Treatment of Bipolar Disorder With Antipsychotic Medication: Issues Shared With Schizophrenia

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Atypical antipsychotics are increasingly used in bipolar disorder as antimanic, antidepressant, and maintenance treatments. Many of the clinical issues related to switching antipsychotics are similar between schizophrenia and bipolar disorder. These include similar motivations for switching due to limited efficacy and unacceptable adverse effects. Particular attention must be paid to the phase of treatment and coprescribed medications. *(J Clin Psychiatry 2007;68[suppl 6]:24–25)*

True Apothecary
Two diagnoses, both alike in dignity,
In fair Psychiatry, where we lay our scene,
From ancient balms break to new treatments,
For psychoses truly patients' lives demean.

From forth the crises of these two foes
Many star-cross'd souls may take their life;
The adventured physician overthrows
Do with their wisdom bury their patients' strife.

The fearful passage of their delusions—mark'd above,
And the continuance of their parents' sorrow,
Which, but their children's health, nought could remove,
Is now the few pages' traffic of our stage;
The which if you with patient eyes attend,
What here shall miss, our toil shall strive to mend.

—With apologies to Mr. William Shakespeare

Although Elizabethan playwrights describe some psychiatric syndromes that are recognizable to the modern clinician,[1] current psychiatric nosology has its roots in the late 19th century. The twin diagnoses that have preoccupied general psychiatrists for more than a century since then are schizophrenia and bipolar disorder. Originally formulated by Kraepelin as *dementia praecox* and *manic-depressive psychosis*, these were conceptualized as "functional" psychoses to distinguish them from clearly organic brain disorders such as the (then) recently described Alzheimer's disease.

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Kraepelin sought to disentangle these 2 scourges on the basis of careful clinical description and observation of natural history. Nevertheless, more than a century later, this diagnostic scheme is essentially still provisional. Recent research has reminded us of the shared etiopathogenesis of bipolar disorder and schizophrenia and has led to calls for an end to the "Kraepelinian dichotomy."[2] Although such calls may be premature, they do highlight how, on many levels, bipolar disorders and schizophrenia are inextricably linked.

ANTIPSYCHOTIC USE IN BIPOLAR DISORDER

The issues dealt with in this volume concerning drug treatment of schizophrenia are therefore very pertinent to bipolar disorder; indeed, antipsychotic medication was first used to treat mania very shortly after the introduction of this class of drugs.[3] Despite the widespread use of first-generation antipsychotic drugs in bipolar disorders, the relevant evidence base is surprisingly small.[3,4] The evidence base for the use of newer agents is much larger, driven in part by the requirements of regulatory agencies in Europe and North America. All of the new antipsychotic agents, when carefully examined, have shown significant efficacy as antimanic treatments with some effect sizes among the largest reported thus far in psychiatry.[5,6] Emerging literature also suggests that some of the new antipsychotics may act as an antidepressant for bipolar depression, and significant relapse prevention has also been reported.[7,8]

As with schizophrenia, there are many reasons for the physician to recommend that a patient with bipolar disorder change their medication. Lack of efficacy is an obvious reason but must be considered in the context for which the antipsychotic was prescribed (i.e., as an antimanic, antidepressant, or maintenance regimen). An additional complication is that, for treatment of mania at least, combination of an antipsychotic with lithium or valproate is an acceptable and evidence-based alternative to switching for lack of efficacy.[9] The choice facing the physician is not limited,

therefore, to simple switching from one antipsychotic to another, but also includes augmentation.

