Published in final edited form as:

Am J Alzheimers Dis Other Demen. 2012 November ; 27(7): 468–473. doi:10.1177/1533317512456450.

Agitation and psychosis associated with dementia with Lewy bodies exacerbated by modafinil use

Eduardo Prado, MD¹, Pongsatorn Paholpak, MD², Myha Ngo³, Verna Porter, MD⁴, Liana Apostolova, MD, MS^{3,4}, Rogério Marrocos, MD⁵, and John M. Ringman, MD, MS^{3,4}

¹Department of Psychiatry, State University of Londrina, Brazil ²Department of Psychiatry, Srinagarind Hospital, Khon Kaen University, Thailand ³Mary S. Easton Center for Alzheimer's Disease Research at UCLA, Los Angeles, CA, USA ⁴Department of Neurology, UCLA, Los Angeles, CA, USA ⁵Department of Neuropsychiatry, Federal University of Rio de Janeiro State, Rio de Janeiro, Brazil

Abstract

Dementia with Lewy bodies (DLB) is commonly associated with excessive daytime somnolence (EDS). Modafinil is a wakefulness-promoting agent that is considered to have limited interaction with the dopaminergic system. As individuals with DLB are predisposed to psychotic symptoms which might be exacerbated by dopaminergic stimulation, modafinil is considered to be an attractive option for the treatment of EDS in DLB. We describe two cases in which administration of modafinil exacerbated agitation and hallucinations in DLB, and we also review data that may explain the mechanisms underlying this effect. In both cases, psychotic symptoms emerged concomitantly with modafinil administration, and remitted following its discontinuation. Although definitive data regarding the benefits and adverse effects of modafinil for the treatment of EDS in DLB await controlled prospective randomized studies, our observations warrant caution regarding its use in this context.

Keywords

modafinil; dementia with Lewy bodies; excessive daytime somnolence; psychosis; agitation

Introduction

Dementia with Lewy bodies, or DLB, is the second most common cause of neurodegenerative dementia¹. In addition to parkinsonism and visual hallucinations, marked fluctuations in cognition and arousal characterize DLB. REM behavior disorder (RBD) and excessive daytime somnolence (EDS) are among the alterations in arousal that occur in DLB. EDS is also common in Parkinson's disease (PD), and various medications have been

Corresponding Author: Eduardo Prado, M.D. Department of Psychiatry, State University of Londrina, Brazil, eduardostp@hotmail.com.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

tried for its treatment. Traditional psychostimulants can be effective, but they can also precipitate hallucinations and other psychotic symptoms, likely due to their dopaminergic effects².

Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide) is a wakefulness- promoting agent that is currently approved by the United States Food and Drug Administration to treat EDS in association with narcolepsy, shift work sleep disorder, and obstructive sleep apnea/hypopnea syndrome³. Modafinil may also be efficacious for a variety of off-label indications, including treatment-resistant depression, attention-deficit/hyperactivity disorder, and schizophrenia. Another emerging target for modafinil is cognitive dysfunction, as evidence has indicated that it can improve working memory, episodic memory, and processes requiring cognitive control⁴. Modafinil has also been used for EDS in PD because it is thought to have limited interaction with the dopaminergic system and therefore reduced risk of exacerbation of behavioral symptoms. Because individuals with DLB are also predisposed to psychotic symptoms, modafinil is an attractive option for EDS in DLB as well⁵. In an open-label study, 5 of 8 patients with various forms of dementia showed improvement in EDS symptoms at doses of 100 to 200 mg per day of modafinil⁶. The effect of modafinil for the treatment of sleep disturbance in DLB has not, to our knowledge, been documented. In this report, we describe two cases that suggest the administration of modafinil may exacerbate agitation and hallucinations in DLB, and we review data that may explain the mechanisms underlying this effect.

