cognitive dulling (e.g., benzodiazepines, anticholinergics). This information would enable us to discern the extent to which modafinil's effect is attributable to the drug itself or the confounding effects of drug cocktails of variable sedative potency.

While the available data suggest good tolerability and a possible effect on sedation and cognitive domains, the small sample sizes and methodological limitations make it difficult to draw conclusions about the overall effectiveness of modafinil as an adjunct in the treatment of schizophrenia. To date, there are only a few controlled, double-blind trials examining the use of modafinil as an adjunctive treatment for antipsychotic-induced sedation/fatigue, negative symptoms, and cognitive dysfunction in schizophrenia patients. The study of modafinil as an adjunctive treatment for cognitive deficits in schizophrenia would benefit from using the MATRICS guidelines to achieve more consistency in methodology and in outcome measures. Such a clinical trial is presently underway.<sup>56</sup> Until the results of these studies are available, clinicians should carefully evaluate the benefits and risks of using modafinil for sedation and cognitive dysfunction in schizophrenia and closely monitor patients who are treated with this compound.

**Drug names:** clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), methylphenidate (Concerta, Ritalin, and others), modafinil (Provigil).

## REFERENCES

1. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006 Apr;67(4):554–566
2. Madras BK, Xie Z, Lin Z. Modafinil occupies dopamine and norepine-

- ephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *J Pharmacol Exp Ther* 2006;319:561–569
3. Scammell T, Estabrooke I, McCarthy M. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* 2000; 20:8620–8628
  4. Lin JS, Hou Y, Jouvett M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. *Proc Natl Acad Sci U S A* 1996;93:14128–14133
  5. Saletu B, Frey R, Krupka M, et al. Differential effects of a new central adrenergic agonist—modafinil—and d-amphetamine on sleep and early morning behaviour in young healthy volunteers. *Int J Clin Pharmacol Res* 1989;9:183–195
  6. Perez de la Mora M, Aguilar-Garcia A, Ramon-Frias T. Effects of the vigilance-promoting drug modafinil on the synthesis of GABA and glutamate on slices of rat hypothalamus. *Neurosci Lett* 1999;259:181–185
  7. Ferraro L, Tanganelli S, O'Connor WT, et al. The vigilance-promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local GABAergic mechanism. *Eur J Pharmacol* 1996;306:33–39
  8. Li Y, Gao XB, Sakurai T, et al. Hypocretin/orexin excites hypocretin neurons via a local glutamate neuron: a potential mechanism for orchestrating the hypothalamic arousal system. *Neuron* 2002;36:1169–1181
  9. Ko EM, Estabrooke IV, McCarthy M, et al. Wake-related activity of tuberomammillary neurons in rats. *Brain Res* 2003;992:220–226
  10. Makela EH, Miller K, Cutlip WD 2nd. Three case reports of modafinil use in treating sedation induced by antipsychotic medications [letter]. *J Clin Psychiatry* 2003 Apr;64(4):485–486
  11. Rammohan KW, Rosenberg JH, Lynn DJ, et al. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* 2002;72: 179–183
  12. Damian MS, Gerlach A, Schmidt F, et al. Modafinil for excessive daytime sleepiness in myotonic dystrophy. *Neurology* 2001;56:794–796
  13. Teitelman E. Off-label uses of modafinil. *Am J Psychiatry* 2001 Aug;158(8):1341
  14. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry* 2000 May;61(5):378–381
  15. Shearer J. The principles of agonist pharmacotherapy for psychostimulant dependence. *Drug Alcohol Rev* 2008 May;27(3):301–308
  16. Dackis C. New treatments for cocaine abuse. *Drug Discov Today Ther Strategies* 2005;2:79–86
  17. Robertson P, Hellriegel E. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet* 2003;42:123–137
  18. Ballas C, Kim D, Baldassano C, et al. Modafinil: past, present and future. *Exp Opin Neurother* 2002;2:449–457
  19. Turner D, Robbins T, Clark L, et al. Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology* 2003;165:260–269
  20. Myrick H, Malcolm R, Taylor B, et al. Modafinil: preclinical, clinical, and post-marketing surveillance—a review of abuse liability issues. *Ann Clin Psychiatry* 2004;16:101–109
  21. Stoops W, Lile J, Fillmore M, et al. Reinforcing effects of modafinil: influence of dose and behavioural demands following drug administration. *Psychopharmacology* 2005;182:186–193
  22. Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology* 1987;91:415–433
  23. Lieberman JL, Kane JM, Gadaleta D, et al. Methylphenidate challenge as a predictor of relapse in schizophrenia. *Am J Psychiatry* 1984;141: 633–638
  24. Korean AR, Lieberman JA, Alvir J, et al. The behavioral effect of m-chlorophenylpiperazine (mCPP) and methylphenidate in first-episode schizophrenia and normal controls. *Neuropsychopharmacology* 1997 Jan;16(1):61–68
  25. Carpenter MD, Winsberg BG, Camus LA. Methylphenidate augmentation therapy in schizophrenia. *J Clin Psychopharmacol* 1992 Aug;12(4): 273–275
  26. Bilder RM, Lieberman JA, Kim Y, et al. Methylphenidate and neuroleptic effects on oral word production in schizophrenia. *Neuropsychiatry Neuropsychol Behav Neurol* 1992;5:262–271
  27. Szeszko PR, Bilder RM, Dunlop JA, et al. Longitudinal assessment of methylphenidate effects on oral word production and symptoms in first-episode schizophrenia at acute and stabilized phases. *Biol Psychiatry* 1999 Mar;45(6):680–686
  28. Sanfilippo M, Wolkin A, Angrist B, et al. Amphetamine and negative symptoms of schizophrenia. *Psychopharmacology* 1996;123(2):211–214
  29. Goldberg TE, Bigelow LB, Weinberger DR, et al. Cognitive and behavioral effects of the coadministration of dextroamphetamine and haloperidol in schizophrenia. *Am J of Psychiatry* 1991 Jan;148(1):78–84
  30. Green MF, Nuechterlein KH, Kern RS, et al. Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS Psychometric and Standardization Study. *Am J Psychiatry* 2008 Feb;165(2):221–228
  31. Pierre JM, Pelioian JH, Wirshing DA, et al. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry* 2007 May;68(5):705–710
  32. Sevy S, Rosenthal MH, Alvir J, et al. Double-blind, placebo-controlled study of modafinil for fatigue and cognition in schizophrenic patients treated with psychotropic medications. *J Clin Psychiatry* 2005 Jul;66(7):839–843
  33. Hunter MD, Ganesan V, Wilkinson ID, et al. Impact of modafinil on prefrontal executive function in schizophrenia. *Am J Psychiatry* 2006 Dec;163(12):2184–2186
  34. Spence SA, Green RD, Wilkinson ID, et al. Modafinil modulates anterior cingulate function in chronic schizophrenia. *Br J Psychiatry* 2005;187:55–61
  35. Turner DC, Clark L, Pomarol-Clotet E, et al. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. *Neuropsychopharmacology* 2004;29:1363–1373
  36. Rosenthal MH, Bryant SL. Benefits of adjunct modafinil in an open-label, pilot study in patients with schizophrenia. *Clin Neuropharmacol* 2004;27(1):38–43
  37. Hofer A, Kemmler G, Eder U, et al. Attitudes toward antipsychotics among outpatient clinical attendees with schizophrenia. *J Clin Psychiatry* 2002 Jan;63(1):49–53
  38. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. *Prim Care Companion J Clin Psychiatry* 2004;6(suppl 2):3–7
  39. Kirkpatrick B, Fenton WS, Carpenter WT, et al. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr Bull* 2006;32(2): 214–219
  40. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. *Schizophr Res* 1999 Jan;35(1):51–68
  41. Stone JM, Morrison PD, Pillowsky LS. Glutamate and dopamine dysregulation in schizophrenia: a synthesis and selective review. *J Psychopharmacol* 2007;21(2):440–452
  42. Davis KL, Kahn RS, Ko G, et al. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry* 1991;148:1474–1486
  43. DeBattista C, Dohramji K, Menza MA, et al. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. *J Clin Psychiatry* 2003 Sep;64(9):1057–1064
  44. Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 2007;164:1242–1249
  45. Sharma T, Antonova L. Cognitive function in schizophrenia: deficits, functional consequences, and future treatment. *Psychiatr Clin North Am* 2003 Mar;26(1):25–40
  46. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996;153:321–330
  47. Matza LS, Buchanan R, Purdon S, et al. Measuring changes in functional status among patients with schizophrenia: the link with cognitive impairment. *Schizophr Bull* 2006;32(4):666–678
  48. Keefe RSE, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Arch Gen Psychiatry* 2007;64:633–647
  49. Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry* 2001;158:176–184
  50. Provigil (modafinil). Physicians' Desk Reference. 56th ed. Montvale, NJ: Medical Economics; 2002:1193–1196
  51. Mariani JJ, Hart CL. Psychosis associated with modafinil and shift work [letter]. *Am J Psychiatry* 2005 Oct;162(10):1983
  52. Narendran R, Young CM, Valenti AM, et al. Is psychosis exacerbated

- by modafinil? [letter] Arch Gen Psychiatry 2002;59:292–293
53. Ranjan S, Chandra PS. Modafinil-induced irritability and aggression: a report of 2 bipolar patients [letter]. J Clin Psychopharmacol 2005;25:628–629
54. Wolf J, Fiedler U, Angheliescu I, et al. Manic switch in a patient with treatment-resistant bipolar depression treated with modafinil [letter]. J Clin Psychiatry 2006 Nov;67(11):1817
55. Vorspan F, Warot D, Sonsoli A, et al. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry 2005;162:813–814
56. Study to evaluate the efficacy and safety of armodafinil as adjunctive

therapy in adults with cognitive deficits associated with schizophrenia. ClinicalTrials.gov identifier: NCT00487942 Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00487942?term=NCT00487942&rank=1>. Accessibility verified Aug 15, 2008

*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Marlene Freeman, M.D., at [mfreeman@psychiatrist.com](mailto:mfreeman@psychiatrist.com).