Case Report

MODAFINIL INDUCED PSYCHOSIS IN A PATIENT WITH RECURRENT DEPRESSIVE DISORDER: A CASE REPORT

Gopika SS[1], Diya P Albert[2*], Vidhukumar Karunakaran[3]

1. Junior Resident, 2.Assistant Professor, 3. Professor & Head, Department of Psychiatry, Government TD Medical college Alappuzha

*Corresponding Author: Assistant Professor, Department of Psychiatry, Government TD Medical college Alappuzha

email: dr.diyapalbert@gmail.com

Abstract

Background: Modafinil is the first FDA-designated "wakefulness-promoting agent" and is approved for use as an adjuvant in mood disorders. In depressive disorders, it is reported to be effective in alleviating fatigue and related symptoms. The molecule is widely used today. Since it belongs to the group of stimulants, theoretically, it can cause psychosis. **Case Report**: We report the case of a 48-year-old woman with recurrent depressive disorder who developed psychotic symptoms, including visual and auditory hallucinations, within two days of initiating modafinil (100 mg/day) for fatigue. Symptoms worsened following venlafaxine addition but entirely resolved within five days of modafinil discontinuation, with no recurrence over six months. **Conclusion**: This case highlights the risk of modafinil-induced psychosis, even at standard doses, and suggests a possible interaction with venlafaxine. Clinicians should monitor for psychotic symptoms in vulnerable patients, warranting further investigation into modafinil's neurobiological effects.

Keywords: Modafinil, Depressive Disorder, Medication Induced Psychosis, Drug Monitoring

INTRODUCTION

Modafinil is approved by the Food and Drug Administration (FDA) as a wakefulness-promoting agent, now being increasingly used as an augmenting agent to antidepressants in the treatment of depression. It is included in the CANMAT guidelines as a second-line recommendation for adjunctive treatment with antidepressants in the treatment of bipolar depression.[1] The drug has been found to improve fatigue and daytime somnolence. As the molecule is distinct from conventional psychostimulants, the abuse liability and propensity to cause psychosis are theoretically and clinically lower. However, at higher doses, especially above 1000 mg, cases of psychosis have been reported.[1] Clinical usage recommendations of the drug are 200 to 400 mg/day. [1]There are two previous reports of psychotic symptoms developing at clinical doses, with the minimum dose being 100 mg/ day. In the report by Aytas and Havriye, an 18-year-old student treated with modafinil for ADHD developed psychotic symptoms on the 4th day of starting treatment, and symptoms subsided after one week of stopping modafinil.[2] Complex visual hallucinations have been described with low-dose venlafaxine treatment.[3] In another report by Di Scullio et al., psychosis was reported in a 48-year-old woman two days after taking 100 mg modafinil for the treatment of bipolar depression. The patient was also on venlafaxine, quetiapine, and valproate. Psychotic symptoms subsided following the stoppage of modafinil.[4]

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There are case reports on developing psychosis in patients on treatment for other approved uses of modafinil and bipolar depression[1, 4]. We are reporting the case because the index patient had unipolar depression, unlike previous case reports. Informed consent was obtained from the patient when the patient regained capacity and had normal judgement.

CASE REPORT

A 48-year-old lady was on maintenance treatment for recurrent depressive disorder for the last 17 years with 10 mg escitalopram and 0.5mg clonazepam. The current episode of behavioral disturbance started 3 months before admission. She had a moderate depressive episode, and the dose of escitalopram was increased to 15 mg. Her depressive symptoms improved, but daytime somnolence and fatigue persisted, and hence she was started on 50 mg modafinil. 2 days after, she stopped the modafinil by herself as she didn't find any improvement and continued escitalopram 15mg. She was doing her routine activities even though her complaints of fatigue and tiredness persisted. 2 months later, as her symptoms did not improve, she reported for consultation and was started on modafinil 50 mg along with escitalopram 10 mg. 1 week after this, she reported not much improvement. Venlafaxine 37.5 mg was added. She developed transient perceptual alterations on day two of starting the medication, like seeing her image on the wall and seeing images on hearing the sound of a fan. She had discontinued all the medications by herself, and the perceptual alterations subsided. After two weeks, she reported again with her preexisting complaints of fatigue and somnolence along with depressive symptoms. She was restarted on escitalopram 10 mg, modafinil 50 mg, and venlafaxine 37.5 mg. Visual hallucinations occurred again, and she discontinued, but as her depressive symptoms persisted, she restarted after 2 weeks of stopping. The dose of modafinil was increased to 100mg on follow-up. She continued the medications for two weeks. On continuous use for the two weeks, her perceptual alterations and behavioral problems worsened. She started experiencing visual hallucinations, functional hallucinations, and persecutory delusions. She was brought to our outpatient department with agitation, fearfulness, hearing voices, muttering, laughing to self and assaultiveness. The patient had no past history of psychotic symptoms during her depressive episodes and no family history of psychotic disorder. There is no history of substance use, no history suggestive of an infectious or other organic etiology contributing to her present condition. She was not using modafinil in the past. Her physical examination was normal, with stable vital signs. Her blood investigations were normal; her total blood count, liver function tests, renal function tests, and thyroid function tests were normal.

She was started on risperidone at a dose of 0.5 mg and gradually increased to 4 mg, along with her previous medications, but there was no response, and her psychotic symptoms persisted at the same intensity. Upon reviewing her history and records, it was found that her symptoms began after the introduction of modafinil, indicating a temporal correlation. A diagnosis of modafinil-induced psychosis was made, and all medications were discontinued. Olanzapine 5 mg was then started along with escitalopram 10 mg to manage her symptoms. Her psychotic symptoms completely subsided within five days of stopping modafinil and venlafaxine. She was discharged after one week, and during follow-up, olanzapine was gradually tapered and discontinued within a few weeks. There have been no psychotic symptoms in the last six months.

DISCUSSION

This case study is similar to the previous report of modafinil-induced psychosis in a patient with bipolar depression with similar perceptual alterations. This demonstrates the risk of developing psychosis from using modafinil, which can be a distinct phenomenological entity and not specific to the mood disorder, warranting further study. Isolated reports of psychosis, predominantly with delusions, have been reported at higher doses for longer durations.[5, 6] The distinct phenomenology, with predominantly perceptual alterations, is similar to previous reports. The contribution of low-dose venlafaxine in the production of psychotic symptoms also needed to be explored, as this was also similar to the previous report by Di Scullio et al.

As the molecule is distinct from conventional psychostimulants, the abuse liability and propensity to cause psychosis are theoretically and clinically lower. The mechanism of psychosis with modafinil is less studied. Modafinil promotes dopaminergic activity by acting on the dopamine transporter (DAT), with minimal or no action on the noradrenaline transporter (NET).[8] Such an increased dopaminergic activity increases adrenergic mechanisms either directly or indirectly. Such enhanced dopaminergic mechanisms are implicated in reduced GABAergic or enhanced glutaminergic action.[7] The distinct property of modafinil from psychostimulants is that the latter acts by increasing catecholamine release, whereas modafinil does not. A combination of venlafaxine and modafinil might have contributed to the increase in dopamine and norepinephrine, which could have triggered the onset of psychotic symptoms, which were exacerbated by the continuation of modafinil.

Modafinil is now increasingly used as a cognitive enhancer adjunct to antidepressant medications to improve the functioning and enhance the cognitive performance of patients. However, caution should be exercised for the side effects of the synergistic effects. The neurobiological mechanisms underlying such effects are also worth exploring. Insight into this aspect of possible interactions among medications can facilitate early initiation of necessary steps to enhance clinical response and promote prompt recovery and treatment adherence in patients.

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