

# Modafinil-Associated Weight Loss in a Clozapine-Treated Schizoaffective Disorder Patient

DAVID C. HENDERSON, MD, and PEARL M. LOUIE, MD

Massachusetts General Hospital Schizophrenia Program, Freedom Trail Clinic, Boston, MA, USA and Harvard Medical School, Boston, MA, USA.

PAMPOSH KOUL, BS, and LEAH NAMEY, BS

Northeastern University, Boston, MA, USA.

TARA B. DALEY, MPH, and DANA D. NGUYEN, PhD

Massachusetts General Hospital Schizophrenia Program, Freedom Trail Clinic, Boston, MA, USA.

**Background.** We report a case of weight loss associated with modafinil-initiation in a clozapine-treated man with schizoaffective disorder.

**Methods.** To report the impact of modafinil, a wake promoting agent that lacks the unwanted side effects brought on by many psychostimulants, on weight in a clozapine-treated patient.

**Results.** Modafinil was initiated, and over the course of 1 year, Mr. B. experienced a weight loss of 40 lbs (from 280 lbs to 240 lbs) and a reduction in body mass index (BMI) of 5.08 Kg/m<sup>2</sup> (from 35.52 Kg/m<sup>2</sup> to 30.44 Kg/m<sup>2</sup>). After 3 years on the combination of clozapine and modafinil, his weight stabilized at 230 lbs (BMI = 29.59 Kg/m<sup>2</sup>). A 30-lb weight gain over a 6-month period occurred following discontinuation of modafinil. Reinstitution of modafinil resulted in a 10-lb. weight loss over a 6-week period.

**Conclusions.** Modafinil treatment resulted in a significant weight loss in this patient, possibly due to reducing clozapine-associated fatigue. Randomized placebo-controlled trials are necessary to evaluate the safety and efficacy of modafinil for clozapine-associated weight gain.

**Keywords** Modafinil, sedation, schizoaffective, clozapine, weight-gain, weight-loss

## INTRODUCTION

Clozapine, an atypical antipsychotic agent, offers reduced extrapyramidal side effects and is indicated for the treatment-resistant schizophrenia population. Worrisome side effects of clozapine include sedation, hypersalivation, constipation, seizures, weight gain, hyperglycemia, hyperlipidemia, and agranulocytosis (1,2). Many psychotropic medications, including antipsychotic agents, are associated with significant weight gain. Allison et al. (3) performed a meta-analysis and estimated the average weight change for subjects treated with antipsychotic agents over a 10-week period ranged from 0.39 Kg

reduction with molindone to 4.15 Kg and 4.45 Kg increase with olanzapine and clozapine, respectively.

Weight gain, a significant concern in clozapine-treated patients, may continue for up to 46 months after clozapine-initiation (1,2). Several studies have reported substantial weight gain with clozapine (4-9) which significantly correlated with clinical response in two studies (6,9). Obesity is associated with an increased risk for hypertension, dyslipidemia, insulin resistance; type 2 (non-insulin-dependent) diabetes mellitus, cardiovascular disease, respiratory dysfunction, and gallstones (10).

Modafinil is a schedule IV wake-promoting agent, which is FDA-approved for the treatment of narcolepsy. It is chemically and pharmacologically distinct from other psychostimulants. Modafinil does not appear to have the same dopaminergic activation or cause jitteriness, anxiety, or involuntary movements

Address correspondence to Dr. Henderson, Freedom Trail Clinic, 25 Staniford Street, Boston, MA 02114. E-mail: dchenderson@partners.org

that are routinely seen in other CNS stimulant drugs (11). Additionally, modafinil has a low potential for abuse (12–15). Mild headache and nausea are the two most frequently observed adverse experiences with modafinil (11). The wake-promoting mechanism of action of modafinil remains uncertain, despite numerous reports of its neuropharmacological action in the brain (14–16).

Modafinil may be useful in relieving the sedating and fatiguing side effects of other medications such as clozapine; however, significant weight loss is not an expected outcome. We present a case of modafinil-associated weight loss in a clozapine-treated male with schizoaffective disorder.

### CASE REPORT

Mr. B. is a 33-year-old non-smoker, African-American male with a 10-year history of schizoaffective disorder, bipolar type. He gained over 100 lbs over several years of treatment on a number of antipsychotic agents including haloperidol, risperidone, olanzapine, quetiapine, and finally, clozapine. Clozapine was initiated because of persistent psychotic symptoms and mood instability. Although Mr. B. exhibited excellent improvement in psychotic symptoms and mood instability, he experienced severe side effects from clozapine (i.e., sedation, fatigue, and weight gain), which greatly interfered with his ability to function in his college courses. As a result, modafinil 200 mg/day was initiated 6 months into clozapine treatment, and was tolerated without any adverse events for 3 years. During the first year, on the combination of clozapine and modafinil alone, Mr. B. experienced a weight loss of 40 lbs (from 280 lbs to 240 lbs) and a reduction in BMI of 5.08 Kg/m<sup>2</sup> (from 35.52 Kg/m<sup>2</sup> to 30.44 Kg/m<sup>2</sup>). He had not altered his diet nor increased his exercise routine during this period. Mr. B. continued on the combination of clozapine and modafinil for another 2 years. Throughout the 3-year period, fasting glucose (range 92 mg/dl to 94 mg/dl) and vital signs, including blood pressure (systolic blood pressure range 114–124mmHg; diastolic blood pressure range 60–71mmHg) and pulse, remained stable and within normal limits. After 3 years on the combination of clozapine and modafinil, his weight stabilized at 230 lbs (BMI = 29.59 Kg/m<sup>2</sup>). However, restrictions were placed on modafinil prescriptions by the Medicaid Formulary and modafinil was discontinued. This resulted in a 30-lb weight gain over 6 months, without significant change in mood or psychiatric symptoms. Modafinil was restarted with the aid of modafinil samples and resulted in a 10-lb weight loss over a 6-week period.

