The Case for Atypical Antipsychotics in Bipolar Disorder

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Abstract:

Shattell and Keltner present a case for atypical antipsychotics in bipolar disorder. Moreover, they review current research that supports the effectiveness of several antipsychotics, including olanzapine, quetiapine, and ziprasidone, in treating such disorder. They assert that managing symptoms through psychotropic medications can help people with mental disabilities better manage their lives.

Article:

Nothing is more addictive than the high of a manic euphoria.
-Margo Orum, 1996

Bipolar disorder has risen almost to the level of diagnosis du jour. Sheer numbers will not allow it to eclipse the attention directed at social anxiety disorder, depression, or attention deficit hyperactivity disorder, but a quick review of mailings received in the last 6 months will reveal a tremendous surge of interest in this disorder. Major conferences, drug company symposia, and online continuing education programs have increasingly focused on this mental health problem.

Scenario

Demographics A young man (Bob, age 30) and a young woman (Mary, age 26) betrothed, with wedding date planned for the near future.

Background Both college educated with particularly promising careers.

The Setting Mary flies into a rage and breaks off the engagement when Bob asks her if she'll let the pets out. Mary leaves for 3 weeks, then returns the day before a relative's funeral. Bob attends with her, and she introduces him as her fiancé.

The Crisis After the funeral she tells Bob: "I got married to my old boyfriend while I was gone. It was a mistake. I went to see my doctor. he thinks I have bipolar disorder."

The incidence of bipolar varies considerably among studies-from 0.4% to 1.6%, with ranges to 7% suggested when the full spectrum of bipolar disorders is included (American Psychiatric Association, 2000; Ghaemi, 2001; Kessler, Stang, Wittchen, Stein, & Walters, 1999). Typically, a first-time diagnosis occurs around 20 years of age but, as in the scenario above, 26 is within the

normal limits. Even though diagnosis may not be made until the third decade, prodromal behaviors during the teenage years often give hints of future morbidity. Treatment is often lifelong, because the disorder tends to be lifelong. It is a significant problem and seems to figure more prominently in society's thinking today than it was just 10 or 15 years ago.

As the scenario above suggests, a manic episode can wreak havoc in the life of the individual and those close to that person. Since such scenarios are not uncommon, the search for effective treatment continues to be a high priority for clinicians and patients. While lithium is still the gold standard, about 50% of patients do not improve substantially on this medication (Scares, Mallinger, & Gershon, 1997). Likewise, valproates (i.e., divalproex, sodium valproate, valproic acid) and carbamazepine are effective pharmacologie interventions for many, but not for all, bipolar patients. This reality has triggered extensive efforts to develop and/or find suitable adjunctive or monotherapies for the many individuals who are unsatisfactorily treated with lithium and anticonvulsants. A drug category of major interest, and most often the focus of the aforementioned conferences, symposia, etc., is the atypical antipsychotic drug (or medication) group.

Until recently, antipsychotics were not considered first-line agents for treating bipolar disorder. Algorithms developed to assist clinicians recommended atypical antipsychotics when lithium and the anticonvulsants were ineffective, and typically only then in an adjunctive role. The Texas Medication Algorithm Project for Mania supports the use of the atypical olanzapine, an alternative to lithium or divalproex, for acute mania (Suppes et al., 2003).

Before reviewing individual agents, it should be noted that a commonly used tool for measuring mania is the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). The scale has 11 items (Table 1), with a maximum score of 60. Table 2 expands one of the items of the YMRS for those unfamiliar with the scale. A typical minimum score for inclusion in a clinical trial is 20. Improvement is often defined as a decrease in symptoms by 50%; however, for some studies, remission may be the objective and defined as an YMRS of <15. It is important to notice how success is being measured on a particular study.

Table 1. Items on the Young Mania Rating Scale

1. Elevated mood
2. Increased motor activity-energy
3. Sexual interest
4. Sleep
5. Irritability
6. Speech (rate and amount)
7. Language-thought disorder
8. Content
9. Disruptive-aggressive behavior
10. Appearance
11. Insight

Source: Young, Biggs, Ziegler, & Meyer, 1978.

Table 2. Expansion of Item #3 of the Young Mania Rating Scale

#3. Sexual interest

- Normal; not increased
- Mildly or possibly increased
- Definite subjective increase on questioning
- Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
- Overt sexual acts (toward patients, staff, or interviewer)

Source: Young, Biggs, Ziegler, & Meyer, 1978.

