A Randomized, Double-Blind, Crossover Trial of Modafinil on Mood

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Abstract: Modafinil, a medication for the excessive sleepiness associated with narcolepsy, has been hypothesized to improve not just alertness but mood as well. The purpose of this study was to determine how treatment with modafinil affects mood in healthy volunteers. Normal healthy volunteers (n = 12, 10 men and 2 women; 30–44 years) underwent a 3-day, counterbalanced, randomized, crossover, inpatient trial of modafinil (400 mg daily) versus placebo with 4-day washout period between 2 treatments. Mood was assessed daily using both the Positive and Negative Affect Schedule and a general mood scale, which consisted of 10 bipolar adjective ratings based on a severity scale ranging from 1 to 10. Modafinil increased general mood and Negative Affect scales relative to placebo and had a significant effect on Positive Affect scales. These results suggest that modafinil may have general mood-elevating effects accompanied by increased negative affect (anxiety). The findings may have implications for clinical practice, in particular for the adjunctive use of modafinil in treatment-resistant depression.

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Modafinil is an agent that promotes wakefulness and is approved by the Food and Drug Administration broadly for treatment of narcolepsy.[1] Originally, it was considered to increase alertness by a mechanism that was dissimilar to stimulants.[2,3] However, it is now considered to have certain properties similar to stimulants such as amphetamines.[4] Earlier observations suggest the use of modafinil in improving fatigue, mood, cognitive functioning, and health-related quality of life in patients with narcolepsy[5] and healthy controls.[6] It has also been proposed that modafinil may be a useful adjunct in the treatment of major depression[7,8] and attention-deficit hyperactivity disorder[9] possibly by improving fatigue and cognitive impairment.

Positive and negative affects (PA and NA, respectively) are relatively independent dispositional dimensions of mood. High PA reflects a heightened level of pleasurable engagement with the world, whereas low PA is consistent with depressed mood and anhedonia.[10,11] Elevations in NA, on the other hand, reflect increased subjective distress and unpleasurable engagement, as would be described by adjectives such as "nervous," "jittery," and "irritable;" low NA is characterized by an absence of distress. Negative affect is a common factor, which underlies disorders such as major depression and generalized anxiety disorder.[11] To our knowledge, there are no studies examining the effects of modafinil on PA and NA in healthy subjects.

Proposed advantages to modafinil over other stimulants include a relative lack of side effects such as agitation and anxiety, which are facets of NA.[4] For instance, Becker and colleagues used the Profile of Mood States to assess the impact of modafinil for 6 weeks on tension-anxiety and anger-hostility (components of high NA) and depression-dejection (akin to low PA) in patients with narcolepsy. They found nonsignificant improvements in the NA and depression subscales and concluded that there were no adverse effects of modafinil on mood.[4] However, another study using the Profile of Mood States in patients with myotonic dystrophy concluded that modafinil significantly increased the tension-anxiety factor while improving other aspects of mood.[3] Clouding the picture further, Randall et al[6] concluded that, compared with placebo, modafinil increased physiological symptoms of anxiety, but subjective negative affective states were not impacted except under challenge conditions. Thus, the specific impact of modafinil on PA and NA is unclear. We undertook this study to look into the effects of modafinil on overall mood and individual components of mood in healthy volunteers. In addition, the overarching study evaluated a number of aspects of modafinil on autonomic nervous system.[12] The mood ratings was specifically added to address the effects of modafinil on mood and is a separate study, although the 2 studies were done in parallel. We performed a randomized, double-blind, crossover study of single oral dose of modafinil in hospitalized normal subjects.

MATERIAL AND METHODS

The study was reviewed and approved by the Vanderbilt University Institutional Review Board. Written informed consent was obtained from all participants. Participants were screened by clinical interview, physical examination, and laboratory testing (hematocrit, chemistry, and liver function tests, pregnancy test for women, urinalysis). All were free of significant medical or psychiatric disorder or treatment with any psychotropic drugs.

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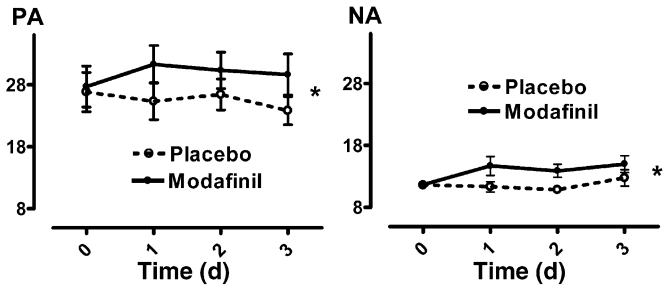

FIGURE 1. Modafinil increases PA and NA. The PA increased significantly with modafinil as compared with placebo (P drug = 0.021). There was no significant time and order affect. The NA increased significantly with modafinil as compared with placebo (P drug = 0.021). Positive and negative affect scores were calculated, the mean PA and NA, respectively, during the 3 days of single oral daily dose of modafinil or placebo (n = 12). *$P < 0.05$, group mean differences (repeated-measures test).

