ROLE OF ANTIPSYCHOTIC MEDICATIONS IN TREATING BIPOLAR DISORDER

Mary Jane Strong, APRN, MS, CS

ABSTRACT

Although no cure exists for bipolar disorder, treatment can decrease the associated morbidity and mortality. Nursing goals for patients experiencing a manic or mixed episode initially include injury prevention, maintenance of a safe environment, and patient assistance to meet basic needs and subsequently a return to normal levels of psychosocial functioning. Effective use of medications—often in combination with psychotherapy—enables most patients with manic depression to lead essentially normal lives. This article offers an overview of the role of antipsychotic medications in achieving this long-term goal and reviews indications for switching therapies.

of this lifelong disorder. The American Psychiatric Association offers several strategies for long-term management, including establishing and maintaining a therapeutic alliance, monitoring treatment response, educating patients and their families, enhancing treatment compliance, and evaluating and managing functional impairments (see Sidebar on page 156).

**Approaches to Treatment**

Although no cure exists for bipolar disorder, treatment can decrease the associated morbidity and mortality. The primary goal of treatment for patients experiencing a manic or mixed episode is to control symptoms so patients can return to normal levels of psychosocial functioning. Effective use of medications, often in combination with psychotherapy, allows 75% to 80% of patients with manic depression to lead essentially normal lives.

Lithium, valproate, and antipsychotic medications have shown efficacy in the treatment of acute mania, although the time to onset of action for lithium may be somewhat slower than that for valproate or antipsychotics. The evolution of therapies for treatment of acute mania and hypomania is presented in Figure 1. Despite their widespread use, lithium and anticonvulsant therapies have not been extensively evaluated in bipolar disorder within the setting of controlled clinical trials. Lithium and divalproex, however, are approved by the US Food and Drug Administration (FDA) for treatment of bipolar disorder. Among antipsychotic therapies, chlorpromazine, olanzapine, quetiapine, and risperidone are approved for the treatment of acute mania, and the FDA is currently reviewing other antipsychotic agents for use in bipolar disorder. These efforts to expand the current list of drug choices continue for many of the same reasons clinicians seek to expand the armamentarium for schizophrenia: atypical antipsychotic agents have been shown to reduce risks of extrapyramidal side effects (EPS), prolactin elevation, and tardive dyskinesia while improving depressive symptoms. For these reasons, the American Psychiatric Association recommends treatment with an atypical psychiatric medication during a manic or mixed episode.

![Table 1. Behaviors Associated with Mania](image1)

<table>
<thead>
<tr>
<th>Affective</th>
<th>Physiologic</th>
<th>Cognitive</th>
<th>Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elation or euphoria</td>
<td>Dehydration</td>
<td>Ambitiousness</td>
<td>Aggressiveness</td>
</tr>
<tr>
<td>Expansiveness</td>
<td>Inadequate nutrition</td>
<td>Denial of realistic danger</td>
<td>Excessive spending</td>
</tr>
<tr>
<td>Humorlessness</td>
<td>Needs little sleep</td>
<td>Distractibility</td>
<td>Grandiose acts</td>
</tr>
<tr>
<td>Inflated self-esteem</td>
<td>Weight loss</td>
<td>Flight of ideas</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td>Intolerance of criticism</td>
<td></td>
<td>Grandiosity</td>
<td>Increased motor activity</td>
</tr>
<tr>
<td>Lack of shame or guilt</td>
<td></td>
<td>Illusions</td>
<td>Irresponsibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of judgment</td>
<td>Irritability or argumentativeness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loose associations</td>
<td>Poor personal grooming</td>
</tr>
</tbody>
</table>

![Table 2. Risk Factors and Nursing Interventions for Other-Directed Violence](image2)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Nursing Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>Provide a safe environment</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>Decrease environmental stimuli</td>
</tr>
<tr>
<td>Agitation</td>
<td>Administer drug therapy</td>
</tr>
<tr>
<td>Hostile behavior</td>
<td>Provide a consistent, structured environment; set goals with the patient as soon as possible</td>
</tr>
<tr>
<td>Threatened or actual aggression toward self or others</td>
<td>Give simple, direct explanations for routine actions, procedures, tests, etc. Do not argue with the patient</td>
</tr>
<tr>
<td>Low self-esteem</td>
<td>Encourage the patient to verbalize feelings of anxiety, anger, or fear; Explore ways to relieve stress and tension with the patient as soon as possible; Encourage supervised physical activity</td>
</tr>
</tbody>
</table>

Risperidone was approved by the FDA in December 2003 as monotherapy or combination therapy (with lithium or valproate) for the treatment of acute manic or mixed episodes. Several studies support this indication. Hirschfeld and colleagues reported significant improvements in Young Mania Rating Scale (YMRS) scores at day 3 and at each subsequent time point. After 3 weeks of treatment, the YMRS score was reduced by 5 points in patients taking placebo versus 11 points in those patients taking risperidone ($P < .001$). Vieta and colleagues showed a surprising 73% response versus 36% with placebo. Six controlled studies showed olanzapine to be effective, with some studies using placebo for control and others using more conventional therapies, such as haloperidol and divalproex. One study showed a 68% response rate to olanzapine with a therapeutic dose of only 10 mg at the study’s completion. A summary of study findings regarding the efficacy of olanzapine for the treatment of acute mania is shown in Figure 2. Recent clinical research has also shown ziprasidone to be effective in half of the 216 subjects participating in a double-blind clinical trial. In a study of combination therapy using quetiapine as adjunctive therapy with divalproex, a remarkable 87% response rate was reported in an adolescent population. Efficacy was somewhat less pronounced in adults but nonetheless significant, with 53% of patients responding to this drug combination.

