Treatment of Agitation in Bipolar Disorder Across the Life Cycle

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Agitation is a common and difficult problem in psychiatric patients; patients with bipolar disorder constitute a substantial proportion of the agitated psychiatric population. Agitation is often seen in bipolar patients during acute manic states, when increased energy levels and reduced need for sleep lead patients to collide with the limits of others. Agitation also occurs during mixed and depressive states, which are characterized by fluctuating energy levels and periods of irritability. Although the prevalence of agitation is similar in men and women, its presentation often differs between the sexes. In addition, the presentations of bipolar disorder in children and in geriatric patients, and thus the manifestations of illness-related agitation, differ both from each other and from that of younger adults. Intensive treatment is required to manage agitated bipolar patients in a manner that rapidly decreases their suffering and maintains their safety and the safety of those around them. Considerations of speed and predictability tend to drive decisions in this setting more than concerns about tolerability. Oral or parenteral benzodiazepines, alone or in combination with an antipsychotic, are recommended as first-line treatment for the termination of behavioral emergencies in mania. Once behavioral control is restored, evidence suggests the combination of orally loaded divalproex sodium with an atypical antipsychotic is associated with more rapid improvement. Medication treatment of children and of geriatric patients must take into account developmental influences on the presentation of bipolar disorder in these different patient groups. *(J Clin Psychiatry 2003;64[suppl 4]:3–9)*

Agitation is common among psychiatric patients, and agitated patients are difficult to treat. The cause of their agitation is often unknown, and while agitated they place staff members, other patients, and themselves in danger. Goodwin and Jamison[1] summarized 4 studies of bipolar patients, reporting a weighted mean of 49% with a lifetime history of assaultive or violent behavior. According to the Epidemiologic Catchment Area study,[2] the prevalence of violence in all of those who responded was 3.7%. In people without a mental illness diagnosis, only 2.05% had a history of violence. However, if a respondent had a history of any mental illness (not including social phobia), the rate of violence increased to 10.66% to 12.69%. With a substance use disorder, the risk for violence increased 10-fold over the well population to 20.30%. And finally, for those with an affective disorder or schizophrenia, in addition to a substance abuse disorder, the risk for violence then increased 15-fold to 30%.[2] Patients with bipolar disorder, of whom approximately 60% will abuse substances,[3] represent a significant portion of the agitated psychiatric population. Although the prevalence of type I bipolar disorder is less than 2% of the general population,[4] one national survey estimates that bipolar disorder accounts for 13.2% of psychiatric emergency visits.[5] These patients require thought and care in treating them effectively to decrease their suffering and to maintain their own safety and the safety of those around them.

This article will review behavioral disturbances in bipolar disorder in 3 main age-at-onset groups. It will begin with the phenomenology of adult onset, then move to prepubescence and adolescence, and finally the geriatric population. The article will then focus on the treatment of agitation in bipolar disorder and, when possible, will use evidence related to that phenomenon. However, there is a paucity of data on this topic, and thus at times it is necessary to generalize from the treatment of agitation, independent of etiology. It will also make the assumption that the treatment of the condition underlying agitation, for example acute mania, will lead to resolution of the agitation. In this context, a relative value is attached to rapid symptom control rather than tolerability, and studies providing evidence of rapid improvement are presented.

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PHENOMENOLOGY

Adult Patients

One should think of treating bipolar disorder in phases of the disease, and agitation can occur in several of the phases. Most people think of agitation in bipolar disorder as associated with the acute mania phase, which is certainly one time when these patients are agitated. During this phase of the illness, patients are commonly very energetic, are hypervigilant, often fail to consider or recognize the consequences of their actions, and may state or feel that they are invincible and thus drive too fast or pick fights. In the midst of these behaviors, they are also sleeping significantly less and thus are awake, hyperactive, and available for more hours of each day and at times that the average person is asleep. Therefore, it is common for these patients while manic to collide with the limits of others and to get into altercations as a result.