ADVERSE EFFECTS OF MEDICATION

Medication should also be switched in bipolar disorder when patients suffer intolerable adverse effects that impair health or quality of life or result in nonadherence to medication. Adverse effects of antipsychotic medication used to treat bipolar disorder are similar to those reported for schizophrenia, and a general rule of thumb is to consider the side effects that are linked to the medication rather than the treated disorder. However, some, such as drug-induced motor side effects, may be even more pronounced in patients with bipolar disorder than in their counterparts with schizophrenia. A recent example of this was outlined in an article by Cavazzoni et al.[10] These authors examined the rates of treatment-emergent extrapyramidal symptoms in patients with bipolar mania or schizophrenia during olanzapine clinical trials. Data from more than 4000 patients treated with olanzapine, haloperidol, or placebo were analyzed. Interestingly, patients with bipolar mania receiving haloperidol were more likely to develop extrapyramidal side effects than were patients with schizophrenia receiving haloperidol, although the atypical drug olanzapine caused similar amounts of treatment-emergent symptoms in both patient groups.[10]

The weight gain and metabolic adverse effects of certain (but possibly not all) new antipsychotic medications have also been reported to occur when these drugs are used to treat bipolar disorder, and published data suggest a great similarity between the patient groups with respect to these metabolic consequences.[11] This is particularly important as recent surveys have shown that adverse effects are a major driver of medication switch for bipolar disorder and may override efficacy considerations.[12]

SWITCHING ANTIPSYCHOTICS IN BIPOLAR DISORDER

As with the treatment of schizophrenia, the process of switching antipsychotics must be done carefully when treating patients with bipolar disorder with due consideration given to the pharmacokinetics of the drugs involved. The use of multiple drugs is frequent in the treatment of bipolar disorder,[13] and most of this polypharmacy is not evidence-based. However, there is some preliminary evidence that mood stabilizers may ameliorate relapse rates consequent upon antipsychotic withdrawal. Lithium in particular may have a protective effect, reducing the rate of manic relapse when an atypical antipsychotic is withdrawn.[14]

In general, the process of switching antipsychotic medications in bipolar disorder follows the same principles and protocols as in schizophrenia, although the clinician will have to be cognizant of specific factors related to this diagnosis. As outlined above, crucial considerations are the phase of treatment (mania/depression/maintenance) and any other medications that the patient is taking. Lithium, for example, is associated with a pronounced discontinuation syndrome and toxicity that may occur at normal serum levels, both of which may complicate switching to antipsychotics.

CONCLUSION

Antipsychotics are increasingly used in bipolar disorder as antimanic, antidepressant, and maintenance treatments. Although the clinical issues related to antipsychotics and switching are similar between schizophrenia and bipolar disorder, there are issues specific to bipolar disorder that must be attended to if the clinician is to be a "true apothecary."

Drug names: haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Butler FG. Some aspects of Elizabethan psychiatry in two of Shakespeare's plays. Adler Mus Bull 1991;17:2–12
2. Craddock N, Owen MJ. The beginning of the end for the Kraepelinian dichotomy. Br J Psychiatry 2005;186:364–366
3. Hellewell JS. A review of the evidence for the use of antipsychotics in the maintenance treatment of bipolar disorders. J Psychopharmacol 2006;20: 39–45
4. Cipriani A, Rendell JM, Geddes JR. Haloperidol alone or in combination for acute mania. Cochrane Database Syst Rev 2006;3:CD004362
5. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. Br J Psychiatry 2005; 187:229–234
6. Surja AA, Tamas RL, El-Mallakh RS. Antipsychotic medications in the treatment of bipolar disorder. Curr Drug Targets 2006;7:1217–1224
7. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162:1351–1360
8. Corya SA, Perlis RH, Keck PE Jr, et al. A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression. J Clin Psychiatry 2006;67:798–806
9. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord 2005;7(suppl 3):5–69
10. Cavazzoni PA, Berg PH, Kryzhanovskaya LA, et al. Comparison of treatment-emergent extrapyramidal symptoms in patients with bipolar mania or schizophrenia during olanzapine clinical trials. J Clin Psychiatry 2006;67:107–113
11. Mackin P, Watkinson HM, Young AH. Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. Diabetologia 2005;48:215–221
12. Weiden PJ. Switching antipsychotics: an updated review with a focus on quetiapine. J Psychopharmacol 2006;20:104–118
13. Lloyd AJ, Harrison CL, Ferrier IN, et al. The pharmacological treatment of bipolar affective disorder: practice is improving but could still be better. J Psychopharmacol 2003;17:230–233
14. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005;162: 1281–1290