Aripiprazole has been shown in large-scale studies to achieve a response comparable to other atypical antipsychotic drugs (40%; 50% and 51%). The remarkable findings were that positive results were reported as soon as 4 days after initiation of therapy (Figure 3). Psychiatric nurses with inpatient experience recognize the importance of obtaining immediate results for patients with acute mania, so this rapid onset of action is a significant finding. By day 10, a near-full response was reported and was sustained until the study’s completion at week 3. The safety profile for aripiprazole as reported in the studies for acute mania was, not surprisingly, similar to that reported in studies for schizophrenia: patients showed little weight gain and a decrease in prolactin levels. EPS were comparable to those seen with placebo; however, slight elevations in akathisia and insomnia have also been reported. In summary, aripiprazole has proven efficacy in acute mania in 2 placebo-controlled studies and in 1 study in which haloperidol was used as the control. This treatment has a demonstrated rapid onset of action.
showing clinically meaningful improvement in symptoms based on YMRS findings with a favorable safety and tolerability profile in patients with bipolar disorder.

**Switching Antipsychotic Agents**

Because there is no cure for bipolar disorder, most patients require lifelong medication. At some point during the course of a patient's treatment, the nurse clinician may consider questions about the patient's drug therapy. Is the patient still experiencing problematic symptoms? Are the medication's adverse effects jeopardizing the patient's physical health and/or significantly compromising quality of life? Is the patient able to follow the treatment regimen? Could the patient achieve better results with a different drug? Can a different medication achieve more of the therapeutic goals? These are questions to address with the patient and the family. When the clinician is considering a change in the patient's antipsychotic therapy, a structured clinician and patient worksheet may help to guide the discussion and the timing of the decision. Sometimes patients will decide for themselves that a medication is no longer tolerable by simply refusing to take it. Indications for switching antipsychotics from the perspective of the clinician, the patient, and the family are shown in Table 3.22

**Figure 3. Aripiprazole in Acute Mania: Mean Change in YMRS from Baseline**

![Graph showing mean change in YMRS from baseline for patients on placebo and aripiprazole.]

*P < .01 vs placebo; last observation carried forward. YMRS = Young Mania Rating Scale. Data from Keck et al.20*

**Table 3. Indications for Switching Antipsychotics from the Perspective of the Clinician, the Patient, and the Family***

<table>
<thead>
<tr>
<th>Clinician's Perspective</th>
<th>Patient's Perspective</th>
<th>Family's Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent positive symptoms</td>
<td>Distress from positive symptoms</td>
<td>Disruptiveness and agitation</td>
</tr>
<tr>
<td>Persistent negative symptoms</td>
<td>Inability to meet life’s goals</td>
<td>Emotional and financial burden of caregiver role</td>
</tr>
<tr>
<td>Persistent EPS† and/or tardive dyskinesia</td>
<td>Dyshoria or distress from EPS</td>
<td>Dealing with multiple crises and setbacks</td>
</tr>
<tr>
<td>Hyperprolactinemia (galactorrhea and amenorrhea in women, gynecomastia and impotence in men)</td>
<td>Annoyance from increased complexity of regimen and side effects from addition of anticholinergic medications</td>
<td>Heartbreak of seeing loved one burdened by akathisia or tardive dyskinesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disappointment or frustration of sexual partner</td>
</tr>
</tbody>
</table>

*Assumes the patient is taking therapeutic doses of a conventional antipsychotic and that persistent symptoms are not attributable to compliance problems and/or substance abuse.
†Assumes the patient is taking treatment with optimal doses of a conventional antipsychotic and unsuccessfully attempted treatment with anti-Parkinson or antiakathisia agents. EPS = extrapyramidal symptoms.
Adapted with permission from Weiden et al. Switching antipsychotic medications. *J Clin Psychiatry.* 1997;58(suppl 10):s3-s72. Copyright 1997 Physicians Postgraduate Press.22
There are major clinical concerns in changing patients’ antipsychotic medications: patients will become destabilized and perhaps relapse during the drug switch or they will suffer from new adverse effects. An interesting finding across studies is that patients who were changed to one of the first-line atypical antipsychotic agents improved regardless of whether their previous medication was conventional or atypical—even though investigator bias may have influenced these findings. Differential efficacy, however, is consistent with the varied pharmacologic profiles seen across the spectrum of antipsychotic agents.