### CONCLUSION

While modafinil decreased the fatiguing side effects of clozapine, it also resulted in a 40-lb weight loss over 1 year and a 50-lb weight loss over 3 years. Additionally, following discontinuation of modafinil, significant weight gain was

observed over several months. Upon reinstatement, weight loss again occurred in this patient. As there are few successful interventions for weight gain associated with atypical antipsychotic agents, the addition of modafinil to clozapine may be helpful in some patients. The potential mechanism of modafinil-associated weight loss in a clozapine-treated patient is unknown, but may be related to increased activity (17). This may include non-aerobic activity such as activities of daily living, fidgeting, and posture movement.

Mr. B. noted a significant improvement in his fatigue and sedation while tolerating the combination of clozapine and modafinil. No worsening of psychotic or manic symptoms was observed. There are two cases reported in the literature of modafinil added to clozapine that resulted in an increase in psychotic symptoms (18,19), possibly due to a decrease in clozapine blood levels. Modafinil may induce P450 1A and 3A4 isoenzymes, both important in the metabolism of clozapine. However, this was not evident in Mr. B.'s case as he experienced an improvement in fatigue and sedation, and without an exacerbation of psychotic symptoms from modafinil.

Antipsychotic agents may not only increase appetite leading to an increase in caloric intake, but may also reduce caloric expenditure by decreasing physical activity secondary to sedative and fatiguing side effects. The sedative and fatiguing effects of antipsychotic agents may contribute to reduced activity and exercise in schizophrenic patients. Weight gain and obesity in the chronically mentally-ill are contributing factors for medical disorders such as hypertension, diabetes mellitus, and cardiovascular disease. Modafinil may offer an approach to reduce or reverse weight gain and associated morbidity in antipsychotic- or psychotropic-treated patients. However, randomized placebo-controlled trials are necessary to evaluate the safety and efficacy of modafinil for clozapine-associated weight gain.

### REFERENCES

1. Kane JM: Clinical efficacy of clozapine in treatment-refractory schizophrenia: an overview. *Br J Psychiatry* 1992; 160(suppl. 17): 41–45
2. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC: Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. *Am J Psychiatry* 2000; 157(6):975–981
3. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; 156(11):1686–1696
4. Umbricht DSG, Pollack S, Kane JM: Clozapine and weight gain. *The Journal of Clinical Psychiatry* 1994; 59(supplement B):157–160
5. Bustillo J, Buchanan R, Irish D, Brerer A: Differential effect of clozapine on weight: A controlled study. *Am J Psychiatry* 1996; 153(6):817–819
6. Lamberti JS, Bellnier T, Schwarzkopf SB: Weight gain among schizophrenic patients treated with clozapine. *Am J Psychiatry* 1992; 149(5):689–690

7. Cohen S, Chiles J, MacNaughton A: Weight gain associated with clozapine. *Am J Psychiatry* 1990; 147:503–504
8. Bai YM, Lin CC, Chen JY, Lin CY: Weight gain among patients on clozapine. *Psychiatr Serv* 1999; 50(5):704–705
9. Leadbetter R, Shutty M, Pavalonis D, Vieweg V, Higgins P, Downs M: Clozapine-induced weight gain: Prevalence and clinical relevance. *Am J Psychiatry* 1992; 149:68–72
10. Pi-Sunyer F: Medical hazards of obesity. *Annals of Internal Medicine* 1993; 119(7):655–660
11. US Modafinil in Narcolepsy Study Group: Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. *Ann Neurol* 1998; 43(1):88–97
12. Jasinski DR, Kovacevic-Ristanovic R: Evaluation of the abuse liability of modafinil and other drugs for excessive daytime sleepiness associated with narcolepsy. *Clin Neuropharmacol* 2000; 23(3):149–156
13. Jasinski DR: An evaluation of the abuse potential of modafinil using methylphenidate as a reference. *J Psychopharmacol* 2000; 14(1):53–60
14. Nishino S, Mao J, Sampathkumaran R, Shelton J: Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants. *Sleep Res Online* 1998; 1(1):49–61
15. Scammell TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, Miller MS, Saper CB: Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* 2000; 20(22):8620–8628
16. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM: Dopaminergic role in stimulant-induced wakefulness. *J Neurosci* 2001; 21(5):1787–1794
17. Dinges DF, Weaver TE: Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Med* 2003; 4(5):393–402
18. Narendran R, Young CM, Valenti AM, Nickolova MK, Pristach CA: Is psychosis exacerbated by modafinil? *Arch Gen Psychiatry* 2002; 59(3):292–293
19. Dequardo JR: Modafinil-associated clozapine toxicity. *Am J Psychiatry* 2002; 159(7):1243–1244