

Bipolar Disorder: Quality of Life and the Impact of Atypical Antipsychotics

Lana A. Vornik, MSc; and Robert M. A. Hirschfeld, MD

Abstract

This article reviews the impact of bipolar disorder on the quality of life of affected individuals. In particular, the impact of atypical antipsychotics on the quality of life of individuals with bipolar disorder is addressed. Among atypical antipsychotics, olanzapine has been studied most with regard to quality of life. In general, symptomatic improvements have been associated with improvements in quality of life.

(*Am J Manag Care.* 2005;11:S275-S280)

agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, as well as recurrent thoughts of death or suicidal ideation, or suicide attempt.³ These symptoms affect the physical, emotional, and social functioning of an individual and can have a significant effect on the overall quality of life.

Bipolar Disorder: Prevalence and Illness Characteristics

Bipolar disorder is a recurrent and sometimes long-term mental illness that can seriously affect the lives of patients and their families. The lifetime prevalence of bipolar I disorder, the most severe form of the illness, is approximately 1%. The lifetime prevalence of all forms of the illness, often referred to as bipolar spectrum disorders, has been estimated to be 5% in the general population.^{1,2}

Bipolar disorder is characterized by intermittent episodes of mania and depression. Symptoms of mania include increased energy, restlessness, and feelings of euphoria. States of mania are often characterized by impulsivity, excessive libido, recklessness, social intrusiveness, and diminished need for sleep, all of which may lead patients to inflicting harm on themselves and others.³ It is not uncommon for manic patients to find themselves on spending sprees, to get involved in reckless behavior, and to start abusing alcohol. Bipolar depression, on the other hand, is characterized by depressed mood or loss of or markedly diminished interest or pleasure in nearly all activities, significant weight loss when not dieting or weight gain, insomnia or hypersomnia nearly every day, psychomotor

Impact of Bipolar Disorder on Patient Lifestyle

Bipolar disorder causes significant psychosocial morbidity, because it frequently affects patients' relationships with family members as well as workplace functioning. A recent community survey investigated the impact of bipolar disorder on people's lives, using the Mood Disorder Questionnaire (MDQ) as a screening instrument. Subjects screening positive for bipolar disorder on the MDQ reported significantly more work and relationship problems and a greater burden of comorbid medical illness than subjects who were negative for bipolar disorder. Significantly more respondents with positive screens for bipolar disorder had been arrested, convicted, or jailed for a crime compared with respondents with negative screens for bipolar disorder.⁴

Another study conducted in a primary care practice demonstrated that individuals who screened positive for bipolar disorder on the MDQ experienced significant disability in health, social, family, and occupational functioning. Even after adjusting for the presence of any current mental condition, impairment in health-related quality of life, social activities, and family life remained significantly associated with a positive screen for bipolar disorder. Moreover, nearly one

fifth (19%) of those who screened positive for bipolar disorder in this study reported suicidal ideation at least some days during the previous 2 weeks compared with 4% of those who screened negative.⁵ Even after remission of acute episodes, impaired functioning may persist.⁶ Many patients with bipolar disorder do not fully recover the ability to function in work and social activities, and they remain impaired even during the stable phase of their illness.⁷⁻¹¹

Research demonstrates that bipolar depression (and not mania) predicts greater illness burden and chronicity.¹² Depressive symptoms are more frequent than manic symptoms and are more likely to disrupt work as well as social and family life functioning than manic symptoms. Moreover, bipolar depressed patients experience significantly worse depressive symptoms than unipolar depressed patients.^{13,14} Bipolar depressed patients are also more likely to report being impaired all or most of the time in their ability to work than unipolar depressed patients. Despite the central importance of depression in the overall care of bipolar patients, this phase of the illness remains remarkably underinvestigated.¹⁵ Options for the treatment of patients with bipolar depression are particularly limited when compared with the options available in the treatment of unipolar depression. Indeed, until a few years ago, lithium was the only medical treatment with substantial research evidence of efficacy in bipolar depression. More recently, studies of olanzapine, olanzapine/fluoxetine combination, quetiapine, lamotrigine, and divalproex reported on the efficacy of these drugs in bipolar depression.