Fluctuations in dietary sodium and potassium affect renal dopamine and mood;[13] so at least 3 days before the study, subjects consumed a diet containing 150 mEq sodium/70 mEq potassium in the Vanderbilt General Clinical Research Center. The subjects were nonsmokers and their diets were free of caffeine-containing beverages. The study subjects were randomly given placebo or modafinil (400 mg once daily orally) for 3 days. All, then, were crossed over to the other drug (modafinil or placebo) after a drug washout period of 4 days. Given that the half-life of modafinil is 12 to 15 hours,[14] this washout period (>5 half-lives) should have minimized any risk of carryover effects. Subjects were studied as inpatients to minimize the variations in mood due to change in environment and diet.

Assessment of Mood

Subjective mood during the previous 24 hours was assessed daily at 8 PM using the Positive and Negative Affect Schedule (PANAS)[10] and a general mood scale. The PANAS is a commonly used, 20-item, self-report scale consisting of adjectives describing mood comprising 2-factor dimensions incorporating arousal (high and low) and valence (positive vs. negative). These largely independent factor dimensions have been shown to be both reliable and valid.[10,11] Positive affect is composed of ratings on 10 adjectives such as "interested," "excited," "enthusiastic," and "alert." Negative affect is also composed of ratings on 10 adjectives, including "hostile," afraid," "jittery," and "nervous." Each item is scored from 1, "I have felt this way very slightly or not at all," to 5, "I have felt this way extremely." Participants were asked to rate their mood during the previous 24 hours. PA and NA were averaged during the 3 days of each condition and compared with the ratings at baseline.

In addition, a general mood scale was used to evaluate overall mood. Participants were asked to make ratings on 10 bipolar adjectives based on a scale ranging from 1 to 10. Adjective pairs included depressed-elated, calm-tense, tired-energetic, withdrawn-sociable, muddled-clearheaded, easily distracted–able to concentrate, relaxed-restless, drowsy-overalert, slow–quick-witted, and bored-interested. Scores were rated in a bipolar fashion within item (ie, 1 = depressed, 10 = elated). The higher value of score indicated higher score

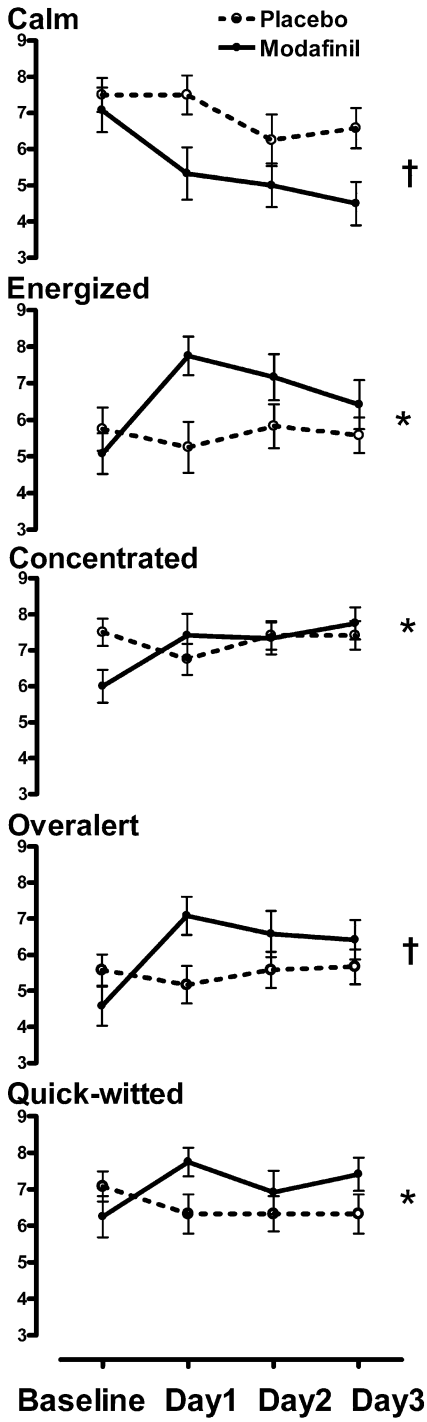

FIGURE 2. Modafinil affects general mood. All the values are represented as mean ± SE. Modafinil, as compared with placebo, decreased the general mood scores on calm and increased the scores on energized, concentrated, over-alert, and quick-witted. *$P < 0.05$ and †$P < 0.01$, group mean differences (repeated-measures test).

