DOI: 10.5455/bcp.20111216010146

Late Onset Mania Possibly Related to Modafinil Use: A Case Report

Meltem Gullu Kanal[1], Cetin Ozkan[1], Ozge Doganavsargil[1], Mehmet Eryılmaz[1]

ÖZET:

Muhtemelen modafinil kullanımıyla ilişkili geç başlangıçlı mani: Bir olgu sunumu

Modafinil gündüz uykululuğu ile giden çeşitli klinik durumların tedavisinde kullanılmaktadır. Modafinil ekleme tedavisinin aynı zamanda, unipolar ve bipolar depresyon ile şizofrenide görülen yorgunluk ve uykululuk gibi rezidüel belirtileri düzeltebileceği öne sürülmektedir. Bu ilacın psikoz ve mani oluşturma olasılığı ile ilgili bir durum söz konusu olmakla birlikte, bu konuya ilişkin çok az sayıda olgu bildirimi yayınlanmıştır. Bu yazıda, modafinil tedavisi sırasında gelişen psikotik özellikli geç başlangıçlı bir mani olgusu sunmaktayız. Hastanın psikiyatrik öyküsü ve klinik gidişi, maninin büyük olasılıkla modafinil kullanımıyla ilişkili olabileceğini düşündürmektedir ve bilgilerimize göre bu olgu literatürdeki modafinile bağlı olarak gelişen ilk geç başlangıçlı mani bildirisidir. Modafinil tedavisi alan hastaların dikkatli psikiyatrik izlemi gerektiğini önermekteyiz.

Anahtar sözcükler: Mani, modafinil, geç başlangıç

Klinik Psikofarmakoloji Bülteni 2012;22(1):71-4

ABSTRACT:

Late onset mania possibly related to modafinil use: a case report

Modafinil is used in the treatment of excessive day time sleepiness associated with several clinical conditions. Adjunctive modafinil therapy has also been suggested to improve residual symptoms such as fatigue and sleepiness in unipolar and bipolar depression and also in schizophrenia. Although there have been concerns about the possible occurrence of psychosis and mania with the use of this drug, very few case reports have been reported. We hereby present a case of late onset mania with psychotic features in a man treated with modafinil. The psychiatric history and clinical course of this patient suggest that the mania is likely to be related to modafinil use and, to our knowledge, this is the first report of late onset mania related to modafinil use in the literature. We suggest that careful psychiatric monitoring of patients receiving modafinil is needed.

Key words: Mania, modafinil, late onset

Bulletin of Clinical Psychopharmacology 2012;22(1):71-4

This paper was presented at the 4th Biennial Conference of the International Society of Bipolar Disorders, 17-20 March Sao Paulo, Brazil, as a poster presentation.

[1]Akdeniz University Psychiatry Department, MD, Antalya-Turkey

Yazışma Adresi / Address reprint requests to: Meltem Gullu Kanal, Akdeniz University Psychiatry Department, MD, Antalya-Turkey

Telefon / Phone: +90-242-249-6835

Elektronik posta adresi / E-mail address: meltemgullu@gmail.com

Gönderme tarihi / Date of submission: 21 Şubat 2011 / February 21, 2011

Kabul tarihi / Date of acceptance: 16 Aralık 2011 / December 16, 2011

Bağıntı beyanı:
M.G.K., C.O., O.D.B., M.E.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
M.G.K., C.O., O.D.B., M.E.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Modafinil is proven to promote wakefulness and to have psychostimulant-like properties without the abuse potential of stimulants. Its neurochemical profile and exact molecular mechanism of action are not well understood, although it is thought to have indirect GABA inhibition, dopamine receptor agonism, alpha-1 adrenergic agonism, and dopamine reuptake inhibition (1,2). It is indicated for the treatment of excessive day time sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift-work sleep disorder (3). In the literature several studies have reported the potential antidepressant effect of the drug in narcolepsy patients (4). The recommended dose is 200-400 mg /d in a single dose or two divided doses. Several studies investigating adjunctive modafinil therapy in refractory unipolar and bipolar depression and also in schizophrenia, especially for the management of residual symptoms such as fatigue and sleepiness, found it to be effective (5-7). Additional data from controlled studies suggest that modafinil may improve symptoms of fatigue and day time somnolence in patients with Parkinson's disease and multiple sclerosis (5). Furthermore, controlled studies hint at the efficacy of modafinil in attention deficit hyperactivity disorder and cocaine dependence (2). However, there have been concerns about the possible psychosis- and mania-inducing properties of this drug. So far very few case reports of psychosis and mania associated with modafinil use have been reported. We hereby present a case of late onset

mania with psychotic features in a man treated with modafinil.