Olanzapine

Olanzapine (Zyprexa) is approved for bipolar disorder; companies producing other drugs are also pursuing this indication. Olanzapine has been shown to be more effective than placebo (Chengappa et al., 2003; Sanger et al., 2003; Tohen et al., 1999, 2002), superior to haloperidol (Shi et al., 2002; Tollefson et al., 1997), and as effective as lithium or divalproex (Berk, Ichim, & Brook, 1999; Revicki et al, 2003; Sanger et al, 2001; Tohen et al., 2003; Zajecka et al., 2002) in treating bipolar disorder (Keltner, 2003). In head-to-head measurements with divalproex,

olanzapine caused a 50% decline in YMRS scores in a 12-week study, while divalproex did not (Tohen et al., 2002). Although differences in outcome were not statistically significant, this study indicated olanzapine produces a slightly better effect than divalproex. Further, the olanzapine-treated group responded more rapidly, a potentially important effect (Stimmel, 2003).

Somnolence, weight gain, and rhinitis developed in 45%, ~25%, and ~15% of patients, respectively (Tohen et al., 2002). Typical dosage for olanzapine was between 15 and 45 mg/day. Dennehy, Doyle, and Suppes (2003) found olanzapine to be highly effective in treating mania and less effective in treating depression in a sample of outpatients diagnosed with bipolar disorder.

Anecdotal reports of olanzapine causing manic-type symptoms were not supported in a study by Baker, Milton, Stauffer, Gelenberg, & Tohen (2003). These authors suggest that changes in manic behavior are the result of the natural variations in bipolar disorder, not the result of olanzapine (or other atypical antipsychotic drug). Because of these and other studies, olanzapine has received Food and Drug Administration (FDA) approval as an antimanic drug.

Quetiapine

Quetiapine (Seroquel) has recently gained FDA approval for bipolar disorder. It has been associated with low to moderate weight gain, few extrapyramidal effects, and little if any elevation in prolactin (McConville et al., 2003). The latter effect is probably related to improvements in sex life when patients are switched to quetiapine (Byerly et al., 2002). Major adverse responses include relatively high levels of somnolence, dizziness, and postural hypotension. Zarate, Rothschild, Fletcher, Madris, and Zapatel (2000) noted improvement in patients with psychotic mood disorders prescribed quetiapine. Ereshefsky (2003) reports a study presented at the 2003 American Psychiatric Association meeting in which quetiapine was found comparable to lithium and haloperidol for bipolar disorder treatment. This study found quetiapine effective not only at 3 weeks (a typical study length) but also at 12 weeks, suggesting a sustained effect. When data were pooled to align quetiapine against placebo, significance was even more pronounced (Keltner, 2003). McConville et al. studied the long-term use (88 weeks) of quetiapine in adolescents with bipolar disorder and schizoaffective disorder and found that it was highly effective, with no extrapyramidal side-effects and minimal weight gain. This is the first known long-term study of its use with an adolescent population and holds promise for further study and treatment.

Risperidone

Risperidone (Risperdal) has proved comparable to haloperidol and lithium in reducing manic symptoms (Segal, Berk, & Brook, 1998) and superior to placebo as an adjunctive to lithium (Keck et al., 2000; Sachs, Printz, Kahn, Carpenter, & Docherty, 2000). It can be given on a once per day basis. Weight gain has been recorded as moderate in scope, but extrapyramidal side effects have been more pronounced. In a risperidone vs. placebo study, risperidone was found to have a rapid effect and a sustained advantage over the course of the study (Hirschfeld, 2003). Risperidone is typically dosed at < or =6 mg/day. Risperidone is not FDA approved for bipolar disorder.

Ziprasidone

Ziprasidone (Geodon) has been compared favorably to placebo for the treatment of mania (Keck et al., 2003). In this study, separation of effects were observed after 2 days, indicating a rapid onset, and ziprasidone continued to enjoy significantly better decline in YMRS scores than placebo after 2 weeks. This study and its findings are somewhat diminished by the large number of dropouts (46% for ziprasidone, 56% in the placebo group). Ziprasidone study patients suffered a greater level of extrapyramidal effects, dizziness, and somnolence than the placebo group; however, neither weight gain nor significant changes in vital signs occurred. QT interval elongation was not observed. Patients were titrated rapidly to 60-80 mg/day. Ziprasidone is not FDA approved for bipolar disorder.

Aripiprazole

Aripiprazole (Abilify), the newest antipsychotic drug, also has been studied for efficacy in bipolar disorder. Aripiprazole has the unique property of providing partial agonism at dopamine receptors (Keltner & Johnson, 2002) and is promoted as a dopamine system stabilizer. Ereshefsky (2003) reports a study that compared aripiprazole (n = 123) to placebo (n = 122) at a dose of 30 mg per day. A significant separation of effect developed within four days and was sustained over the study. This research indicates, and anecdotal reports support, a relatively high occurrence of nausea and akathisia with this drug.