Quality of Life in Individuals With Bipolar Disorder

Quality of life usually refers to satisfaction with major areas of daily functioning, including physical, emotional, social, and spiritual well-being.^{7,16} Health-related quality of life is specifically concerned with those aspects of functioning that can be directly attributed to illness and consequent therapy.⁷

Few studies have evaluated the impact of bipolar disorder on health-related quality of

life. A systematic review of bipolar disorder literature covering the period between 1966 and 1998 found 72 articles on studies of bipolar disorder, of which only 10 included a health-related quality-of-life assessment.⁷ When patients with bipolar disorder were compared with patients with schizophrenia using the Quality of Life Interview (QLI), bipolar patients reported significantly less satisfaction with their quality of life than patients with schizophrenia. This is particularly interesting in view of the findings that on objective measures of life quality (ie, level of education, financial situation, health impairment), bipolar patients reported higher levels of achievement than schizophrenic patients.¹⁷

Among individuals with bipolar disorder, women reported lower scores on quality-of-life measures than men.⁷ When psychotic patients were compared with nonpsychotic bipolar patients, it was found that although the psychotic patients were more symptomatic than the nonpsychotic group during the index episode, it did not result in a higher degree of functional impairment.⁷

Another recent study compared quality of life across the mood states of bipolar disorder.¹⁸ The manic/hypomanic group manifested significantly lower self-reported quality of life than euthymic patients. This finding refutes the popular conceptualization that manic/hypomanic patients have an inflated sense of well-being and subjective life quality. Also of note is the finding that depressive symptoms play a key role in determining the quality of life of bipolar patients. Specifically in patients in mixed episode, the depressive component appeared to predominate in the evaluation of quality of life.¹⁸

Treatment Issues in Bipolar Disorder: Atypical Antipsychotics

The first drug that was approved by the US Food and Drug Administration for the treatment of bipolar mania was lithium in the early 1970s. Although its efficacy in bipolar disorder is well established, lithium is associated with infrequent serious adverse effects and medical risks, including tremors, weight gain, gastrointestinal disturbances, cognitive slowing, neurotox-

ic effects with overdose, thyroid toxicity, and diabetes insipidus. Moreover, the requirement for therapeutic drug monitoring, including occasional blood tests, to minimize these risks is unattractive to patients and physicians.¹⁵ More common adverse events include nausea, vomiting, diarrhea, sedation, tremor, polyuria, polydipsia, weight gain, acne, and psoriasis, and it is these milder but more common side effects that make lithium less acceptable over the long term among individuals with bipolar disorder.

First-generation conventional antipsychotic drugs, such as chlorpromazine and haloperidol, are effective in the acute treatment of mania, but undesirable side effects (including extrapyramidal side effects and neuroleptic-induced movement disorders, such as parkinsonism, dystonia, akathisia, and tardive dyskinesia)¹⁹ limit their use in bipolar patients. These side effects lead many patients to discontinue use of these antipsychotic drugs, despite improvements in patient symptoms.

Adherence to long-term therapy with antipsychotic drugs is closely linked to the incidence and nature of side effects.²⁰ The rate of discontinuation cannot be solely attributed to the lack of the patient's insight into the disorder or the necessity for treatment. Many factors, such as the positive

influence of a good patient–physician relationship, are important in compliance with therapy. However, the patient's initial subjective experience during treatment with an antipsychotic drug is a major predictor of compliance.²⁰ A more favorable benefit–risk ratio throughout all phases of treatment can contribute to greater patient adherence and will help patients adhere to long-term therapy. Patients' subjective dissatisfaction with treatment is difficult to capture with objective examinations, but it is readily reported by patients on quality-of-life measurements.²⁰

Newer generation atypical antipsychotics offer several tolerability benefits over conventional antipsychotics, particularly with respect to extrapyramidal symptoms, and are therefore viewed as superior to conventional antipsychotics in improving quality of life, particularly from the patient's perspective.²⁰ Indeed, it has been demonstrated that atypical antipsychotics at low doses can be efficacious in the treatment of psychosis without inducing neurotoxic side effects.²¹ The findings of a large number of studies of atypical antipsychotics currently on the market (ie, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) have now been published and reviewed.^{21,22} Atypical antipsychotics are effective in the treatment of bipolar mania, either alone or in combination with tradi-

Table. Quality-of-Life Assessments in Individuals With Bipolar Disorder Treated With Atypical Antipsychotics

Drug	Study design	Quality-of-life assessment	Results
OLZ ²³	3 wk DB; 49 wk OL	SF-36	Sign improvements on several dimensions of SF-36 at 3 wk and at 49 wk
OLZ + Li vs PCB + Li ²⁴	6 wk	QLI	OLZ + Li > PCB + Li on 5 of 9 QLI scales
Risperidone ²⁵	3 wk DB; 9 wk OL	GAS	Risperidone > PCB
Quetiapine ²⁶	12 wk DB vs PCB vs Li	GAS	Quetiapine > PCB; Li > PCB
Ziprasidone ²⁷	3 wk DB vs PCB	GAS	Ziprasidone > PCB

OLZ indicates olanzapine; DB, double-blind; OL, open-label; PCB, placebo; Li, lithium; SF-36, Short Form-36 of the Medical Outcomes Study; QLI, Lehman Brief Quality of Life Interview; GAS, Global Assessment of Functioning Scale.

tionally used mood stabilizers, such as lithium and divalproex.