The other common phase of bipolar disorder during which patients become agitated is mixed states. These patients with bipolar disorder will often present themselves with the chief complaint of feeling depressed, but on evaluation are experiencing the simultaneous mixture of dysphoria and irritability. According to DSM-IV-TR,[6] they must meet full criteria for both mania and depression concurrently. However, there is evidence that there are in fact 2 clinically different mixed states: both meet criteria for mania, but one meets full criteria for depression while the other is characterized by mania and subsyndromal depressive symptoms or dysphoric mania.[7] The importance of subsyndromal depressive symptoms is demonstrated by the finding that when patients meet full criteria for mania, a Hamilton Rating Scale for Depression score of 18 is a better predictor of suicidal ideation than full syndromal criteria for major depression.[8]

It is also important to remember that it is more common to see mixed states, depressive episodes, and a rapid-cycling course in women.[8–11] Patients in this state will report alternating periods of sluggishness and lassitude with periods of electrical energy and an inability to sit still, and they will often be very irritable. This tends to be expressed differently in the lives of men and women, with female patients concerned that they are treating their children and husbands poorly and men frequently worrying about losing their jobs because they are unable to control their verbal aggression toward their boss. At first glance, this population of patients appears to be functioning pretty well in society, as they are employed and in many respects appear to be doing well. However, upon further questioning, they are getting into verbal altercations and putting themselves into other difficult and dangerous situations, and then they often drink alcohol in attempts to deal with it, which just makes them more irritable and ultimately their situation worse. Therefore, patients with bipolar disorder can be agitated either when experiencing a euphoric mania or when tormented by the reactivity of a mixed state, and both phases can contribute to significant dysfunction in their lives and can be difficult to treat.

There seems to be a common misperception that women with bipolar disorder are less likely to be aggressive than men with bipolar disorder, when in reality the prevalence is equal. However, the pattern of women's versus men's aggression is different, which may contribute to this confusion. Aggressive mentally ill women tend to do more slapping and scratching, while similarly aggressive men do more punching and kicking. Men also are more likely to use weapons, and thus men's aggression is generally more severe, making it seem that women are less aggressive.[12] Therefore, providers must remember that agitated manic patients, independent of gender or phase of illness, may be quite gregarious and friendly one minute, but in the context of being told that they may not leave or may not smoke, they can become quite violent the next minute.

Prepubescent and Adolescent Patients

Bipolar disorder in children (prepubertal onset) has some similarities and many differences when compared with that in adults. According to Kraepelin,[13] only 0.4% of bipolar disorder presents before the age of 10 years; however, the rates of diagnosis have continued to rise. There is an ongoing and significant discussion in the child and adolescent psychiatric community about the diagnostic difficulties of bipolar disorder in children. One of the main issues underlying this controversy stems from the large amount of symptomatic overlap between mania and attention-deficit/hyperactivity disorder, with comorbidity rates as high as 57% to 86%.[14] Explanations for this overlap vary from the limitations of our current diagnostic systems to the high prevalence of many psychiatric comorbidities in children with bipolar disorder.[15] Classic mania and depression in children with bipolar disorder certainly do exist,[16,17] although they seem much less common than in adults, in whom clinicians are also seeing less of the classic presentation. Children with bipolar disorder tend to have fewer discrete episodes and rather have more consistent states of volatility of affect, belligerence, and irritability without pure mania.[18,19] These states can be associated with dangerous aggression during which they may do very aggravated things such as challenge a whole classroom of students and adults. It is unclear how much of this daring can be accounted for by the baseline poorly developed decision-making abilities and impulsivity of a normal child, and what component grandiosity may play.[20,21] Children also present with more attentional problems than adults, and because their main responsibility is school, where they spend most of the day at a desk disallowed from moving about freely, these problems cause them great dysfunction.