Case Reports

Case 1

The first subject was an 80-year-old Caucasian male with 12 years of education and a history of benign prostatic hyperplasia and non-insulin-dependent diabetes mellitus who had a history of progressive cognitive decline since the age of 76. His symptoms began with the insidious onset and progression of memory deficits, hypersomnolence, and visual hallucinations. He was initially diagnosed with Alzheimer's disease (AD) by an outside physician at age 78. He was treated with donepezil at 5 mg but when the dose was increased to 10 mg he was thought to have worsened confusion. The dose was therefore decreased and maintained at 5 mg per day. Olanzapine was added for hallucinations and titrated upwards to 7.5 mg per day with improvement in his hallucinations without substantial worsening in his motor function. Memantine was added and titrated upwards to 10 mg twice per day. At age 79, he was placed on modafinil 100 mg/day for hypersomnolence. Two days later, the patient's hallucinations worsened, and the dose of modafinil was decreased to 50 mg; there was a gradual reduction of the psychotic symptoms during the following week. When initially seen by our group at age 80, the patient was described as having persisting hypersomnolence, intermittent confusion, and episodes of physical hyperactivity and talking in his sleep consistent RBD. On examination, he had a Mini-Mental Status Exam (MMSE) score of 20/30 and was found to have hypomimia and bradykinesia, and a diagnosis of DLB was made. Two months later, modafinil was discontinued because of ongoing hallucinations; improvement was observed one week after discontinuation. Three months later, a single dose of 200 mg modafinil was administered by the caregiver so that the patient

would be awake for a specific social event. He became agitated, displayed an increased pathological obsession with specific events of the past, and experienced more intense visual hallucinations. These symptoms gradually improved over the following week.

Case 2

A 70-year-old Caucasian male Holocaust survivor with 12 years of education began developing memory problems, increased irritability, and agitation simultaneously. He underwent a routine evaluation at an outside institution, including an MRI that was interpreted as showing discrete global atrophy. A diagnosis of dementia was made and treatment with donepezil instituted at 10 mg per day. Two years later, treatment with memantine was initiated, the dose titrated to 10 mg twice a day, and the patient displayed improved memory and behavior. He was initially evaluated at our center at age 74, by which time he had begun having visual hallucinations of people and delusions, including the idea that his wife was being persecuted by “hundreds of people”. The patient’s wife described him as having significant behavioral fluctuations. A long-standing history of limb thrashing during sleep in a manner consistent with RBD was initially documented at this time, and the patient’s physical exam revealed the presence of mild cogwheel rigidity of the upper extremities bilaterally. His MMSE score was 13/30, and a diagnosis of probable DLB was made. The patient also demonstrated EDS, and, consequently, an outside physician initiated treatment with modafinil. The exact dose and duration of the patient’s treatment is unknown, but the patient’s wife indicated that he soon began having symptoms of agitated mania and sleeplessness, was abusive and loud, and destroyed things in his house. His condition improved markedly with discontinuation of modafinil.

Discussion

We report two patients with clinically diagnosed DLB who had marked behavioral worsening on initiation of therapy with modafinil for EDS. EDS is a common and significant problem in DLB, and its pharmacologic treatment is challenging due to the potential of most psychostimulant medications to worsen behavioral symptoms.

DLB results from the accumulation of intracellular aggregates of α -synuclein, secondary cellular injury, and apoptotic neurodegeneration⁷. Because DLB and dementia associated with idiopathic Parkinson’s disease (Parkinson’s disease dementia or PDD) have many overlapping features, the degree to which they represent distinct diseases is a matter of controversy⁸. These diseases are distinguished clinically by the time course of symptom onset: DLB begins with dementia which is complicated by visual hallucinations and parkinsonism, while PDD begins with the motor symptoms of Parkinson’s disease and progresses over at least one-year to also feature cognitive impairment⁹. Although some differences in the nature and distribution of pathology in PDD and DLB exist, there is also substantial overlap between the two diseases. Considering the clinical and neuropathological overlap between PD and DLB, we can extend the broader understanding of PD psychosis to explain the mechanism of psychosis in DLB¹⁰.