Clozapine

Clozapine (Clozaril) is the gold standard for antipsychotic treatment and may be one of the best drugs for hard-to-treat cases of bipolar disorder as well. Clozapine carries a small risk for agranulocytosis and because of this, is a second-tier choice for bipolar disorder. Nonetheless, clozapine has proved effective in trials. Green et al. (2000) compared clozapine to treatment-as-usual (defined as the treatment to which the patient with chronic bipolar disorder had been exposed) for patients who were refractory to treatment (defined as no improvement after 6 weeks of treatment with chlorpromazine [Thorazine] or lithium). A significantly higher number of patients who switched to clozapine did improve. As noted earlier, it is important to understand how improvement is operationally defined. In this study, improvement was defined as a decrease in YMRS scores of 30%.

Ciapparelli et al. (2003) studied the long-term effect of clozapine on patients with bipolar disorder, schizoaffective disorder, and schizophrenia. The authors found that all groups improved significantly, measured with the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity of Illness scale. The bipolar group improved more rapidly than the other two groups; the bipolar groups cut in half its baseline data in just 3 months, the schizoaffective group in 6 months, and the schizophrenia group in 24 months. Both of these studies indicate that clozapine may be an important agent in hard-to-treat cases of bipolar disorder.

Summary

As the opening scenario illustrates about Mary and Bob, bipolar disorder can be devastating to individuals and families. Managing symptoms through psychotropic medications can help people with mental illness better manage their lives. Our brief review of the current research supports the effectiveness of atypical antipsychotic medications and, therefore, supports their use in treating bipolar disorder.

References

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (text revised). Washington: Author.

Baker, R.W., Milton, D.R., Stauffer, V.L., Gelenberg, A., & Tohen, M. (2003). Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. Journal of Affective Disorders, 73(1-2), 147-153.

Berk, M., Ichim, L., & Brook, S. (1999). Olanzapine compared to lithium in mania: A double blind randomized controlled trial. International Clinical Psychopharmacology, 14, 339-343.

Byerly, M., Lescouflair, E., Weber, M.T., Holland, R.M., Fisher, R., & Carmody, T. (2002, June 10). An open-trial of quetiapine for antipsychotic-induced sexual dysfunction. Paper presented at the New Clinical Drug Evaluation Unit Annual Meeting, Boca Raton, FL.

Chengappa, K.N., Baker, R.W., Shao, L., Yatham, L.N., Tohen, M., Gershon, S., et al. (2003). Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania. Bipolar Disorder, 5(1), 1-5.

Ciapparelli, A., dell'Osso, L., Bandettini di Poggio, A., Carmassi, C., Cecconi, D., Fenzi, M., et al. (2003). Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: A naturalistic 48-month follow-up study. Journal of Clinical Psychiatry, 64, 451-158.

Dennehy, E.B., Doyle, K., & Suppes, T. (2003). The efficacy of olanzapine monotherapy for acute hypomania or mania in an outpatient setting. International Journal of Clinical Psychopharmacology, 18,143-145.

Ereshefsky, L. (2003). Enhancing patient adherence to treatment in bipolar disorder. Continuing Medical Education Teleconference. Accessed May 2003 from www.rnhsource.com/maniacme

Ghaemi, S.N. (2001). Bipolar disorder and antidepressants: An ongoing controversy. Primary Psychiatry, 8(2), 28-34.

Green, A.I., Tohen, M., Patel, J.K., Banov, M., DuRand, C., Berman, L, et al. (2000). Clozapine in the treatment of refractory psychotic mania. American Journal of Psychiatry, 157, 982-986.

Hirschfeld, R.M. (2003). The efficacy of atypical antipsychotics in bipolar disorders. Journal of Clinical Psychiatry, 64(Suppl. 8), 15-21.

Keck, P.E., Mendlwicz, J., Calabrese, J.R., Fawcett, J., Suppes, T., Vestergaard, P.A., et al. (2000). A review of randomized, controlled clinical trials in acute mania. Journal of Affective Disorders, 59, S31-S37.

Keck, P.E., Jr., Versiani, M., Potkin, S., West, S.A., Giller, E., & Ice, K. (2003). Ziprasidone in the treatment of acute bipolar mania: A three-week, placebo-controlled, double-blind, randomized trial. American Journal of Psychiatry, 160, 741-748.

Keltner, N.L. (2003). Successful outcomes: Enhancing patient adherence to treatment in bipolar disorder. Continuing Medical Education Teleconference. Accessed june 25 & 30, 2003, from www.mhsource.com/ maniacme

Keltner, N.L., & Johnson, V. (2002). Aripiprazole: A third generation of antispsychotics begins? Perspectives in Psychiatric Care, 38,157-159.

