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 pharmacologic 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


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)


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
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