CASE

A 54 year-old patient who had his first manic episode with psychotic features during modafinil treatment was referred to our hospital. His psychiatric history and previous hospital records were examined carefully. Physical and neurological examinations were performed and then a psychiatric evaluation with mental status examination and the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) were conducted. Symptoms of mania were assessed by the Young Mania Rating Scale (YMRS). General medical and neurological conditions and any substance abuse diagnosis, which might cause manic symptoms, were excluded by examination and laboratory tests. The laboratory tests included complete blood count, kidney function tests, liver function tests, blood sugar, serum electrolytes, thyroid function tests, serum vitamin B12 and folic acid, and brain magnetic resonance imaging.

Mr. M. was a 54 year-old married and retired officer who had been suffering from symptoms of somatization disorder for 30 years. During this period of 30 years, although he was diagnosed with recurrent unipolar depression, he had no known history of any manic, hypomanic, or psychotic episodes. Some of his symptoms such as depressed mood, anhedonia or feelings of worthlessness responded well to treatment with antidepressants, but fatigue, loss of energy, and hypersomnia had never improved with antidepressants in his life time survey of depression. He had always been compliant with his treatment. In summary, he had five major depressive episodes with interepisode recovery of symptoms such as depressed mood, anhedonia or feelings of worthlessness, but no improvement in fatigue, loss of energy, and hypersomnia. Clomipramine 150 mg /d., sertraline 100 mg /d., citalopram 40 mg/d. and escitalopram 20 mg /d. had been prescribed at various times to treat his depression over 30 years. Furthermore, he had no known manic or hypomanic episodes associated with these antidepressants. There was no family history of any psychiatric illness and he had no known history of any medical illness. In the second month of escitalopram 20 mg /d. therapy for the last depressive episode, his symptoms of fatigue, loss of energy, and severe day time sleepiness had persisted. Any psychosocial stressor that could be related to the last depressive episode had not been reported by the patient. To treat these intractable complaints, modafinil was added to his preexisting medication regimen. In the first week of the treatment, the modafinil dosage was 200 mg /d., and then the dosage was increased to 400 mg /d. in the second week of treatment. During the third week of modafinil use, a full manic episode with psychotic features developed, including elevated and irritable mood, logorrhea, grandiosity, pressured speech, psychomotor agitation, decreased need for sleep and paranoid delusions. He was hospitalized and modafinil was stopped. There were no abnormalities in the laboratory tests and brain imaging. The YMRS score was 38. The manic symptoms required pharmacological treatment with olanzapine 10 mg/d. and valproate 1000 mg/d. The symptoms disappeared within a month and the patient did well in the second month after stopping modafinil and starting the mania treatment. His YMRS score was 6 in this time period. The patient has been followed up at the outpatient clinic of our hospital for the next thirteen months and has been in remission. His medications, including olanzapine, were tapered off and stopped over a period of two months after discharge and he stopped valproate treatment due to side effects.

DISCUSSION

Modafinil has been used successfully in patients with excessive day time sleepiness due to narcolepsy and other sleep disorders (3). This drug has been also found to be effective for the treatment of fatigue and sleepiness associated with both unipolar and bipolar depression (6,7). Studies of modafinil as an adjunctive agent in the treatment of depression have found improvements in fatigue and daytime sleepiness and also showed improvements in overall depression levels (8). Recent studies exploring the role of modafinil in schizophrenia have suggested that this drug might be useful in treating fatigue and sleepiness. Improvements in cognitive functions and global functioning were also found in these studies (5). Furthermore, case reports of modafinil treatment for sedation associated with the use of antipsychotics and mood stabilizers have been published (9,10).