One open-label phase 3 study evaluated the safety and tolerability of switching patients from other antipsychotic therapies to aripiprazole and whether there were any clinical differences between switching strategies. A total of 311 patients with stable chronic schizophrenia were enrolled in the aripiprazole switching trial. These patients were taking stable doses of an antipsychotic agent (olanzapine, risperidone, or any conventional agent) for 1 month or longer. The reasons for switching therapies were not specified in the study design, and the decisions to switch were based on clinician opinion. In an 8-week trial, patients were randomly assigned to 1 of 3 groups with different switching strategies, using an open-label manner. Group 1 (immediate) initiated aripiprazole therapy at 30 mg daily while immediately discontinuing any previous antipsychotic drug. Group 2 (taper 1) initiated aripiprazole therapy at 30 mg daily and tapered off the other antipsychotic drug over a 2-week period. In group 3 (taper 2), aripiprazole was titrated over 2 weeks (from 10 to 30 mg daily), and the other antipsychotic...
was tapered off over the same time period. Most patients were taking olanzapine (56%) or risperidone (36%) prior to switching; only 8% were receiving conventional agents (mainly haloperidol). A total of 224 patients (72%) completed the study: 69% in group 1, 66% in group 2, and 81% in group 3. The reasons for discontinuation were similar across treatment groups. Discontinuations for lack of efficacy or adverse events occurred with similar frequencies in the 3 treatment groups.

Analyses were also performed after pooling all 3 groups and stratifying patients according to previous therapy (olanzapine, risperidone, or haloperidol). In this analysis, significant improvements from baseline in Positive and Negative Syndrome Scale (PANSS) total score were observed regardless of prior therapy. Baseline PANSS total scores were 69.4 among patients previously taking olanzapine, 69.9 among previous risperidone users, and 68.8 among those who switched from haloperidol. These findings suggest that clinicians should not become too complacent in their use of medications—further improvement for patients may be within reach.

FROM THEORY TO PRACTICE: CLINICAL IMPLICATIONS

In the manic state, patients with bipolar disorder frequently demonstrate a propensity for being physically, emotionally, and/or sexually harmful to themselves or others. Initial nursing goals include preventing injury, maintaining a safe environment, and helping the patient meet basic needs, with a subsequent goal of the patient returning to normal levels of psychosocial functioning. Effective use of medications—often in combination with psychotherapy—enables most patients with bipolar disorder to lead essentially normal lives. An algorithm for medication management is presented in Figure 4.25

Nursing Strategies for the Management of Bipolar Disorder

ESTABLISH AND MAINTAIN A THERAPEUTIC ALLIANCE
Over time, knowledge gained about the patient and the illness course allows early identification of usual prodromal symptoms and early recognition of new episodes.

MONITOR TREATMENT RESPONSE
Monitoring is especially important during manic episodes, when patient insight is often limited or absent. Be aware that small changes in mood or behavior may herald the onset of an episode.

EDUCATE THE PATIENT AND FAMILY
During different phases of illness, patients will vary in their ability to understand and retain information and accept and adapt to the need for long-term treatment. Education should be an ongoing process in which the nurse gradually but persistently introduces facts about the illness and its treatment. Printed and Internet material (e.g., www.psych.org, www.nimh.nih.gov) may be helpful.

ENHANCE TREATMENT COMPLIANCE
Ambivalence about treatment is often expressed as poor adherence to medication or other treatments. Causes of ambivalence include lack of insight about having a serious illness and even a reluctance to give up the experience of hypomania or mania. Other deterrents that need to be discussed include medication side effects, cost, and other demands of long-term treatment. Because many adverse effects can be corrected with careful attention to dosing, scheduling, and medication formulation (e.g., sustained release, liquid), the psychiatric nurse plays an indispensable role by remaining vigilant of such issues.

PROMOTE AWARENESS OF STRESSORS AND REGULAR PATTERNS OF ACTIVITY AND SLEEP
Stressors commonly precede episodes in all phases of the illness. Social rhythm disruption with disrupted sleep-wake cycles may specifically trigger manic episodes. Patients and their families should be informed about the potential effects of sleep disruption in triggering manic episodes. Regular patterns for daily activities should be promoted, including sleeping, eating, physical activity, and social and emotional stimulation.

WORK WITH THE PATIENT TO ANTICIPATE AND ADDRESS EARLY SIGNS OF RELAPSE
As the clinician most likely to come into frequent contact with patients and their families, the psychiatric nurse should help patients, family members, and significant others recognize early signs and symptoms of manic or depressive episodes. Early markers of episode onset are often predictable across episodes for an individual patient.

EVALUATE AND MANAGE FUNCTIONAL IMPAIRMENTS
Assist the patient in scheduling absences from work or other responsibilities. Encourage the patient to avoid major life changes while in a depressive or manic state. Assess and address the needs of children of patients with bipolar disorder.

Data from the American Psychiatric Association.
REFERENCES