

Retrospective Study of Olanzapine in Depressive and Anxious States in Primary Care

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Context: Bipolar spectrum and treatment-resistant unipolar mood disorders are increasingly identified in primary care settings. Olanzapine demonstrates efficacy in the treatment of acute mania and bipolar depression and in bipolar maintenance therapy. Olanzapine-fluoxetine combination therapy shows efficacy in treatment-resistant depression.

Objective: To examine the efficacy and tolerability profile of olanzapine in various difficult-to-treat depressive and/or anxious states in primary care outpatients.

Method: A retrospective chart review was conducted for all identifiable patients prescribed olanzapine for mood disorders (DSM-IV) during a 3-year period (July 1998–July 2001), utilizing clinician and nurse recall, sampling of general continuity clinic records, and a hand search of mood disorder clinic records.

Main and Secondary Outcome Measures: Initial and final scores on the Global Assessment of Functioning (GAF) scale, duration of therapy, and adverse effects.

Results: Thirty-seven patients were identified as having received treatment with olanzapine; 3 were referred to the mental health specialty sector at the time of treatment initiation, and 2 were lost to follow-up. Of the 32 patients receiving ongoing treatment by primary care clinicians, most were female (N = 23; 72%) and all were white (100%). Most were diagnosed with a mental illness in the bipolar spectrum (N = 25; 78%) and demonstrated treatment resistance with antidepressants and/or mood stabilizers (mean number of previous psychotropic medications = 3.7). In the group completing therapy (24 patients [75%]; mean duration of treatment = 242 days), GAF scores demonstrated a clinically and statistically significant improvement (mean initial GAF score = 59 ± 9 ; mean final GAF score = 76 ± 11 ; $p < .0001$). Twenty (83%) of these 24 patients demonstrated sustained improvement in their GAF scores. In the group that discontinued therapy (8 patients [25%]; mean duration of treatment = 123 days), GAF scores also demonstrated a clinically and statistically significant improvement (mean initial GAF score = 51 ± 15 ; mean final GAF score = 70 ± 11 ; $p < .0001$). Six (75%) of these 8 patients demonstrated sustained improvement in their GAF scores. For all patients, observed adverse effects included weight gain (25 patients [86%]; mean = 3.63 kg), sedation (6 patients [19%]), and dry mouth (1 patient [3%]).

Conclusion: Olanzapine shows promise as an effective pharmacotherapeutic agent for primary care patients with mood disorders that lie along the bipolar spectrum or that are resistant to treatment with antidepressant monotherapies, but is associated with mild-to-moderate weight gain.

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Olanzapine is a thienobenzodiazepine compound originally classified as an atypical antipsychotic based on its relatively low potential for causing extrapyramidal syndrome, tardive dyskinesia, and prolactin elevation.¹ Olanzapine is a serotonin-2 (5-HT₂) receptor antagonist² similar to the antidepressants mirtazapine, nefazodone, and trazodone. Such antagonism at this negative feedback receptor increases the release of serotonin from the presynaptic membrane, ultimately resulting in increased serotonin activity at the 5-HT₁ receptor. This increase in serotonergic tone is thought to explain olanzapine's antidepressant and anxiolytic qualities and enhanced dopamine activity in the frontal cortex. Olanzapine reduces the symptoms of mania in bipolar patients, an effect thought to be attributable to its dopamine inhibition.³ Controlled investigations of olanzapine in bipolar depression^{4,5} and bipolar maintenance therapy⁶ reveal significant efficacy; in addition, olanzapine has been combined with fluoxetine effectively for patients with treatment-resistant depression.⁷

We hypothesized that olanzapine's efficacy, safety, and tolerability profile, and its relative ease of use, would offer utility in the management of bipolar spectrum conditions and treatment-resistant depression in primary care. We began prescribing olanzapine for patients with mood disorders in the bipolar spectrum, most suffering from "soft" bipolar illness based on Akiskal and Mallya's modification of the DSM-IV criteria.⁸ The majority of these patients had previously been diagnosed with major de-

pression or an anxiety disorder and had failed multiple antidepressant trials. Our anecdotal experience with olanzapine in these patients was impressive, leading to a retrospective chart review to more rigorously assess the clinical efficacy of this drug in our primary care setting.

METHOD

The first 2 authors (W.C.J./J.S.M.) functioned as clinical faculty seeing patients at 3 outpatient teaching centers. Patients may present initially to the clinicians' general continuity clinics, or be referred to "mood disorder clinics," which are conducted in the same teaching centers.⁹ A retrospective chart review was conducted for all identifiable patients prescribed olanzapine for mood disorders (DSM-IV) by either clinician during a 3-year period (July 1998–July 2001), utilizing clinician and nurse recall, sampling of general continuity clinic records, and a hand search of mood disorder clinic records. No patients were excluded from the analysis.

Demographic and historical data gathered included previous diagnoses, current diagnosis, number of family members with mood disorders, and number of previous psychotropic medications. Treatment data gathered included the start date of treatment, end date of treatment (or last day observed while on therapy), maximal dose of olanzapine, number of psychotropic medicines on the last day of observation, initial and final weight, and adverse effects.

