Modafinil Dependence: A Case with Attention-Deficit/Hyperactivity Disorder

Huseyin Alacam¹, Omer Basay², Selim Tumkaya¹, Mehmet Mart¹, and Gokce Kar¹

¹Department of Psychiatry, Faculty of Medicine, Pamukkale University, Denizli, Turkey
²Department of Child and Adolescent Psychiatry, Faculty of Medicine, Pamukkale University, Denizli, Turkey

INTRODUCTION

Modafinil is generally known as a drug with low addiction potential. There are few case reports in the literature demonstrating that Modafinil, stated being capable of diminishing symptoms of attention deficit/hyperactivity disorder (ADHD), causes addiction. In the present article a Modafinil addicted ADHD case, consuming usurious doses (5,000 mg/per day) of Modafinil is presented. The case presented to our psychiatry outpatient clinic due to: requirement of in taking high dose Modafinil in order to achieve the initial effects, difficulty in obtaining the drug, irritability, anxiousness, sleep irregularities, fatigue and unpleasant vivid dreams when he did not use the drug. It was realized that the patient, himself increased doses of Modafinil incrementally, in order to keep its effects on attention symptoms at the same level. It has to be kept in mind that ADHD patients can develop Modafinil addiction. It is necessary to carry out systemic studies on this subject.

Key Words Modafinil, Dependence, Attention-deficit/hyperactivity disorder.

CASE

Twenty-four years old male, single student, living in county town with his parents stated, in his own words that; he had been facing difficulty in listening to classes since primary school, had issue in concentrating, difficulty in making friends, had low academic success, had coerced particularly during transition to higher education and due to performance anxiety had clinical psychologist visits. Developmental and past psychiatric history, corroborated by his parents confirmed these

Received: April 7, 2016 Revised: June 20, 2016 Accepted: October 25, 2016

Correspondence: Huseyin Alacam, MD
Department of Psychiatry, Faculty of Medicine, Pamukkale University, Camlaralti Street, No: 7, 20800, Pamukkale, Denizli, Turkey
Tel: +90 258 296 60 01-4509, Fax: +90 258 296 60 01
E-mail: dr.huseyinalacam@hotmail.com

© This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Psychiatry Investig 2018;15(4):424-427
complaints. During childhood he was obviously more active than peers, and he was easily distracted by external stimulus. The parents reported that, when he was 10 years old, they admitted to a child psychiatry policlinic complaining of inattention, difficulty in completing school work, organizing activities, following instructions, committing frequent mistakes, losing belongings and forgetting daily routines. He was diagnosed with ADHD by the child psychiatrist and stimulant medication was indicated. However, parents refused medical treatment due to concerns related to side effects. No further treatment was searched.

Patient reported that approximately 5 years ago, he begun consuming omega 3-6-9 preparations and vitamin supplements in order to increase his social and academic performance. Subsequently approximately 3 years ago, without any doctor suggestion, he commenced taking Modafinil in 50 mg/day dose, and gained improvements in attention, self-reliance, academic success and social activity. After a while, in order to be able to maintain initial effects, he necessitated increasing the dose and went on using Modafinil at 300–400 mg/day dose during 2 years. It was ascertained that since his ailments were not totally resolved and his exam load increased, 1 year ago he presented to a different psychiatry clinic than ours, where 20 mg/day short-acting Methylphenidate was initiated for attention deficiency and hyperactivity disorder diagnose. It’s realized that, as an addition to Modafinil he used short-acting Methylphenidate 60 mg/day. The patient stated that, even though he benefited from the Methylphenidate treatment, he did not use regularly and discontinued the drug. During the last year, he increased the Modafinil dose, in order to achieve the initial effects Modafinil and resulted in consuming 100 mg tablets, 5 times a day and 10 tablets most of the time. Whenever he quit using Modafinil or diminished the amount, he experienced irritability, anxiosness, sweating, tremor and an urge to take excessive Modafinil. The case presented to a different psychiatry clinic with a desire to quit Modafinil, where Modafinil was stopped and Venlafaxine at 75 mg/day, Risperidone 2 mg/day, Propranolol 80 mg/day and Olanzapine 5 mg/day were initiated. After discontinuation of Modafinil, he experienced fatigue, vivid and unpleasant dreams, sleeping irregularities, anxiosness, and functionality impairment, as previously. Since, despite the given treatment his complaints did not subside, he abandoned treatment and revert using Modafinil.