TABLE 1. Modafinil Increased General Mood and Had No Order Affect

Variable	*P* Drug Placebo vs. Modafinil	*P* Time (d)	*P* Drug × Time	*P* Order of Randomization
Calm (decrease)	0.008*	0.007*	0.385	0.555
Energized	0.199	0.044†	0.030†	0.991
Quick-witted	0.070	0.723	0.029†	0.374
Over-alert	0.298	0.117	0.005*	0.427
Concentrated	0.621	0.243	0.016†	0.118
Elated	0.650	0.864	0.752	0.151
Sociable	0.888	0.987	0.174	0.268
Clearheaded	0.140	0.934	0.158	0.205
Relaxed	0.381	0.068	0.685	0.111
Interested	0.321	0.606	0.145	0.329

Results analyzed by repeated-measures analysis of variance.
*$P < 0.01$.
†$P < 0.05$.

on the second adjective of the adjective pairs (ie, elated, tense, energetic… interested). The scores were reverse scaled for calm-tense and relaxed-restless, so that all positive valence adjectives were at one end of the questionnaire. The scores from each these 10 adjective pairs were averaged for 12 subjects to create the total general mood scale score and compared during the 3-day treatment periods. The use of daily diary methods (ie, rating scales completed once a day by participants) has demonstrated utility in pharmacological research and is commonly used to assess mood over time.[15,16] The measure was internally consistent (coefficient $\alpha = 0.90$ for baseline assessment).

Statistical Analysis

All analyses were conducted using the SPSS for Windows Version 11 statistical package (SPSS, Inc, Chicago, Ill). Mood responses in placebo and modafinil conditions were compared using paired sample *t* tests. Daily mood scores were averaged; change in overall mood (general mood scale), PA, and NA as compared with the reference day (day 0) and comparison between placebo and modafinil treatment phases were the outcome variables. We used a general linear model repeated-measures analysis of variance to assess change in mood scores associated with treatment (modafinil vs. placebo) across the 4 days of the study. The carryover effect was assessed by including a variable for order (placebo first vs. modafinil first) in the model. A 2-tailed probability value of $P < 0.05$ was chosen as the criterion for statistical significance. All means are presented as mean ± SE. The sample size of 8 subjects was estimated to have a power of 0.88 to reject the null hypothesis with an effect size equivalent to 1 SD.

RESULTS

Twelve healthy adult subjects (10 men, composed of 8 whites, 1 hispanic, and 1 black, and 2 women, composed of 1 white and 1 hispanic), averaging 30 ± 2.5 years, participated in the study. Their body mass index was 27 ± 1.3 kg/m^2. We observed an increase in PA following modafinil as compared with placebo (Fig. 1, $P = 0.021$). NA also increased following modafinil as compared with placebo (Fig. 1, $P = 0.021$).

Comparing the adjectives on the general mood scale individually, on a total score of 1 to 10, subjects had a higher score on the adjectives "energized," "overalert," "concentrated," "quick-witted," and lesser score on the adjective "calm" following modafinil as compared with the placebo treatment period (Fig. 2). There was no significant time and order affect (Table 1).

DISCUSSION

This study showed that modafinil elevates both PA and NA as measured by the general mood scale and the PANAS in healthy volunteers. This is important both for theoretical and practical reasons. Our finding of elevated arousal and NA with modafinil is consistent with a previous report of increased subjective anxiety and aggression following modafinil administration,[6,17] although it is in contrast to claims that modafinil does not elevate negative mood states.[4] Earlier research by our group found that modafinil heightens apparent sympathetic outflow increasing heart rate, systolic blood pressure, catecholamines but decreases muscle sympathetic nerve activity[18] and does not cause analgesia.[19] It is possible that the energizing effect of modafinil may be experienced as negative by some individuals who interpret elevated sympathetic activity as signs of anxious arousal. The effects we saw are similar to those produced by the classical stimulants such as amphetamine[20] and methylphenidate.[21] Together, these data suggest that the effects on mood may be mediated via mechanisms that are similar to the stimulants.

Considering dopamine's role in mood regulation,[22] this is the first study in which we studied positive and negative affective components of mood in controlled environment. The exact mechanism of its action is unknown, although it is thought to produce arousal by indirectly decreasing γ-aminobutyric acid levels via serotonergic, adrenergic, and glutamaminergic systems.[23,24] It has also been suggested to act through histaminergic neurons and increase the dopamine level in the nucleus accumbens through the inhibition of GABA release.[25]

This study is limited by several factors, including the small sample size. Because only normal volunteers were included, different results might be expected with other samples, including persons with depression or narcolepsy. Finally, the treatment periods were brief; future studies should evaluate the longer-term effects of modafinil on mood. These findings may have implications for clinical practice with regard to the use of modafinil for the treatment of narcolepsy, depression, and attention-deficit hyperactivity disorder.

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