The Global Assessment of Functioning (GAF)¹⁰ was used as a measure of overall symptomatic and functional impairment. Utilizing the patients' records and clinician input, initial and final GAF scores were assigned by a trained researcher (O.G.D.) and reviewed for validity by the treating clinician (J.S.M. or W.C.J.). Interrater reliability for GAF score assignment was high, with the κ coefficient > 0.75 . To determine statistical significance, categorical variables were compared utilizing the χ^2 test; dimensional variables were compared utilizing the Student t test.

RESULTS

Thirty-seven patients were identified as having been treated with olanzapine for a mood disorder by one of the faculty clinicians within the past 3 years. Of these 37 patients, 3 (8%) were referred to a psychiatrist or inpatient facility within 2 weeks of presentation due to severity of illness, diagnostic uncertainty, or unsuitability for treatment in a primary care setting. Two patients (5%) were lost to follow-up. Those patients referred or lost to follow-up did not differ significantly from the treatment group with respect to age, gender, ethnicity, or diagnosis.

Thirty-two patients (86% of the intent-to-treat group) were treated with olanzapine, remained in the primary

Table 1. Olanzapine Dosing, Weight Gain, Global Assessment of Functioning (GAF) Scores, and Therapeutic Duration for Those Continuing and Discontinuing Therapy^a

Variable	Continuation (N = 24)	Discontinuation (N = 8)	p Value (t test)
Olanzapine dosing, mg/d	7.5 ± 5.0	4.4 ± 2.6	.10
Weight gain, kg (lb)	3.4 ± 3.1 (7.6 ± 6.9)	4.6 ± 2.8 (10.2 ± 6.2)	.60
Initial GAF score	59.2 ± 9.3	50.9 ± 15.0	.07
Final GAF score	75.5 ± 11.2	70.3 ± 10.6	.25
Days on olanzapine treatment	242.5 ± 241.0	123.4 ± 74.5	.18

^aValues shown as mean ± SD.

care setting for psychiatric care, and were followed longitudinally. Of these 32 patients in the treatment arm, the majority were young (mean age = 39.1 ± 10.9 years), white (32 patients; 100%), female (23 patients; 72%) and were diagnosed with a mental illness in the bipolar spectrum (Bipolar I, II, or not otherwise specified) (25 patients; 78%). Other recorded diagnoses included major depressive disorder (5 patients; 16%), generalized anxiety disorder (1 patient; 3%), and schizoaffective disorder (1 patient; 3%). Table 1 lists olanzapine dosing, weight gain, GAF scores, and therapeutic duration for those who were still taking olanzapine at the end of the observation period versus those who discontinued olanzapine therapy. Most patients had symptoms recalcitrant to multiple previous attempts at pharmacotherapy (mean number of previous psychotropic medications = 3.7).

In the group completing therapy (24 of 32 patients; 75%), the mean duration of treatment was 242 ± 241 days. GAF scores demonstrated a clinically and statistically significant improvement (mean initial GAF score = 59 ± 9; mean final GAF score = 76 ± 11; $p < .0001$). Twenty (83%) of these 24 patients showed sustained increases in their GAF scores throughout the observation period.

A total of 8 patients (of 32 patients; 25%) discontinued therapy. Four patients discontinued because of weight gain, 3 because of sedation, and 1 secondary to complaints of sexual dysfunction. Mean duration of treatment in this group was 123 ± 75 days. Despite a shorter duration of treatment, GAF scores also demonstrated a clinically and statistically significant improvement (mean initial GAF score = 51 ± 15; mean final GAF score = 70 ± 11; $p < .0001$). Six (75%) of these 8 patients showed sustained increases in their GAF scores during their treatment period.

Observed adverse effects included weight gain (25 of 29 patients for whom complete weight data were available; 86%), sedation (6 of 32 patients; 19%), sexual dysfunction (1 of 32 patients; 3%), and dry mouth (1 of 32 patients; 3%) (Table 2).

Table 2. Observed Adverse Effects of Olanzapine

Side Effect	N	%
Weight gain (total N = 29)	25	86
Sedation (total N = 32)	6	19
Sexual dysfunction (total N = 32)	1	3
Dry mouth (total N = 32)	1	3

For the 32 patients in the treatment arm, complete weight data were available for 29 patients. Mean weight gain was 3.6 ± 3.1 kg. (8.1 ± 6.8 lb). Four patients (14%) gained no weight or lost weight. Patients who completed therapy gained less absolute weight (3.4 ± 3.1 kg [7.6 ± 6.9 lb]) than those who discontinued therapy (4.6 ± 2.8 kg [10.2 ± 6.2 lb]), but the discontinuance group gained less weight as a percentage of total body weight (5.2%) than the completion group (5.6%). In the completion group, 7 (32%) of 22 patients for whom data were available gained $\geq 7\%$ of their initial body weight. In the discontinuance group, 4 (57%) of 7 patients for whom data were available gained $\geq 7\%$ of their initial body weight. For all patients in the treatment arm for whom data were available, 11 (38%) of 29 patients gained $\geq 7\%$ of their initial body weight.