Modafinil that could be purchased over the counter before, became a prescription medicine with recent regulations in Turkey. Therefore the patient encountered difficulty in accessing the drug and presented to our polyclinic. During his anamnesis he presented his complaints as necessity to consume usurious doses of Modafinil, to be able to achieve the initial effects, difficulty in obtaining the medicine, irritability, tremor, anxiety, sleep disorder, fatigue, and unpleasant vivid dreams when he did not use the drug. It was realized that he was consuming 5,000 mg/day Modafinil since 1 month. After evaluation, he was admitted to our psychiatry ward with the initial diagnosis of “stimulant use disorder” according to DSM-5 classification.

During mental state examination performed in our clinic, he appeared at his age, was self-sufficient, his associations were normal, his speaking rate and amount was partially increased, and was anxious. He did not have active psychotic thought content, evaluation of actuality was normal. He had irregular sleeping pattern, decreased appetite and normal libido.

Family history revealed that his elder brother previously had alcohol addiction.

In our psychiatry ward, the patient was introduced Lorazepam 2.5 mg/day, Risperidone 1 mg/day and Ketapin 25 mg/day. Following abandoning of Modafinil, cravings, psicomotor agitation, sweating, tremor, fatigue were observed. Therefore his treatment was modified to Diazepam 15 mg/day, Ketapin 100 mg/day, Risperidone 2 mg/day. On the third day of his admission, the patient was discharged from the ward upon his own will. During his first control in outpatient clinic, it was realized that, although he had some benefits from treatment, his compliance to medication was poor. He requested prescription of Modafinil, and he did not attend to further control visits.

**DISCUSSION**

Due to weak inhibition of dopamine reuptake pumps, Modafinil increases dopamine in some areas of the brain, mainly the cortex, striatum and nucleus accumbens. Studies investigating this mechanism revealed that, cortex and striatum are diffusely activated following amphetamine administration to rats. With Modafinil use, activated areas are restricted with paraventricular and suprachiasmatic nuclei, anterior hypothalamus, amygdala and tuberomamillary nucleus. Modafinil increases the effects of dopamine and norepinephrine by binding to carrier proteins of these catecholamines. Unlike amphetamine, Modafinil does not have an influence on dopamine release and cycle in mouse striatum, has very little influence on blood flow to the brain cortex, and results in a metabolic activation that is different from amphetamine. This may be the explanation for its low abuse potential. Despite all these diversities, Modafinil’s effect related with stimulation and behavioral activity are supposed to be at least partially involving dopamine. D1 and D2 receptors also take role in effects of Modafinil on cognitive functions and behavior.
Modafinil Dependence

Affinity of Modafinil to dopamine receptors resembles methylenidate. This can be reason of possible risk for abuse.\(^\text{13,17}\) Modafinil dependence may be related to its dopamine increasing effect in dopaminergic areas of the brain via reuptake inhibition.\(^\text{3}\) Postsynaptic D1 receptors are one of the mediators of sensitization; increased dopamine transmission results in increased stimulation of D1 receptors, compulsive use of Modafinil may be related to this.\(^\text{18-20}\)

Modafinil is thought to enhance cognitive functions such as attention, learning and memory via acting differently from the typical psychostimulants.\(^\text{5}\) Promotion of cognitive functions by Modafinil has been investigated in many mental disorders that result in decreased cognitive functions.\(^\text{6}\) As an example, a study with schizophrenic patients using Modafinil, in addition to antipsychotic treatment, aiming to decrease cognitive functions had promising results.\(^\text{21}\) Our case had symptoms of ADHD that impaired cognitive functions, such as lack of attention, difficulty in concentrating and difficulty in educational life. Modafinil was helping him to overcome these symptoms. There are also studies that presented Modafinil to be effective in treatment of ADHD.\(^\text{22,23}\) Illega use of Modafinil has been reported in substance abusers and patients with organic mental disease in order to enhance cognitive functions. This is also supported with the fact that two of the previously reported cases had history of alcohol and benzodiazepine addiction, and the third reported case had schizoaffective disorder.\(^\text{24}\)

One report from India mentioned 1,200 mg/day Modafinil dose, whereas one report from Turkey mentioned 3,000 mg/day Modafinil dose.\(^\text{10-12}\) In the present case, utilization of Modafinil at extremely high doses up to 5,000 mg/day may be due to a self-medication in order to reinforce its cognitive enhancing property and to treat symptoms of ADHD. High doses of Modafinil can cause several side effects like agitation, insomnia, tachycardia and elevated blood pressure.\(^\text{25}\) Our case described palpitations, agitation and insomnia after using high doses of Modafinil. This was one of the reasons why for seeking treatment. These symptoms were taken into account during his treatment planning. There is no controlled study on Modafinil dependence; treatment with antidepressants like Bupropion and Duloxetine and treatment with benzodiazepines like Clonazepam had been attempted in previously reported cases.\(^\text{10-12}\)

There are 2 case reports in the literature stating that Modafinil dependence can occur in patients with previous history of addiction.\(^\text{10,11}\) ADHD patients are known to be more prone to addiction, however as far as we know, this is the first study demonstrating Modafinil dependence of a case with ADHD. Recent suggestion on Modafinil use for ADHD increases the significance of the present case report.\(^\text{23}\)

Another important point in this case report is that, to our knowledge, there is no report in the literature demonstrating Modafinil use as high as 5,000 mg/day. Despite symptoms presenting at high dose, the drug did not cause any life threatening condition.