Psychotic symptoms in PD and DLB result from a complex interplay of extrinsic and disease-related (intrinsic) factors¹¹. Intrinsic factors include visual processing deficits,

neurochemical and structural abnormalities involving site-specific Lewy body deposition, genetic influences, and sleep dysregulation¹². Extrinsic factors include the use of dopaminergic stimulating medications and cholinergic inhibition¹³. Visual hallucinations in PD and DLB may be related to the degeneration of the dopaminergic pathways and high-density aggregation of α -synuclein in the temporal lobe^{10,14}. Cholinergic deficits and Lewy body pathology in acetylcholine-producing neurons in the brain are also associated with the occurrence of psychosis in both disorders¹⁵. Many studies demonstrate that nigrostriatal dopamine denervation, caused either by the neurodegenerative process or by selective lesioning, results in a significant compensatory up-regulation of striatal dopamine receptors (denervation supersensitivity). The resulting dopaminergic overactivity due to stimulation of supersensitive receptors by replacement therapy may provide a favorable environment for the development of psychosis¹³. The dopaminergic model of psychosis has been expanded to include a cascade of activations and inhibitions, a serotonergic-dopaminergic imbalance, and a monoaminergic-cholinergic imbalance¹⁶. Nevertheless, alterations in glutaminergic systems have also been observed in DLB, thus making it difficult to determine the underlying mechanism for any given cognitive or behavioral symptom¹⁷.

To minimize the likelihood of exacerbating agitation or psychosis in DLB, a non-dopaminergic drug for the treatment of EDS would be optimal. Modafinil is thought to have a different mechanism of action than amphetamine, and its use has become widespread because of a decreased risk for abuse and a lower risk of cardiovascular effects. Mignot and colleagues¹⁸ and Simon and colleagues¹⁹ published studies demonstrating a lack of action on dopamine by modafinil. Subsequent research has suggested that modafinil's effects in the brain involve hypocretin, histamine, epinephrine, gamma-aminobutyric acid, and glutamate^{20, 21}. Modafinil has been shown to directly bind to the dopamine transporter (DAT) and to the norepinephrine transporter (NET)^{22, 23, 24}. Modafinil administration also leads to significantly elevated extracellular dopamine, norepinephrine, serotonin, glutamate, and histamine levels, and to decreased gamma amino-butyric acid levels²⁵. These effects are particularly prominent in the neocortex, and are generally less potent or minimal in subcortical areas. The effects of modafinil on dopamine and norepinephrine appear to be primary; the effects on serotonin, gamma amino-butyric acid, glutamate, orexin, and histamine may be secondary to catecholamine effects^{3, 26}. Consistent with this hypothesis, mice lacking dopamine transporters or D1/D2 receptors demonstrated no response to the arousal effects of modafinil^{27, 28}. Finally, Volkow and colleagues²⁹ showed that at clinically relevant doses, modafinil significantly increases dopamine in the human brain by blocking dopamine transporters. These authors propose a reconsideration of the hypothesis of the non-dopamine mechanism of action of modafinil. Thus, there is a lack of consensus about the precise mechanism of action of modafinil although dopaminergic effects appear to be present. We argue that the recently demonstrated dopaminergic action of modafinil is associated with psychosis and agitation exacerbation in DLB. Probably, the dopamine supersensitivity observed in DLB promotes a brain environment with a high liability for psychosis and agitation, and a propensity for dopaminergic overactivity with modafinil use.