Although a number of studies addressed the efficacy profile of atypical antipsychotics in bipolar disorder, very few addressed the impact of treatment with atypical antipsychotics on quality of life.

Quality-of-Life Assessments in Individuals With Bipolar Disorder Treated With Atypical Antipsychotics

Although social functioning, integration of patients back into society, and a normalization of their life situation are the goals of treatment, few studies include measures of social functioning and quality of life in their analyses. In fact, to date no reported studies of atypical antipsychotics, except the studies of olanzapine, included psychosocial functioning and quality-of-life evaluations in their analyses.

Quality-of-life outcomes were assessed in patients with the diagnosis of bipolar I disorder in a manic or mixed episode who were treated with olanzapine versus placebo in a 3-week acute double-blind study (Table).²³ The acute phase was followed by a 49-week open-label extension during which all patients were treated with olanzapine. During the open-label extension, the use of lithium or fluoxetine was permitted for patients with breakthrough episodes. Health-related quality of life was measured using the Short Form-36 (SF-36) of the Medical Outcomes Study, a form that covers multiple dimensions of quality of life. Olanzapine-treated patients experienced significant improvements in manic symptoms as measured by the Young Mania Rating Scale (YMRS) scores during the 3-week acute phase compared with the placebo-treated group, and patients continued to improve throughout the 49 weeks of open-label olanzapine treatment. With regard to quality-of-life outcomes, in the acute phase of the trial, olanzapine-treated patients improved on all dimensions of the SF-36, but these improvements were not significantly different from improvements in the placebo group, except for the "physical functioning" dimension of SF-36, on which olanzapine-treated patients improved significantly compared with placebo.

bo. However, during this period significantly more olanzapine-treated than placebo-treated patients were discharged from the hospital. During the open-label treatment period, olanzapine-treated patients showed further improvements on all SF-36 dimensions compared with at the end of the acute treatment period. Moreover, a relationship was determined between improvements on the YMRS scale and SF-36, suggesting that as patients improve clinically during olanzapine treatment, they may start to experience functional improvement as well.

A separate study investigated quality-of-life improvements in patients with bipolar disorder treated with olanzapine added to lithium or valproate for 6 weeks (Table).²⁴ Patients receiving olanzapine added to a mood stabilizer experienced statistically more significant clinical improvements (as measured by YMRS and the Hamilton Depression Scale) than patients treated with a mood stabilizer alone. These improvements were complemented by significant improvements on the measure of quality of life (Lehman's QLI), and these improvements were greater in patients treated with olanzapine added to a mood stabilizer than in patients treated with a mood stabilizer alone. This study suggests that as individuals treated with olanzapine in combination with a mood stabilizer improve clinically, they also become more satisfied with their social functioning, including improvements in interactions with friends and family, and their living situation.

Quality of life was measured indirectly in risperidone studies using the Global Assessment of Functioning Scale (Table). Assessment of global functioning was performed in two 3-week acute studies of risperidone compared with placebo and in an open-label 9-week extension to these acute trials. In the acute trial, patients treated with risperidone improved statistically more significantly than placebo-treated patients on measures of global functioning; these improvements were sustained during the 9 weeks of open-label treatment with risperidone. At the end of 12 weeks of treatment with risperidone, more than 60% of individuals achieved good global functioning scores.²⁵

Global assessment of functioning was also performed in a 12-week study of quetiapine (Table).²⁶ Significant improvements were seen at 3 and 12 weeks; patients' functioning improved significantly more in the quetiapine group than in the placebo group.²⁶ Similarly, global functioning improved significantly in ziprasidone-treated patients compared with placebo-treated patients in a 3-week acute study of ziprasidone versus placebo (Table).²⁷ Global assessment of functioning was not included in the published studies of aripiprazole in bipolar patients.

Conclusion

When compared with first-generation antipsychotics, second-generation antipsychotics improve medication-adherence behavior, quality of life, and subjective tolerability. Most published studies on second-generation antipsychotics have dealt with issues related to efficacy and safety, but not quality of life. Few studies have focused on effectiveness in terms of such important outcomes as medication-adherence behavior, quality of life, subjective tolerability, and overall satisfaction with treatment. Well-designed, controlled, and adequately powered studies are urgently needed before any firm conclusions can be reached.

