Psychosis Associated With Modafinil and Shift Work

TO THE EDITOR: Modafinil is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and sleep disorders associated with shift work. It is chemically and pharmacologically distinct from other psychostimulants.

Ms. A was a 38-year-old research volunteer who developed mood and psychotic symptoms while taking modafinil as part of a double-blind inpatient laboratory study that was approved by an institutional review board. The purpose of the 23-day study was to examine the effects of modafinil on sleep, cognitive performance, and mood during simulated shift work. Ms. A received a single oral dose of modafinil (0 mg, 200 mg, or 400 mg) 1 hour after waking in 3-day blocks, and each dosing condition was separated by a day during which placebo was administered. Ms. A was studied under two shift conditions: day and night. The shifts alternated three times during the study.

Ms. A had no known history of any psychiatric disorder, and a medical and psychiatric evaluation produced unremarkable results. She was without complaints until day 19 of the study, when she reported anxiety about her family's well-being. It should be noted that Ms. A had received modafinil (400 mg) on days 17–19; her sleep was progressively disrupted over this period. On day 20, Ms. A began to focus increasingly on her children's well-being and expressed guilt about being an inadequate parent.

On day 21, she became markedly disorganized and was internally preoccupied, mumbling prayers and gesturing in a bizarre manner. She did not respond coherently to questioning and was transferred to the psychiatric emergency service. Her psychotic symptoms resolved spontaneously over 24 hours, and she was discharged. Over the next 2 days, she became increasingly depressed and was admitted to a psychiatric hospital. She was treated with risperidone and paroxetine and was discharged after 1 week.

The history and clinical course of this patient suggest that the study procedures, i.e., sleep-cycle manipulations in combination with modafinil, likely precipitated her mood and psychotic symptoms. The patient's family confirmed that she had no history of any psychiatric disorder, and there was no known family history of psychiatric disorders. Although we found no published reports of modafinil causing psychosis in individuals without a psychiatric illness, there is one published case report of modafinil worsening psychotic symptoms in a patient with schizophrenia receiving clozapine (1). The prescribing information for modafinil (2) notes, "There have been reports of psychotic episodes associated with Provigil use" and describes the case of a healthy normal volunteer who developed psychosis after multiple daily doses of 600 mg and sleep deprivation, which resolved 36 hours after discontinuation of the drug. Although the potential risk of modafinil precipitating psychosis in patients with no known psychiatric history is low, clinicians should be aware that the risk may increase when individuals are subjected to sleep disruptions and stress such as that caused by abrupt changes in work schedules.

References

1. Narendran R, Young CM, Valenti AM, Nickolova MK, Pristach CA: Is psychosis exacerbated by modafinil? Arch Gen Psychiatry 2002; 59:292–293
2. Package insert for Provigil. Cephalon Inc., West Chester, Pa

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A Case of Premature Ventricular Contractions With Modafinil

TO THE EDITOR: Modafinil's package insert cautions about using modafinil in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. No mention is made of premature ventricular contractions (PVCs), also called ventricular ectopic beats, in patients without heart disease. Also, a search of the literature did not reveal any citations about PVCs and modafinil. No treatment-emergent pattern of ECG abnormalities was found in placebo-controlled clinical trials after administration of modafinil, according to its package insert.

Written communication with Cephalon Inc. also revealed the following. First, in open-label studies for up to 52 weeks, no adverse cardiac effects were noted. Second, the nature of postmarketing cardiovascular-related events with modafinil has been similar to those observed during the clinical trials. Third, a post hoc analysis of data from seven studies demonstrated that modafinil did not produce clinically relevant changes in ECG intervals and had no adverse effect on cardiac repolarization in any of the studies evaluated.

Mr. A, a 54-year-old Caucasian man in very good health, was administered modafinil, 100 mg every morning, which was soon increased to 200 mg in the morning and then 100 mg b.i.d. to combat fatigue and lack of concentration. Mr. A was not taking any medications; was free of alcohol, tobacco, and substance use; and consumed little caffeine. Modafinil worked rather well for him in that regard, but after 2.5 months, he developed PVCs, which he felt as a sinking feeling in his chest and associated skipped beats when his pulse was taken. No other symptoms, such as dizziness, sweating, chest pain, and shortness of breath, were present. Mr. A was very conscious of the PVCs and disturbed after experiencing them. The results of a physical examination were normal, and a 24-hour Holter monitor showed 1,695 PVCs.

Mr. A's diagnosis was unifocal PVCs and a normal sinus rhythm with symptoms. Modafinil was discontinued, but it took 20 days for the PVCs to remit. After a PVC-free interval of a week, Mr. A was rechallenged with the same dose of modafinil. The PVCs returned after only 10 days of taking modafinil. It was again discontinued, and the PVCs subsided in a matter of 2 weeks. Mr. A has been PVC-free since (more than 1 year).

The exact mechanism of action for modafinil is not known. Modafinil has wake-promoting actions, such as sympathomimetic agents, including amphetamine and methylphenidate, but the pharmacological profile is not identical. Modafinil has been reported to be associated with a positive effect in atten-