Even though the safety profile and tolerance of modafinil are generally good, precipitation or exacerbation of psychosis has been reported. The manufacturer's prescribing information stated that one healthy male had psychosis and sleep deprivation in association with multiple

daily doses of modafinil at 600mg². Another schizophrenic patient was reported to have an exacerbation of psychosis after taking 100 mg of modafinil for 4 days³⁰. Four more case reports are shown in Table 1^{31–34}. As shown, the exacerbations of psychosis in the first three cases were directly influenced by modafinil because the onset of psychosis was temporally related to medication changes. The psychosis in the case 4 might have resulted from the combination of modafinil and caffeine rather than either alone. Muscle twitches, hypertension, tachycardia, agitation, and psychosis from caffeine usually result from consumption of greater than 1g³⁵. This patient also took 500 mg of modafinil, which is a higher dose than is typical. Modafinil and caffeine may have synergistic effects, leading to psychosis in this patient.

Overall, modafinil is well tolerated, with mild to moderate side effects, and there is growing evidence for its utility in EDS in other neurological diseases. It has been used for pramipexole-associated somnolence in PD followed by EDS in PD itself^{36, 37}. Subsequently, several small studies showed a significant reduction in EDS at doses of 100–200 mg/day of modafinil, with few side-effects^{38–42}. On the other hand, a larger, randomized, double-blind, placebo-controlled study (N=37) failed to show the superiority of modafinil to placebo⁴³. Evidence for the efficacy of modafinil EDS in PD is therefore equivocal. Although a small open-label study found some evidence for the efficacy of modafinil for EDS in dementia, evidence of its efficacy in DLB is lacking.

Conclusion

We report two patients with DLB who demonstrated disabling agitation and hallucinations in association with the initiation of treatment with modafinil for EDS. Considering the complexity of neurotransmitter alterations in DLB and the varied neurochemical effects of modafinil, the exact mechanism underlying the behavioral changes we observed cannot be established with certainty, but we cannot discount the possibility that stimulation of the dopaminergic system is involved. Although definitive data regarding the potential benefits and risks of modafinil and related medications for the treatment of EDS in DLB await randomized controlled trials, our observations warrant caution in the use of modafinil in DLB.

Acknowledgments

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Sidell Kagan Foundation, the Shirley and Jack Goldberg Trust, the Alzheimer's Disease Research Center Grant P50 AG-16570 from the National Institute on Aging, a California Alzheimer's Disease Center grant, and the Easton Consortium for Alzheimer's Disease Drug Discovery and Biomarkers. Further support for this study came from the John Douglas French Foundation and the Institute for the Study of Aging.

References

1. Mosimann UP, McKeith IG. Dementia with Lewy bodies – diagnosis and treatment. *Swiss Medical Weekly*. 2003; 133:131–142. [PubMed: 12707840]
2. Dolder CR, Davis LN, McKinsey J. Use of psychostimulants in patients with dementia. *Ann Pharmacother*. 2010; 44:1624–32. [PubMed: 20736422]