It has to be kept in mind that Modafinil can cause dependence in patients with ADHD. Systematic studies are necessary on this field.

REFERENCES

1. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. Drugs 2008;68:1803-1839.
2. Kim D. Practical use and risk of modafinil, a novel waking drug. Environ Health Toxicol 2012;27:e2012007.
3. Wisor J. Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. Front Neurol 2013;4:139.
4. Stone EA, Cotecchia S, Lin Y, Quartermain D. Role of brain alpha 1B-adrenoceptors in modafinil-induced behavioral activity. Synapse 2002; 46:269-270.
5. Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. Psychopharmacology (Berl) 2013;229:415-434.
6. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 2008;33:1477-1502.
7. Anderson AL, Reid MS, Li SH, Holmes T, Shemanski L, Sleen A, et al. Modafinil for the treatment of cocaine dependence. Drug Alcohol Depend 2009;104:133-139.
8. Shearer J, Darke S, Rogers C, Slaet T, van Beek J, Lewis J, et al. A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methylamphetamine dependence. Addiction 2009;104:224-233.
9. Schmaal L, Goudriaan AE, Joos L, Krüse AM, Dom G, van den Brink W, et al. Modafinil modulates resting-state functional network connectivity and cognitive control in alcohol-dependent patients. Biol Psychiatry 2013;73:789-795.
10. Cengiz Mete M, Şenormanacı O, Saraçoğlu O, Atasoy N, Atik L. Compulsive modafinil use in a patient with a history of alcohol use disorder. Gen Hosp Psychiatry 2015;37:e7-e8.
11. Kate N, Grover S, Ghormode D. Dependence on supratherapeutic doses of modafinil: a case report. Prim Care Companion CNS Disord 2012;14.
12. Krishnan R, Chary KV. A rare case modafinil dependence. J Pharmacol Pharmacother 2015;6:49-50.
13. Schmitt KC, Reith ME. The atypical stimulant and nootropic modafinil interacts with the dopamine transporter in a different manner than classical cocaine-like inhibitors. PlaS6 One 2011;6:e25790.
14. Lin JS, Hsu 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;93:1412-14133.
15. Madras BK, Xie Z, Lin Z, Jassen A, Panas H, Lynch L, 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;319:561-569.
16. de Saint Hilaire Z, Orozco M, Rouch C, Blanc G, Nicolaidis S. Variations in extracellular monoamines in the prefrontal cortex and medial hypothalamus after modafinil administration: a microdialysis study in rats. Neuroreport 2001;12:3533-3537.
17. Kim W, Tateno A, Arakawa R, Sakayo I, Ikeda Y, Suzuki H, et al. In vivo activity of modafinil on dopamine transporter measured with
positron emission tomography and [18F]FE-PE2I. Int J Neuropsychopharmacol 2014;17:697-703.

18. Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM, Pradko JF, et al. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. Prim Care Companion J Clin Psychiatry 2005;7:106-113.

19. Hummel M, Unterwald EM. D1 dopamine receptor: a putative neurochemical and behavioral link to cocaine action. J Cell Physiol 2002;191:17-27.

20. Möller HJ. Amisulpride: limbic specificity and the mechanism of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1101-1111.

21. Farrow TFD, Hunter MD, Haque R, Spence SA. Modafinil and unconstrained motor activity in schizophrenia: double-blind crossover placebo-controlled trial. Br J Psychiatry 2006;189:461–462.

22. Biederman J, Swanson JM, Wigal SB, Boellher SW, Earl CQ, Lopez FA, et al. A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. J Clin Psychiatry 2006;67:727-735.

23. Gomez Z, Noble P. Meta-analysis of the effect of modafinil in children and adolescents with attention deficit and hyperactive disorder. Eur Psychiatry 2015;30:577.

24. Spiller HA, Borys D, Griffith JR, Klein-Schwartz W, Aleguas A, Sollee D, et al. Toxicity from modafinil ingestion. Clin Toxicol (Phila) 2009;47:153-156.

25. Lackey G, Alsop J, Albertson T. A 24 month retrospective study of adult modafinil ingestions. Clin Toxicol 2007;45:641.