REFERENCES

1. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord*. 2000;59(suppl 1):S5-S30.
2. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord*. 2003;73:133-146.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, revised (DSM-IV). Washington, DC: American Psychiatric Press; 1994.
4. Calabrese JR, Hirschfeld RM, Reed M, et al. Impact of bipolar disorder on a US community sample. *J Clin Psychiatry*. 2003;64:425-432.
5. Das AK, Olfson M, Gameroff MJ, et al. Screening for bipolar disorder in a primary care practice. *JAMA*. 2005;293:956-963.
6. Tohen M, Zarate CA Jr, Hennen J, et al. The McLean-Harvard First-Episode Mania study: prediction of recovery and first recurrence. *Am J Psychiatry*. 2003;160:2099-2107.
7. Namjoshi MA, Buesching DP. A review of the health-related quality of life literature in bipolar disorder. *Qual Life Res*. 2001;10:105-115.
8. Leidy NK, Palmer C, Murray M, Robb J, Revicki DA. Health-related quality of life assessment in euthymic and depressed patients with bipolar disorder. Psychometric performance of four self-report measures. *J Affect Disord*. 1998;48:207-214.
9. Goldberg JF, Harrow M, Grossman IS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *Am J Psychiatry*. 1995;152:379-384.
10. Harrow M, Goldberg JF, Grossman IS, Meltzer HY. Outcome in manic disorders. A naturalistic follow-up study. *Arch Gen Psychiatry*. 1990;47:665-671.
11. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. *Am J Psychiatry*. 1993;150:720-727.
12. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59:530-537.
13. Hirschfeld RM, Calabrese JR, Frye MA, Wagner KD, Reed M. Burden of manic versus depressive symptoms in patients with bipolar disorder. Poster presented at: Annual Meeting of the American Psychiatric Association; May 17-22, 2003; San Francisco, Calif. [NR388].
14. Hirschfeld RM, Calabrese JR, Frye MA, Wagner KD, Reed M. Impact of bipolar depression compared with unipolar depression. Poster presented at: Annual Meeting of the American Psychiatric Association; May 17-22, 2003; San Francisco, Calif. [NR389].
15. Baldessarini RJ. Treatment research in bipolar disorder: issues and recommendations. *CNS Drugs*. 2002;16:721-729.
16. Ritsner M, Gibel A, Perelroyzen G, Kurs R, Jabarin M, Ratner Y. Quality of life outcomes of risperidone, olanzapine, and typical antipsychotics among schizophrenia patients treated in routine clinical practice: a naturalistic comparative study. *J Clin Psychopharmacol*. 2004;24:582-591.
17. Atkinson M, Zibin S, Chuang H. Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report methodology. *Am J Psychiatry*. 1997;154:99-105.
18. Vojta C, Kinosian B, Glick H, Altshuler L, Bauer MS. Self-reported quality of life across mood states in bipolar disorder. *Compr Psychiatry*. 2001;42:190-195.
19. Wirshing WC. Movement disorders associated with neuroleptic treatment. *J Clin Psychiatry*. 2001;62(suppl 21):15-18.
20. Naber D, Karow A. Good tolerability equals good results: the patient's perspective. *Eur Neuropsychopharmacol*. 2001;11(suppl 4):S391-S396.
21. Hirschfeld RMA. The efficacy of atypical antipsychotics in bipolar disorders. *J Clin Psychiatry*. 2003;64(suppl 8):15-21.
22. Vieta E, Goikolea JM. Atypical antipsychotics: newer options for mania and maintenance therapy. *Bipolar Disord*. 2005;7(suppl 4):21-33.
23. Namjoshi MA, Rajamannar G, Jacobs T, et al. Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania. Results from a

REPORTS

randomized controlled trial. *J Affect Disord.* 2002; 69:109-118.

24. Namjoshi MA, Risser R, Shi L, Tohen M, Breier A. Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid. *J Affect Disord.* 2004;81:223-229.

25. Hirschfeld RMA, Eerdekens M, Kalali AH, et al. An open-label extension trial of risperidone monotherapy in the treatment of bipolar I disorder. *Int Clin Psychopharmacol.* In press.

26. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry.* 2005; 66:111-121.

27. Keck PE Jr, Versiani M, Potkin S, West SA, Giller E, Ice K; Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry.* 2003;160:741-748.