3. Cephalon. Prescribing Information: Provigil (Modafinil) Tablets. Cephalon, Inc; 1999.
4. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*. 2008; 33:1477–502. [PubMed: 17712350]
5. Nieves AV, Lang AE. Treatment of excessive daytime sleepiness in patients with Parkinson's disease with modafinil. *Clin Neuropharmacol*. 2002; 25:111–4. [PubMed: 11981239]
6. Howcroft DJ, Jones RW. Does modafinil have the potential to improve disrupted sleep patterns in patients with dementia? *Int J Geriatr Psychiatry*. 2005; 20:492–5. [PubMed: 15852440]
7. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65:1863–72. [PubMed: 16237129]
8. Lippa CF, Duda JE, Grossman M, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology*. 2007; 68:812–9. [PubMed: 17353469]
9. Cummings JL. Dementia with lewy bodies: molecular pathogenesis and implications for classification. *J Geriatr Psychiatry Neurol*. 2004; 17:112–9. [PubMed: 15312274]
10. Duda JE. Pathology and neurotransmitter abnormalities of dementia with Lewy bodies. *Dement Geriatr Cogn Disord*. 2004; 17 (suppl 1):3–14. [PubMed: 14676464]
11. Papapetropoulos S, Mash DC. Psychotic symptoms in Parkinson's disease. From description to etiology. *J Neurol*. 2005; 252:753–64. [PubMed: 15999234]
12. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging*. 2008; 25:665–82. [PubMed: 18665659]
13. Weintraub D, Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. *Am J Psychiatry*. 2007; 164:1491–8. [PubMed: 17898337]
14. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain*. 2002; 125:391–403. [PubMed: 11844739]
15. Perry EK, McKeith I, Thompson P, et al. Topography, extent, and clinical relevance of neurochemical deficits in dementia of Lewy body type, Parkinson's disease, and Alzheimer's disease. *Ann N Y Acad Sci*. 1991; 640:197–202. [PubMed: 1723256]
16. Wolters EC. Intrinsic and extrinsic psychosis in Parkinson's disease. *J Neurol*. 2001; 248 (suppl 3): 22–7.
17. Albasanz JL, Dalfo E, Ferrer I, Martin M. Impaired metabotropic glutamate receptor/phospholipase C signaling pathway in the cerebral cortex in Alzheimer's disease and dementia with Lewy bodies correlates with stage of Alzheimer's-disease-related changes. *Neurobiol Dis*. 2005; 20:685–93. [PubMed: 15949941]
18. Mignot E, Nishino S, Guilleminault C, Dement WC. Modafinil binds to the dopamine uptake carrier site with low affinity. *Sleep*. 1994; 17:436–7. [PubMed: 7991954]
19. Simon P, Hemet C, Ramassamy C, Costentin J. Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice. *Eur Neuropsychopharmacol*. 1995; 5:509–14. [PubMed: 8998404]
20. Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. *Proc Natl Acad Sci USA*. 1996; 93:14128–33. [PubMed: 8943072]
21. Scammell TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, Miller MS, Saper CB. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci*. 2000; 20:8620–8. [PubMed: 11069971]
22. Wisor JP, Eriksson KS. Dopaminergic-adrenergic interactions in the wake promoting mechanism of modafinil. *Neuroscience*. 2005; 132:1027–34. [PubMed: 15857707]
23. Zolkowska D, Jain R, Rothman RB, Partilla JS, Roth BL, Setola V, Prisinzano TE, Baumann MH. Evidence for the involvement of dopamine transporters in behavioral stimulant effects of modafinil. *J Pharmacol Exp Ther*. 2009; 329:738–46. [PubMed: 19197004]
24. Madras BK, Xie Z, Lin Z, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *J Pharmacol Exp Ther*. 2006; 319:561–9. [PubMed: 16885432]
25. Gerrard P, Malcolm R. Mechanisms of modafinil: A review of current research. *Neuropsychiatr Dis Treat*. 2007; 3:349–64. [PubMed: 19300566]

