Clozapine Levels Lowered by Modafinil: A Case Report and Brief Review of Modafinil in Schizophrenia

Bernard A. Fischer [1], *Elaine Weiner* [1]

Abstract

We present a case report of a probable modafinil-clozapine interaction resulting in decreased clozapine levels, followed by a brief review of modafinil in schizophrenia. Modafinil is a wakefulness-promoting agent that seems to act selectively on centers of circadian rhythm in the brain and does not increase dopamine release. For this reason, it has been used in schizophrenia to address sedation, activity level, negative symptoms, and cognition. Results from randomized controlled trials (RCTs) generally do not support the use of modafinil for these indications.

Key Words: Schizophrenia, Modafinil, Clozapine, Pharmacokinetics

Introduction

Although clozapine is metabolized through multiple cytochrome P450 enzymes, it is not uncommon to observe interactions with other medications (1). A PubMed search using the terms "modafinil" and "clozapine" resulted in two case reports that included clozapine levels. The first was a case reporting clozapine toxicity in response to the addition of modafinil (300 mg/day) (2). However, elevated clozapine levels persisted three weeks after modafinil discontinuation (raising doubt about modafinil's contribution). The second case reported an increase in psychosis with the addition of modafinil (800 mg/day) to clozapine; however, there was no reported premodafinil clozapine level with which to compare the postmodafinil level of 646 ng/mL (3). We report a case of probable modafinil interaction with clozapine resulting in decreased clozapine levels.

[1] *Outpatient Research Program, Maryland Psychiatric Research Center, University of Maryland School of Medicine*

Address for correspondence: Bernard A. Fischer, IV, MD, Maryland Psychiatric Research Center, University of Maryland School of Medicine, PO Box 21047, Baltimore, Maryland 21228
Phone: 410-402-7113; Fax: 410-402-7198;
E-mail: bfischer@mprc.umaryland.edu

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Case Report of Modafinil Decreasing Clozapine Level

Mr. G is a thirty-seven year old African-American smoker with schizophrenia, undifferentiated type *(Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition [DSM-IV]* criteria) (4). He has been on clozapine 100 mg qam/300 mg qhs for over fifteen years. He was diagnosed with sleep apnea in 2005, but has had difficulty using continuous positive airway pressure (CPAP) due to a rash associated with the mask exacerbated by clozapine-related sialorrhea. In October 2006 he agreed to a trial of modafinil 100 mg qam for daytime fatigue. The day prior to initiating modafinil, a total clozapine level was 974 (721 clozapine, 253 norclozapine) ng/mL -- which was consistent with prior recorded levels (representative total levels have ranged 731 to

1078 ng/mL). After one month on modafinil, his total clozapine level was 455 (325 clozapine, 130 norclozapine) ng/mL. A repeat total level was 435 (312 clozapine, 123 norclozapine). All patients in the clinic receive medication weekly in bubble packs, which they return to the clinic for medication monitoring. When approached about adherence, Mr. G reported missing one clozapine 100 mg tablet one day prior to the first postmodafinil level and one 100 mg tablet three days prior to the repeat level. This was confirmed by the clinic pharmacist's assessment of his medication pack. All levels were obtained midmorning using the same laboratory.

It is possible other missing doses led to the drop in Mr. G's clozapine levels, but he has been stable for years and is generally believed to be adherent to his medications. It seems unlikely the doses reported missing would have such a drastic effect on his clozapine level. A possible explanation is modafinil inducing the metabolism of clozapine. Clozapine is metabolized through 1A2 with accessory pathways via 2C9, 2C19, 2D6, and 3A4 (1). Modafinil can induce metabolism at 3A4 and 1A2 (5) and perhaps this induction is the explanation for Mr. G's decreased levels. As Mr. G has not exhibited any change in psychotic symptoms, and the modafinil has seemed beneficial for his daytime fatigue, he has continued on modafinil.

Brief Review of Modafinil Use in Schizophrenia

Modafinil is FDA-approved for excessive daytime sleepiness secondary to narcolepsy, sleep apnea, and shift-work sleep disorder (6). In contrast to other wakefulness-promoting agents, including amphetamines and caffeine, modafinil acts without increasing dopamine. Although a precise mechanism of action is unclear, there is preliminary evidence from animal models that modafinil acts through orexin (hypocretin) and perhaps histamine and glutamatergic mechanisms (7). Orexin is believed to regulate homeostatic activities such as appetite and the sleep/wake cycle, and modafinil stimulates a robust increase in this neuropeptide. It also increases glutamate release in the hippocampus and histamine in the tuberomammillary nucleus. Again, in contrast to traditional stimulants that cause diffuse brain activation, modafinil-related activation is focused in areas related to the sleep/wake cycle.

Considering that modafinil promotes wakefulness without significant increases in dopamine, there has been interest in using the drug off-label in people with schizophrenia. Physical inactivity is problematic in this population and can be compounded by antipsychotic-related sedation. Several case reports and small, open-label studies have cited decreased antipsychotic-related sedation with the addition of modafinil (8, 9). However, levels of sedation in these reports and open-labeled studies were based on subjective impression. In an RCT, modafinil has not been able to statistically separate from placebo regarding sedation/fatigue ratings (10).

In another approach, Farrow et al., using actigraphic monitors, found modafinil increased overall activity versus placebo in people with schizophrenia (11). This study found a significant, inverse correlation between the Scale for the Assessment of Negative Symptoms (SANS) avolition score and response to modafinil. This raises the possibility that modafinil may be useful in treating some of the negative symptoms in schizophrenia. Indeed, one open-label study found modafinil improved activities of daily living such as "spending time with friends" and "laughing or smiling" (8). However, a recent RCT assessing modafinil in patients with high negative symptom ratings found a benefit in the Clinical Global Impressions scale, but no effect on SANS total or subscales scores (12). This study included deficit syndrome patients (those with enduring, primary negative symptoms), as well as patients with secondary negative symptoms.

Modafinil has also been studied as a cognitive enhancing agent in schizophrenia. An open-label study found improvement in a working memory task with modafinil (8); however, RCTs have had more mixed results. Tasks evaluating episodic memory, attention, working memory, and visual memory were no different in patients on modafinil versus placebo in some studies (10, 12-14), while others found a benefit on tasks of working memory, attention, and response inhibition (14). Complicating the picture are the findings from Hunter et al. suggesting that there is a certain subgroup of patients with poor executive function who preferentially improve with modafinil (15).

Of note, postmarketing experience with modafinil has revealed the possibility of severe reactions. Somatic reactions have included severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms), angioedema, and multiorgan hypersensitivity reactions (6). Psychiatric reactions have included psychosis and mania (6). Due to the potential for psychiatric complications, care should be exercised using modafinil in people with psychotic disorders.

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