Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2016;29:290-292
DOI: 10.5350/DAJPN2016290313
Letter to the Editor / Editöre Mektup

Antidepressant Treatment with Low Dose Modafinil

Musa Sahpolat[1]

[1]Kilis State Hospital, Department of Psychiatry, Kilis - Turkey

Address reprint requests to / Yazışma adresi: Musa Sahpolat, Kilis State Hospital, Department of Psychiatry, Asit Mah., Hastane Sok., No: 31, Merkez/Kilis, Turkey
Phone / Telefon: +90-348-822-1111/1280
E-mail address / Elektronik posta adresi: drmsahpolat@hotmail.com
Date of receipt / Geliş tarihi: March 7, 2016 / 7 Mart 2016
Date of the first revision letter / İlk düzeltme öneri tarihi: March 28, 2016 / 28 Mart 2016
Kabul tarihi / Date of acceptance: April 18, 2016 / 18 Nisan 2016

Dear Editor;

Modafinil is a new non-sympathomimetic drug, which is different from other central nervous system stimulators that promote wakefulness with its chemical and pharmacological properties (1). Modafinil was approved in providing wakefulness in patients who were treated for narcolepsy, or excessive sleepiness due to shift-based working or obstructing sleep apnea by the Food and Drug Agency (FDA) of United States of America (1,2). It is reported in recent studies that there are evidences indicating that modafinil is effective in treatments of unipolar and bipolar depression, attention deficit and hyperactivity disorder, schizophrenia, obstructive sleep apnea, multiple sclerosis, Parkinson's disease, myotonic dystrophy, chronic fatigue syndrome, opiate intoxication, post-anesthetic fatigue, and jet-lag in addition to excessive sleepiness during daytime and narcolepsy (3). Daily recommended dose is 200-400mg/day as one or in two divided doses (4). It is believed that this article is noteworthy for a patient initiated study in antidepressive perspective of low doses modafinil (100mg/day) monotherapy.

A 21 years old, male, bachelor patient, who was a worker and graduated from the primary school (5 years education), and the only child of the family, applied to our outpatient clinic with complaints of difficulty in concentration, apathy, nervousness, muscle pains, loss of enjoyment for life, unhappiness, having low spirits, and daytime sleepiness for approximately 20 days. For 3 years, he was diagnosed with depression and received different antidepressant treatments, but he did not recover. In the last year, modafinil 100mg/day was added up to his antidepressant treatment, and he discontinued his antidepressant drug but continued to take modafinil 100mg/day. His clinical picture was recovered for at least 6 months, so he discontinued modafinil treatment nearly 20 days ago. Then he started to experience symptoms such as difficulty in concentration, apathy, nervousness, muscle pains, loss of enjoyment for life, daytime sleepiness, anxiety, fatigue and malaise. In his routine laboratory tests, fasting blood glucose, electrolytes, whole blood count, renal and liver and thyroid function tests were normal with normal vitamin B12 and folic acid levels. In the psychiatric examination, anxiety and depressive signs were slightly predominant, and he did not have any signs of mania or psychosis. According to DSM-IV diagnostic criteria, he was diagnosed with major depressive episode. He had no other comorbid psychiatric disease. Patient had no other illnesses or symptoms on which modafinil might be effective,

such as chronic fatigue syndrome or sleep disorders. Neurological system examination was normal, and he had no chronic systemic disease. In his medical history, he received escitalopram 20mg/day for 3 months, escitalopram 20mg/day and mirtazapine 30mg/day combination for 4 months, fluoxetine 40mg/day for 3 months in the mentioned order, but he did not markedly benefit from them. In the last 1 year, modafinil 100mg/day was added on fluoxetine 40mg/day treatment, but the patient continued his treatment as modafinil 100mg/day as a monotherapy according to his own decision, and he mentioned that his depressive symptoms were markedly improved.

As the present case could not benefit from different antidepressant medications, he discontiued them. The patient experienced antidepressant perspective of modafinil monotherapy. When he discontinued modafinilin majorşty of withdrawal signs (difficulty in concentration, apathy, nervousnes, muscle pains, loss of enjoyment of life, daytime sleepiness, anxiety, and fatigue) were coincided with antidepressant wşthdrawal symptoms (5). These observations suggested that modafinilin had antidepressant effects in the case.

In the literature, there are various studies evaluating modafinil and psychostimulant monotherapy used in major depression. It was reported in those studies that there was generally no significant difference between psychostimulants, modafinil and placebo (6,7). However, similar to our case, there were also studies reporting modafinil 100-200mg/day caused complete remission of symptoms in 7 patients who were partially responsive to antidepressants or resistant with depressive episodes, and no side effect was observed in that open labelled study (8,9).