However, there have been concerns about the

psychosis- and mania-inducing properties of this drug. So far very few case reports of psychosis and mania associated with modafinil use have been published. According to these reports, modafinil is related to exacerbation of psychotic symptoms in schizophrenic patients and induction of manic symptoms in bipolar patients (11-16). Although we found published reports of psychosis or mania associated with modafinil in individuals with a psychiatric illness such as bipolar disorder and schizophrenia (11-16), there have been only three case reports of modafinil causing psychosis or mania in individuals without a prior psychiatric history or without a psychiatric illness such as bipolar disorder or psychotic disorders (17-19). One of the three case reports concerned a 17 year-old boy, without a psychiatric history, who developed mania after modafinil treatment (18). To our knowledge, our case is the second report of modafinil induced mania in a man without a prior history of bipolar disorder and the first report of modafinil induced late onset mania in the literature.

The exact molecular mechanism of modafinil's action remains debated, although it is thought to alter the balance of GABA and glutamate, resulting in activation of the hypothalamus or activation of relatively selective neurons in the wakefulness-promoting tuberomammilary nucleus and the lateral hypothalamus, leading to release of both histamine and orexin. It is also claimed to decrease the release of GABA particularly in the forebrain, perhaps through a serotonin-mediated process and to increase the dopamine level in the nucleus accumbens through the inhibition of GABA release. Dopamine release by modafinil is also related to its weak dopamine reuptake inhibitory properties. Although modafinil is a weak dopamine reuptake inhibitor, concentrations of the drug achieved after oral dosing are quite high and sufficient to have a substantial action on dopamine reuptake (1,2).

Enhancement of extracellular serotonin levels and serotonin neurotransmission are the other possible molecular mechanisms of its action. In view of the role of ascending 5-HT pathways in arousal and depression, it seems likely that modafinil may also have an antidepressant potential in addition to its wakefulness-promoting action via its possible effect on serotonergic transmission especially in the frontal cortex, the amygdala, and the dorsal raphe (20).

In light of the foregoing explanations about the mechanism of the drug's action, modafinil induced mania or psychosis may be related to its indirect dopaminergic action through inhibition of GABA secretion and direct dopaminergic action through inhibition of dopamine reuptake. It is plausible that modafinil, via its inhibition of GABA secretion, can exacerbate or induce psychosis or mania with psychotic features.

It should be emphasized that administration of modafinil concomitantly with antidepressants may pose a risk of potential drug to drug interactions. Modafinil may cause an increase in antidepressant blood levels through inhibition of cytochrome P450 enzyme activities and increased levels of an antidepressant may induce mania (5). The interaction between escitalopram and modafinil in terms of cytochrome P450 enzyme activities may be one of the possible explanations of the mania of our case cited here.

Furthermore, the importance of adequate sleep in the maintenance of mood stability of patients of bipolar disorder is well established. Consequently, it has been hypothesized that sleep reduction associated with modafinil may be related to induction or exacerbation of mania (21).

Considering the role of dopamine in psychotic symptom formation and mood regulation, the direct and indirect dopaminergic actions of modafinil are potential mechanisms underlying the manic and psychotic symptoms induced by this drug in our case cited here. In addition, mood stabilizers act via a GABA'ergic mechanism. Therefore, it has been suggested that inhibition of GABA secretion by modafinil may play a role in the manic and psychotic symptoms observed in our case.

Mania occurring for the first time in the elderly population is relatively rare and is often associated with organic factors, either medical or neurological (22). General medical or neurological conditions which might be related to manic symptoms were excluded in our case by detailed physical examination, including neurological examination, laboratory tests, and brain magnetic resonance imaging. Furthermore, elderly patients are prone to side effects of various psychotropic medications (23), so our case may highlight the fact that one should carefully monitor psychiatric symptoms, especially in this age group.