26. Hou RH, Freeman C, Langley RW, Szabadi E, Bradshaw CM. Does modafinil activate the locus coeruleus in man? Comparison of modafinil and clonidine on arousal and autonomic functions in human volunteers. *Psychopharmacology (Berl)*. 2005; 181:537–49. [PubMed: 15983798]
27. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. *J Neurosci*. 2001; 21:1787–94. [PubMed: 11222668]
28. Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y. Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. *J Neurosci*. 2008; 28:8462–9. [PubMed: 18716204]
29. Volkow ND, Fowler JS, Logan J, et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *JAMA*. 2009; 301:1148–54. [PubMed: 19293415]
30. Spence SA, Green RD, Wilkinson ID, Hunter MD. Modafinil modulates anterior cingulate function in chronic schizophrenia. *Br J Psychiatry*. 2005; 187:55–61. [PubMed: 15994572]
31. Narendran R, Young CM, Valenti AM, Nickolova MK, Pristach CA. Is psychosis exacerbated by modafinil? *Arch Gen Psychiatry*. 2002; 59:292–3. [PubMed: 11879175]
32. Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. *Am J Psychiatry*. 2005; 162:813–4. [PubMed: 15800167]
33. Mariani JJ, Hart CL. Psychosis associated with modafinil and shift work. *Am J Psychiatry*. 2005; 162:1983. [PubMed: 16199854]
34. Wu P, Jones S, Ryan CJ, Michail D, Robinson TD. Modafinil-induced psychosis. *Intern Med J*. 2008; 38:677–8. [PubMed: 18808567]
35. Sadock BJ, Kaplan HI, Sadock VA. Kaplan & Sadock's synopsis of psychiatry behavioral sciences/clinical psychiatry. 10. Philadelphia: Wolter Kluwer/Lippincott Williams & Wilkins; 2007.
36. Hauser RA, Wahba MN, Zesiewicz TA, McDowell Anderson W. Modafinil treatment of pramipexole-associated somnolence. *Mov Disord*. 2000; 15:1269–71. [PubMed: 11104221]
37. Happe S, Pirker W, Sauter C, Klosch G, Zeitlhofer J. Successful treatment of excessive daytime sleepiness in Parkinson's disease with modafinil. *J Neurol*. 2001; 248:632–4. [PubMed: 11518012]
38. Tyne HL, Taylor J, Baker GA, Steiger MJ. Modafinil for Parkinson's disease fatigue. *J Neurol*. 2010; 257:452–6. [PubMed: 19842011]
39. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord*. 2003; 18:287–93. [PubMed: 12621632]
40. Hogl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep*. 2002; 25:905–9. [PubMed: 12489899]
41. Lökk J. Daytime sleepiness in elderly Parkinson's disease patients and treatment with the psychostimulant modafinil: A preliminary study. *Neuropsychiatr Dis Treat*. 2010; 6:93–7. [PubMed: 20396641]
42. Lou JS, Dimitrova DM, Park BS, Johnson SC, Eaton R, Arnold G, Nutt JG. Using modafinil to treat fatigue in Parkinson disease: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol*. 2009; 32:305–10. [PubMed: 19620846]
43. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry*. 2005; 76:1636–9. [PubMed: 16291885]

TABLE 1

Case reports of psychosis induced by modafinil

	Case 1	Case 2	Case 3	Case 4
Age/Gender	61/female	17/male	38/female	31/male
Author	Narendran et al. ³¹	Vorspan et al. ³²	Mariani et al. ³³	Wu et al. ³⁴
Medical history	Hypertension	Narcolepsy	None	Surgical excision, right parietal meningioma ago, narcolepsy
Psychiatric history	Schizophrenia	None	None	None
Medication	Clozapine 300 mg/d, Lorazepam 2 mg/d	None	None	None
Modafinil indication	Narcolepsy	Narcolepsy	Healthy control in modafinil research	Narcolepsy
Modafinil dose	200 mg/d	400 mg/d	400 mg/d	400 mg/day
Psychosis onset	21 days after modafinil	after switching from methylphenidate to modafinil	21 days after modafinil	6 months after modafinil
Other factors	None	None	Shift work; day and night for research trial	Patient took 500 mg of modafinil and 300 mg of caffeine during morning to pass MWT* test to regain driver's license
Features of psychosis	Agitation, disorganized speech, paranoid delusions, auditory hallucinations	Mania with mood incongruent psychosis, agitation, auditory hallucination, complex visual hallucination, delusion of reference	Disorganized, internally preoccupied, mumbling prayers, bizarre gesturing	Agitation, auditory hallucinations, singing or laughing out loud, persecutory delusion by CIA*, right facial tic, impaired attention
Course after modafinil	Return to baseline over 2 weeks	1 st stop: increase depression 2 nd stop: psychosis lead to hospitalization	Psychosis resolved spontaneously over 24 hours, but increased depression after 2 days lead to psychiatric hospitalization	Complete recovery in 36 hours

* Abbreviation: CIA, Central Intelligence Agency; MWT, Maintenance of Wakeful test.