Additionally, there are various studies which evaluated modafinil as an add-on treatment in major depression treatment in the literature. Fava et al. (10) reported that after adding modafinil on antidepressant treatment for 6-8 weeks in 348 patients with major depressive disorder who responded partially to the treatment, there were marked improvements in depressive symptoms, residual fatigue, and daytime sleepiness of these patients. In another study performed on patients with major depression who were treatment non-responsive, modafinil 200mg/day dose added on fluoxetine or paroxetine treatment within the first week resulted in marked decreases in clinical symptoms, and 40% of patients were recovered in the second week whereas 58% were recovered in the sixth week (11). DeBattista et al. (2) reported in their 6-months observational study performed on 136 patients with major depressive disorder who were partially treatment responsive that adding on modafinil 200-400mg/day caused significant improvements in sleepiness within the first week, and in fatigue within the second week when compared with the placebo. Similar to our case, it is noted in these studies that antidepressant efficacy doses of modafinil were lower than the narcolepsy treatment doses.

Although antidepressive effect mechanism of modafinil is unknown currently, it is believed that it exerts this effect by agonism of central alpha 1 adrenergic receptors in cortex, hypothalamus and striatum, decreasing GABA level, increasing glutamate levels and increasing histaminergic neuron activity which may promote wakefulness in tuberomamillary nuclei (12,13). Makela et al. (14) reported in their study that modafinil increased glutamate and serotonin levels while decreasing GABA levels, and they indicated that modafinil might have antidepressant efficacy on serotonin system. It was reported in another study that, reported that differently from amphetamine derivatives, modafinil did not cause any decreases in noradrenaline or dopamine level, and it exerted antidepressant effect by possibly histamine release, and agonism on noradrenaline receptors (10). This information indicates that modafinil may have a complicated antidepressant efficacy especially by alpha-1 adrenergic receptor agonism, increased histamine release, and serotonin system.

In conclusion, it is believed that low doses of modafinil such as 100mg/day may have an antidepressant effect potential, so modafinil may be used as a monotherapy or its addition on antidepressants will be beneficial.

REFERENCES

1. 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; 18:287-293. **[CrossRef]**

2. DeBattista C, Doghramji K, Menza MA, Rosenthal MH, Fieve RR; Modafinil in Depression Study Group. 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; 64:1057-1064. **[CrossRef]**

3. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 2006; 67:554-566. **[CrossRef]**

4. Schwartz JR. Modafinil: new indications for wake promotion. Expert Opin Pharmacother 2005; 6:115-129. **[CrossRef]**

5. Renoir T. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: a review of the clinical evidence and the possible mechanisms involved. Front Pharmacol 2013; 4:45. **[CrossRef]**

6. Vaishnavi S, Gadde K, Alamy S, Zhang W, Connor K, Davidson JR. Modafinil for atypical depression: effects of open-label and double-blind discontinuation treatment. J Clin Psychopharmacol 2006; 26:373-378. **[CrossRef]**

7. Wagner GJ, Rabkin R. Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo controlled trial. J Clin Psychiatry 2000; 61:436-440. **[CrossRef]**

8. Kaufman KR, Menza MA, Fitzsimmons A. Modafinil monotherapy in depression. Eur Psychiatry 2002; 17:167-169. **[CrossRef]**

9. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000; 61:378-381. **[CrossRef]**

10. Fava M, Thase ME, DeBattista CA. A multicenter, placebo controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005; 66:85-93. **[CrossRef]**

11. Ninan PT, Hassman HA, Glass SJ, McManus FC. Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue. J Clin Psychiatry 2004; 65:414-420. **[CrossRef]**

12. Moachon G, Kanmacher I, Clenet M, Matinier D. Pharmacokinetic profile of modafinil. Drugs Today 1996; 32:327-337.

13. Murillo-Rodriguez E, Haro R, Palomero-Rivero M, Millan-Aldaco D, Drucker-Colin R. Modafinil enhances extracellular levels of dopamine in the nucleus accumbens and increases wakefulness in rats. Behav Brain Res 2007; 176:353-357. **[CrossRef]**

14. Makela EH, Miller K, Cutlip WD 2nd. Three case reports of modafinil use in treating sedation induced by antipsychotic medications. J Clin Psychiatry 2003; 64:485-486. **[CrossRef]**