Kessler, R.C., Stang, P., Wittchen, H.U., Stein. M., & Walters, E.E. (1999). Lifetime co-morbidities between social phobia and mood disorders in the US National Comorbidity Survey. Psychological Medicine, 29, 555-567.

McConville, B., Carrerro, L., Sweitzer, D., Potter, L., Chancy, R., Foster, K., et al. (2003). Long-term safety, tolerability, and clinical efficacy of quetiapine in adolescents: An open-label

extension trial. Journal of Child and Adolescent Psychopharmacology, 13(1), 75-82.
Orum M. (1996). Fairytales in reality. Australia: Seraline.
Revicki, D.A., Paramore, L.C., Sommerville, K.W., Swann, A.C., Zajecka, J.M., & Depakote Comparator Study Group. (2003). Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: Health-related quality of life and medical cost outcomes. Journal of Clinical Psychiatry, 64, 288-294.
Sachs, G.S., Printz, D.J., Kahn, D.A., Carpenter, D., & Docherty, J.P. (2000, April). The expert consensus guideline series: Medication treatment of bipolar disorder 2000. Postgraduate Medicine Special Report, pp. 1-104.
Sanger, T.M., Grundy, S.L., Gibson, P.J., Namjoshi, M.A., Greaney, M.G., & Tohen, M.F. (2001). Long-term olanzapine therapy in the treatment of bipolar I disorder: An open-label continuation phase study. Journal of Clinical Psychiatry, 62, 273-281.
Sanger, T.M., Tohen, M., Vieta, E., Dunner, D.L., Bowden, C.L., CaIabrese, J.R., et al. (2003). Olanzapine in the acute treatment of bipolar 1 disorder with a history of rapid cycling. Journal of Affective Disorders, 73(1-2), 155-161.
Segal, J., Berk, M., & Brook, S. (1998). Risperidone compared to both lithium and haloperidol in mania. Clinical Neuropharmacology, 21, 176-180.
Shi, L., Namjoshi, M.A., Zhang, F., Gandhi, G., Edgell, E.T., Tohen, M., et al. (2002). Olanzapine versus haloperidol in the treatment of acute mania: Clinical outcomes, health-related quality of life and work status. International Journal of Clinical Psychopharmacology, 17, 227-237.
Soares, J.C., Mallinger, A.G., & Gershon, S. (1997). The role of antipsychotic agents in the treatment of bipolar disorder patients. International Clinical Psychopharmacology, 12, 65-76.
Stimmel, D.L. (2003). Dosing strategies to ensure efficacy in patients with BD. Bipolar Disorder and Impulse Spectrum Letter, 9(2), 1-3.
Suppes, T., Rush. A. J., Dennehy, E.B., Crismon, M.L., Kashner, T.M., Toprac, M.G., et al. (2003). Texas Medication Algorithm Project, phase 3 (TMAP-3): Clinical results from patients with a history of mania. Journal of Clinical Psychiatry, 64,370-382.
Tohen, M., Ketter, T.A., Zarate, C.A., Suppes, T., Frye, M., Altshuler, L., et al. (2003). Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: A 47 week study. American Journal of Psychiatry, 160, 1263-1271.
Tohen, M., Baker, R.W., Altshuler, L.L., Zarate, C.A., Suppes, T., Ketter, T.A., et al. (2002). Olanzapine versus divalproex in the treatment of acute mania. American Journal of Psychiatry, 159, 1011-1017.
Tohen, M., Sanger, T.M., McElroy, S.L., Tollefson, G.D., Chengappa, R., Daniel, D.G., et al. (1999). Olanzapine versus placebo in the treatment of acute mania. American Journal of Psychiatry, 156, 702-709.
Tollefson, G.D., Beasley, C.M., Jr., Tran, P.V., Street, J.S., Krueger, J.A., Tamura, R.N., et al. (1997). Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: Results of an international collaborative trial. American Journal of Psychiatry, 154, 457-465.
Young, R., Biggs, J., Ziegler, V.D., & Meyer, D. (1978). A rating scale for mania: Reliability, validity, and sensitivity. British Journal of Psychiatry, 133, 4429-4435.
Zajecka, J.M., Weisler, R., Sachs, G., Swann, A.C., Wozniak, P. & Sommerville, K.W. (2002). A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. Journal of Clinical Psychiatry, 63, 1148-1155.

Zarate, C.A., Rothschild, A., Fletcher, K.E., Madrid, A., & Zapatel, J. (2000). Clinical predictors of acute response with quetiapine in psychotic mood disorders. Journal of Clinical Psychiatry, 61, 185-189.