DISCUSSION

Our observation of a statistically significant sustained increase in GAF scores following treatment with olanzapine is particularly encouraging, given the previous failure of multiple pharmacologic interventions in most of these patients and the potential for GAF scores to represent “real-world gains” in terms of patient functioning. Overall, the balance of efficacy, safety, and tolerability with olanzapine was positive, as evidenced by the 75% of patients placed on therapy who continued to take the drug throughout their period of observation.

We believe our study represents the largest data set currently published regarding the use of an atypical antipsychotic for mood disorders in the primary care setting. Careful evaluation of this patient population revealed a high prevalence of mood disorders in the soft bipolar spectrum. This finding is consistent with current evidence from practice-based and epidemiologic studies. Bipolar II and related illness may be more common in primary care settings than previously thought, based on a reassessment of the prevalence of such a bipolar spectrum in the general population¹¹ coupled with current data on the utilization of primary care for mental health services.¹² Direct observation of an increased prevalence of bipolar II and related disorders in primary care also exists.^{9,13,14}

Patients in the treatment arm gained an average of 3.9 kg (8.7 lb), or 5.6% of body weight—an amount that, though not trivial, is below the 7% of body weight defined by the U.S. Food and Drug Administration as being “clinically significant” weight gain during treat-

ment with psychotropics.¹⁵ Neither behavioral nor pharmacologic^{16–18} interventions were systematically instituted, and it is unknown what effects such interventions might have had on weight gain. The amount of weight gained in our patients is similar to the amount reported for patients treated with olanzapine for short durations (approximately 10 weeks).¹⁹ Four patients (12.5% of treatment arm) listed weight gain as a reason for discontinuation of therapy.

Our study should be interpreted in light of the methodological weaknesses inherent in naturalistic and retrospective designs—namely, recall bias and the inability to control potentially confounding factors (e.g., concomitant medications). In addition, the utilization of clinician-assigned GAF scores (rather than patient-driven data) introduces observer subjectivity as a potential source of error, although κ coefficients suggest a high degree of interrater reliability.

CONCLUSION

Olanzapine demonstrated excellent overall efficacy and tolerability in this retrospective review of bipolar and other difficult-to-treat depressed and anxious patients in an academic primary care setting. Mild-to-moderate weight gain was evidenced by most patients, but was uncommonly cited as a reason for discontinuation of treatment, suggesting efficacy gains during treatment may have significantly influenced individual patient assessments of the cost-benefit ratio of therapy.

Drug names: fluoxetine (Prozac and others), mirtazapine (Remeron and others), nefazodone (Serzone), olanzapine (Zyprexa), trazodone (Desyrel and others).

REFERENCES

1. Tollefson GD, Sanger TM, Beasley CM, et al. A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. *Biol Psychiatry* 1998;43:803–810
2. Bymaster FP, Rasmussen K, Calligaro DO, et al. In vitro and in vivo biochemistry of olanzapine: a novel, atypical antipsychotic drug. *J Clin Psychiatry* 1997;58(suppl 10):28–36
3. Tohen M, Jacobs TG, Grundy SL, et al, for the Olanzapine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 2000;57:841–849
4. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine/fluoxetine in combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;60:1079–1088. Correction 2004; 61:176
5. Shi L, Namjoshi MA, Swindle R, et al. Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial. *Clin Ther* 2004;26:125–134
6. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry* 2003;160:1263–1271
7. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001; 158:131–134
8. Akiskal HS, Mallya G. Criteria for the “soft” bipolar spectrum:

- treatment implications. *Psychopharmacol Bull* 1987;23:68–73
9. Manning JS, Zylstra RG, Connor PD, et al. Teaching family physicians about mood disorders: procedure suite for behavioral medicine. *Primary Care Companion J Clin Psychiatry* 1999;1:18–23
 10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994:32
 11. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord* 2003;73:123–131
 12. Regier DA, Narrow WE, Rae DS, et al. The de facto US mental and addictive disorders service system: epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Arch Gen Psychiatry* 1993;50:85–94
 13. Coyne JC, Fechner-Bates S, Schwenk TL. Prevalence, nature, and comorbidity of depressive disorders in primary care. *Gen Hosp Psychiatry* 1994;16:267–276
 14. Manning JS, Haykal RF, Connor PD, et al. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. *Compr Psychiatry* 1997;38:102–108
 15. Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. *J Clin Psychiatry* 1999;60(suppl 21):16–19
 16. Cavazzoni P, Tanaka Y, Roychowdhury SM, et al. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol* 2003;13:81–85
 17. Poyurovsky M, Isaacs I, Fuchs C, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. *Am J Psychiatry* 2003;160:297–302
 18. Levy E, Margolese HC, Chouinard G. Topiramate produced weight loss following olanzapine-induced weight gain in schizophrenia [letter]. *J Clin Psychiatry* 2002;63:1045
 19. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;156:1686–1696