

Brief report

# Absence of mood switch with and tolerance to modafinil: A replication study from a large private practice

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Received 10 August 2005; received in revised form 28 December 2005; accepted 6 January 2006

Available online 5 June 2006

## Abstract

**Background:** Fatigue is a common symptom of depression, especially the bipolar type. Modafinil is a wake-promoting agent that can alleviate fatigue in depressed patients. Many stimulants used to treat fatigue carry the risk of a switch into mania or hypomania in bipolar patients as well as the risk for tolerance or abuse.

**Method:** A retrospective chart review was performed on all patients currently being seen in a large outpatient practice who received modafinil at some point during their treatment. Data collected included patient demographics, MiniSCID diagnoses, clinical diagnoses including history of substance abuse, and length and dosage of treatment with modafinil.

**Results:** Of the 191 patients who were given modafinil at some point during their treatment, 105 patients remained on it for 2 months or more and 37% of these patients were bipolar (18 BPI and 21 BP-II). In addition, 86 patients were on modafinil for less than 2 months and 31% of these patients were bipolar (16% BPI and 15% BP-II). No patients in any group demonstrated a switch into mania or hypomania while on modafinil. There was also no significant difference in final modafinil dosage between patients who had a positive history of chemical abuse/dependence (290 mg/day) and those who did not (258 mg/day).

**Limitations:** Retrospective chart review.

**Conclusions:** Adult affective disorder patients, whether unipolar or bipolar, can use modafinil to relieve symptoms of depression, including fatigue and sleepiness, without risking a switch in their mood or developing tolerance or abuse of this medication.

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**Keywords:** Modafinil; Tolerance; Switching

## 1. Introduction

Bipolar patients experience depression more often than mania (Judd et al., 2003). Fatigue has been reported as a possible clue for bipolarity when patients present with depression (Mitchell et al., 2001). Many stimulants or activating antidepressants used to address fatigue and depressed mood carry the risk of a switch into mania or

hypomania in bipolar patients (Boerlin et al., 1998; Goldberg and Truman, 2003; Ghaemi et al., 2004).

Modafinil is a wake-promoting agent that is used to treat many conditions associated with fatigue, including depression (DeBattista et al., 2001; Nasr, 2004). Modafinil's mechanism of action is possibly mediated through the histamine receptors in the anterior hypothalamus without affecting the dopamine pathways associated with dependence and reward usually targeted by the stimulants (Lin et al., 1996). Modafinil, therefore, may be associated with a lower risk of mood switching in depressed patients.

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Substance abuse is an additional contributing factor to mood switching. It is frequently comorbid with affective disorders raising additional concern for abuse of stimulants by bipolar patients. Modafinil is a class IV drug with the potential for risk of tolerance or abuse. However in previous studies of modafinil for depression augmentation, there were no reports of modafinil-induced mania in participants except for 4 single case reports of modafinil-induced recurrence of psychosis (Menza et al., 2000; DeBattista et al., 2001; Carlson et al., 2004; Nasr, 2004; Fava et al., 2005; Vorspan et al., 2005). There is also lack of evidence for its abuse potential even among cocaine dependent individuals (Warot et al., 1993).

The following study examines modafinil's effect on mood switching, dose stability, and abuse liability in a large series of affective disorder outpatients.

## 2. Method

A retrospective chart review was performed on all patients currently being seen in a private, rural, outpatient psychiatric office who received modafinil at some point during their treatment, usually as an adjunct to other medications. Data collected included patient demographics, MiniSCID diagnoses, clinical diagnoses including history of substance abuse, length and dosage of modafinil treatment, and concomitant use of mood stabilizers. Patients were monitored for manic or hypomanic symptoms (euphoria, dysphoria or irritability with increased activity and insomnia) during their regularly scheduled office appointments, and all changes in modafinil dosage were recorded to monitor for the development of tolerance to the medication. Abuse of modafinil was monitored through a log of prescribed amounts compared to office visit interval.

Because many patients did not take modafinil beyond 2 months, and because mood switching could have occurred in the beginning of treatment the total sample was divided into more or less than 2 months use. St Anthony Memorial Health Center's Institutional Review Board gave permission to conduct a nonidentifying review of records.

## 3. Results

Of approximately 1500 patient charts reviewed, 191 patients were given modafinil at some point during their treatment. There were 134 female patients, and 57 male patients. Over 95% of patients were Caucasian. The average age of all patients given modafinil was 49.3 ( $\pm 12.5$ , range: 20–82); 48.6 ( $\pm 13.4$ ) for patients who quit within 2 months, and 49.8 ( $\pm 12.0$ ) for patients who

remained on at least 2 months. 31 patients had a clinical diagnosis of Bipolar I, 33 patients had a clinical diagnosis of Bipolar II, and 118 patients had a clinical diagnosis of unipolar depression. The remaining 9 patients were diagnosed with other mood disorders.

105 patients remained on it for 2 months or longer (18 BP I, 21 BP II), 60 patients remained on for one year or longer (11 BP I, 16 BP II) and 45 patients remained on for 2 or more years (7 BPI, 9 BP II). 86 patients were on modafinil for less than 2 months and 29% of these patients were bipolar (13 bipolar I, 12 bipolar II). The reasons for stopping the medicine within the first two months were for lack of efficacy ( $N=34$ ), cost ( $N=32$ ), or adverse events, mostly sleep related ( $N=20$ ). Patients who remained on modafinil for more than 2 months stayed on modafinil for an average of 21.9 months ( $\pm 16$ ). The longest observation was for 55 continuous months of modafinil use. There was no difference in the frequency of use of mood stabilizers between the patients who were on modafinil for less than 2 months (42%), more than 2 months (45%), more than one year (50%) or longer than 2 years (51%). As expected there were more bipolar patients on mood stabilizers (69% BPI, 59% BP II) than unipolar patients (33%).

No patients in any group demonstrated a switch into mania/hypomania while on modafinil. There was a statistically significant trend ( $p < 0.02$ ) for bipolar patients to have lower final doses of modafinil (230 mg/day  $\pm 88$ ) than unipolar patients (287 mg  $\pm 128$ ). There was no significant difference in final modafinil dosage between patients who had a positive history of chemical abuse/dependence (290 mg/day  $\pm 114$ ) and those who did not (258 mg/day  $\pm 123$ ). Only 15% of the patients required a dosage adjustment in either direction in the first few months with no further changes past the first 10 months. No patients requested earlier refills than needed or reported an increase of dosage on their own beyond the first 1 month of dosage titration.

## 4. Discussion

The present findings indicated that modafinil did not induce manic/hypomanic switches or either tolerance or abuse in either unipolar or bipolar patients whether or not they had a positive history of chemical abuse/dependence.

Zis and Goodwin (1979) reported that cycle frequency increases with advancing age. This puts patients in this study at higher risk for mood switching yet 45 patients observed for 2 or more years did not show any mood cycling on modafinil (Zis and Goodwin, 1979).

Several studies looked at stimulants for depression augmentation. A study by Feighner et al. of 13 Major

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