In view of the patient's clinical presentation and the fact that general medical and neurological conditions had been

excluded, he was diagnosed with a first manic episode with psychotic features and was started on mania treatment. After the evaluation of the patient's detailed drug history and clinical course, we suggest that these manic symptoms are possibly related to modafinil use. Our observations from the published reports about the possibility of mania induced by modafinil, particularly in predisposed patients, hint at the need for using modafinil with a mood stabilizer in bipolar depression. Although the potential risk of modafinil induced psychosis or mania is relatively low, we suggest that careful psychiatric monitoring of patients receiving modafinil, even in recommended doses, is needed.

References:

1. McClellan KJ, Spencer CM. Modafinil: a review of its pharmacology and clinical efficacy in the management of narcolepsy. CNS Drugs 1998;9(4):311-24.
2. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. J Clin Psychiatry 2006; 67(4):554-66.
3. Keating GM, Raffin MJ. Modafinil: A review of its use in excessive sleepiness associated with obstructive sleep apnea/ hypopnea syndrome and shift work sleep disorder. CNS Drugs 2005;19(9):785-803.
4. Becker PM, Schwartz JR, Feldman NT, Hughes RJ. Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. Psychopharmacology (Berl) 2004;171(2):133-9.
5. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. Drugs 2008;68(13):1803-39.
6. Konuk N, Atasoy N, Atik L, Akay O. Open label study of adjunct modafinil for the treatment of patients with fatigue, sleepiness and major depression treated with SSRIs. Adv Ther 2006;23(4):646-54.
7. Frye MA, Grunze H, Suppes T, McElroy SL, Keck Jr PE, Walden J, et al. A placebo controlled evaluation of adjunctive modafinil in treatment of bipolar depression. Am J Psychiatry 2007; 164(8):1242-49.
8. Mena MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000; 61(5):378-81.
9. Makela EH, Miller K, Cutlip WD. Three case reports of modafinil use in treating sedation induced by antipsychotic medication. J Clin Psychiatry 2003;64(4):485-6.
10. Berigan T. Modafinil treatment of excessive sedation associated with divalproex sodium. Can J Psychiatry 2004;49(1):72-3.
11. Narendran R, Young CM, Valenti AM, Nickolava MK, Pristach CA. Is psychosis exacerbated by modafinil? Arch Gen Psychiatry 2002;59(3):292-3.
12. Ranjan S, Chandra PS. Modafinil induced irritability and aggression? A report of 2 bipolar patients. J Clin Psychopharmacol 2005;25(6):628-9.
13. Ozer S. Demir B. Hypomania in a Schizophrenic Patient Treated with Modafinil for Clozapine-Induced Sedation. Archives of Neuropsychiatry 2010;47(2):171-3 (Turkish).
14. Fountoulakis KN, Siamouli M, Panagiotidis P, Magiria S, Kantartzis S, Iacovides A, et al. Ultra short manic-like episodes after antidepressant augmentation with modafinil. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(3):891-2.
15. Wolf J, Fiedler U, Anghelescu I, Schwertfeger N. Manic switch in a patient with treatment resistant bipolar depression treated with modafinil. J Clin Psychiatry 2006;67(11):1817.
16. Ginsberg DL. Modafinil Associated Mania. Primary Psychiatry 2007;14(1):23-5.
17. Wu P, Jones S, Ryan CJ, Michail D, Robinson TD. Modafinil induced psychosis. Intern Med J 2008;38(8):677-8.
18. Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a Boy Treated With Modafinil for Narcolepsy. Am J Psychiatry 2005;162(4):813-4.
19. Mariani J, Hart C. Psychosis associated with modafinil and shift work. Am J Psychiatry 2005;162(10):1983.
20. Ferraro L, Fuxe K, Tanganelli S, Tomasini MC, Rambert FA, Antonelli T. Differential enhancement of dialysate serotonin levels in distinct brain regions of the awake rat by modafinil: possible relevance for wakefulness and depression. J Neurosci Res 2002; 68(1):107-12.
21. Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res 1999;30(3):267-70.
22. Cassidy F, Carroll BJ. Vascular risk factors in late onset mania. Psychol Med 2002;32(2):359-62.
23. Salzman C. Geriatric psychopharmacology. In Essentials of Clinical Psychopharmacology, Schatzberg AF, Nemeroff C. (editors). 1st ed. Washington DC: America Psychiatric Publishing; 2001. p. 670-94.