Adolescent-onset bipolar disorder tends to be a more severe form of the disorder, as in children, and there is

typically more psychosis,[22] which may be prominent and may complicate the diagnostic picture with other psychotic disorders. Kraepelin reported that the most common age at onset for bipolar disorder is between 15 and 20 years, accounting for 16.4% of his study population.[13] Goodwin and Jamison reported similar statistics after pooling results from 6 studies.[1] By the time age at onset reaches the third decade of life, patients present with what is considered more classic bipolar disorder, with episodic manias and depressions.

Geriatric Patients

In late life, secondary bipolar disorder becomes much more common, with various focal and systemic insults to the brain causing manic episodes or a kind of chronic mania. Ten percent to 25% of geriatric patients with mood disorders have bipolar disorder, and they represent 3% to 10% of all geriatric psychiatric patients.[23–27] Of this population, anywhere from 17% to 43% of geriatric patients will turn out to have a primary central nervous system disorder.[24,27–29] This underlines the importance of looking for an underlying primary cause in an older patient who presents with a first affective episode. There is also clear symptomatic overlap between mania and dementia, with common presentations of impulsivity, irritability, mood lability, psychosis, sleep disturbance, and agitation. Bipolar disorder accounts for between 5% and 12% of geriatric psychiatric admissions.[30–33] Another interesting contrast in geriatric versus non-geriatric bipolar disorder is that mania is more common in women. In unipolar depression, depression is more common in women early in the life cycle, becoming more equal in late life. For bipolar disorder, the prevalence is equal in early life, but by late life, female mania is more common. When an elderly person with bipolar disorder becomes agitated, it significantly increases the caregiver burden and oftentimes is the ultimate reason for requiring nursing home placement.[34]

There is the belief that as people mature over the years, so does their bipolar disorder, in that they often experience fewer manias and more depressions with age.[13] And as more and more research supports, the key to effective treatment of bipolar disorder is prevention of episodes. As the lifetime number of episodes increases, the episodes tend to become more severe, with shorter interepisode periods, and episodes become more refractory to treatment.

TREATMENT

Adult Patients

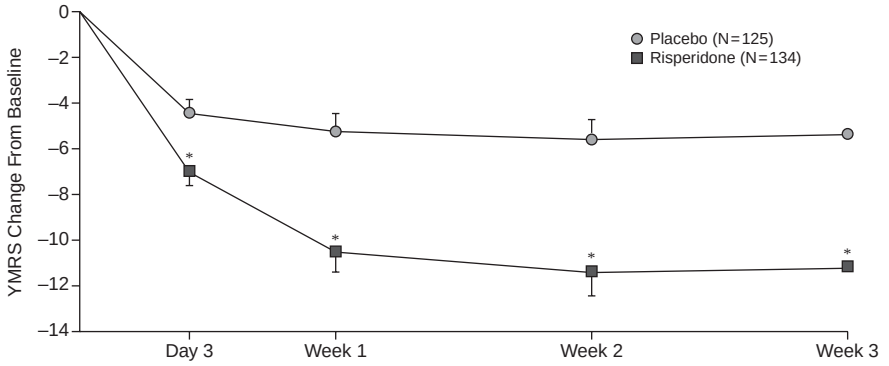
The treatment of agitated states is complex. Time is a critical factor. Behavioral emergencies require stabilization as rapidly as possible, both for the sake of limiting the patient's exposure and to maintain the safety of staff and other patients. The first phase of the treatment is controlling the behavioral emergency with rapid resolution of major target symptoms. At this point in the care, rapid resolution of symptoms outweighs side effect burden. Ideally, this is accomplished in a collaborative way that does not bias the patient against care in the future. However, with efficacy rather than tolerability being the primary consideration in the treatment of behavioral emergencies, one typically uses high doses of combination treatments that might not be tolerated in the long term or in less symptomatic states. There are more data on treatment of the agitated manic patient, and thus the discussion will begin there.

The Expert Consensus Guidelines for Treatment of Behavioral Emergencies[35] suggest that benzodiazepines are first-line treatment for managing the acute phase of an agitated manic patient, whether used orally or parenterally. Benzodiazepines can be used either as monotherapy, with an initial lorazapam dose of 0.5 to 2 mg, or in combination with an antipsychotic. The combination of lorazepam with a high-potency typical antipsychotic such as haloperidol, 5 mg, may be used for parenteral control. However, most patients will assent to oral medications, and in those cases, the combination of an atypical antipsychotic, risperidone liquid concentrate 2 mg, plus lorazepam, 2 mg, has been shown to be equally as effective as intramuscular haloperidol and lorazepam.[36] There are some data on the use of high doses of oral olanzapine, up to 40 mg/day, in heterogenous populations with agitation.[37] Lindenmayer and Kotsaftis[38] have reviewed 17 reports concerning the use of divalproex sodium in the treatment of violent and aggressive behaviors of various etiologies, most organic, finding that 77% responded with a 50% reduction in target behaviors.

There are also emerging data about the use of intramuscular atypical antipsychotics, which will add another tool to the armamentarium for treating agitated patients with bipolar disorder. Intramuscular ziprasidone is now available. It has been studied in 10- and 20-mg doses and has been shown to be effective in treating agitation associated with psychosis.[39,40] Intramuscular olanzapine has been studied in the treatment of agitated manic patients, showing statistically significant improvement over placebo or intramuscular lorazepam on the Positive and Negative Syndrome Scale–excited component subscale.[41] However, concerns have been raised about sinus pauses and lowered blood pressure, resulting in restrictive labeling of intramuscular olanzapine in Europe.[42]

Once the behavioral emergency has been terminated, strategies for the treatment of mania that have demonstrated rapid improvement include rapid loading of divalproex and combinations of mood stabilizers and antipsychotics. Divalproex sodium can be loaded orally at 20 to 30 mg/kg in divided doses for 4 doses, then maintained at 20 mg/kg in divided doses or once at night.[43] A meta-analysis of studies using such strategies[44] demonstrated significant differences in mania at day 3 when patients achieve blood valproate levels over 80 ng/mL. There are also new data and U.S. Food and Drug Administration

Figure 1. Total YMRS Score in Study of Risperidone Vs. Placebo in Acute Mania[a]



[a]From Hirschfeld et al.[50]
*p < .001 versus placebo.
Abbreviation: YMRS = Young Mania Rating Scale.

approval for faster intravenous valproate sodium loading, making intravenous loading in the treatment of the acutely agitated manic patient logistically feasible and safe.[45] The previous guidelines limited the delivery rate to 20 mg/min, resulting in a unrealistically long loading time of approximately an hour. Recent changes allow infusion rates of 1.5 to 3.0 mg/kg/min, decreasing the infusion time for a loading dose to 10 minutes. Case series of this strategy in agitated psychiatric patients have been reported.[46] Although there is a nomogram for predicting lithium dosage,[47] lithium cannot be rapidly titrated due to intolerance.

Antipsychotics have long been used in acute mania because of their early impact on behavioral symptoms. Prien et al.[48] found chlorpromazine superior to lithium at day 3. Segal et al.[49] found risperidone, 6 mg, alone comparable to lithium and haloperidol. In a recent 3-week, double-blind, placebo-controlled study, Hirschfeld et al.[50] found that 1 to 6 mg/day of risperidone (mean dose = 4.1 mg/day) significantly ($p < .001$) improved symptoms of acute bipolar mania as early as treatment day 3 (Figure 1). Olanzapine is available in a rapidly dissolving form, and mean modal doses of 16.4 mg have separated from placebo at 1 week.[51] Another study of olanzapine, 10 mg, versus placebo required 3 weeks to separate from placebo.[52] Ziprasidone at a starting dose of 80 or 160 mg/day has also been shown to be effective as monotherapy in treatment of acute mania.[53] Taken together, these studies suggest that antipsychotics are effective as monotherapy.

However, the most rapid and effective approach to the agitated manic patient appears to be a combination of a mood stabilizer and an antipsychotic. Data show that in schizophrenia, the combination of divalproex loading combined with an atypical antipsychotic is superior to divalproex alone within 3 days.[54] Sachs et al.[55] have also demonstrated this in acute mania. Regardless of the presence or absence of psychotic symptoms, the addition of risperidone at an average dose of 3.84 mg to either new or established mood stabilizer was more rapidly efficacious than mood stabilizer alone. Similar results have been obtained by combining lithium and low-dose haloperidol (5 mg/day), which led to markedly greater clinical response over haloperidol alone, with the difference apparent at day 4.[56] Similar data have been presented for quetiapine. At an average dose of 580 mg, quetiapine added to mood stabilizer resulted in a 45.7% response rate compared with 25.8% for placebo and mood stabilizer.[57]

Prepubescent and Adolescent Patients

In children, treatment recommendations are similar, but can be complicated by the lack of distinct phases of the illness as previously discussed in adults. There are also few data specifically addressing the topic of treatment of agitation in this population, so most of this discussion will be based on extrapolation from the adult data on treatment of agitated bipolar disorder and from child data on treatment of agitation of other etiologies. In the acutely agitated child, typical and atypical antipsychotics tend to be used as first-line agents. Although children weigh less than adults, their hepatic enzyme systems are actually more efficient at metabolizing most medications, leading to similar dosing for adults and children. Benzodiazepines are also commonly used at doses similar to those given to adults.

Lithium and divalproex sodium are the established first-line medications for maintenance treatment in children, as they are in adults.[58] However, because of concerns about the hormonal effects of divalproex sodium on the development of prepubertal and adolescent girls and the potential association between childhood use and adult polycystic ovarian disease, caution is recommended in this population.[59,60] Lithium has been the most extensively

studied mood stabilizer in adults and children, but new evidence suggests that the frequency of mixed states in children with bipolar disorder may be associated with poorer outcome with lithium when compared with divalproex sodium. This would also be consistent with the adult literature.

There is literature to support adjunctive use of atypical antipsychotics in bipolar disorder in children as well. The addition of quetiapine (titrated to 450 mg/day) to divalproex sodium showed a statistically significant decrease in scores on the Young Mania Rating Scale (YMRS) over divalproex alone.[61] Adding olanzapine to mood stabilizers has led to marked improvement in manic symptoms,[62,63] and there is an open study utilizing olanzapine monotherapy (mean dose = 9.4 mg/day, range 2.5 to 20 mg/day) in the treatment of acute mania showing significant declines in YMRS scores.[64] Risperidone has been shown effective as monotherapy or as an adjunct in treatment of aggression in children with subaverage IQs,[65] Tourette's disorder,[66] and mood disorders.[67]

Geriatric Patients

The medication treatment of geriatric bipolar patients must take into account the often secondary nature of the illness in this population. Different pharmacokinetics also must be anticipated, as well as drug-drug interactions and increased vulnerability to side effects. Secondary bipolar disorder has been shown to be less responsive to lithium, and geriatric patients are much more susceptible to its side effects, are more likely to suffer dehydration and renal impairment, and thus are more likely to experience toxicity. Benzodiazepines, a common treatment for agitation associated with bipolar patients in other populations, are less advantageous in this population because in the elderly, benzodiazepines tend to accumulate, are associated with more confusion and falls, and may cause disinhibition. Antipsychotics are commonly used, but particular care must be taken with the typicals as the elderly are at significantly increased risk for tardive dyskinesia. One study showed development of tardive dyskinesia by 50% of an elderly population after just 2 years of treatment with typical antipsychotics.[68]

The atypical antipsychotics have a place in the treatment of agitation in this population, but most of the data relate to treatment of agitation associated with dementia. Also, it is important to remember that significantly lower doses are used with the elderly than with adults and children, on the basis of metabolic changes and susceptibility to side effects. There is one large, randomized, placebo-controlled study demonstrating the safety and efficacy of risperidone in the treatment of nursing home residents with dementia and agitation or psychosis.[69] There are 2 double-blind, placebo-controlled trials showing short-term efficacy, safety, and tolerability of divalproex sodium in the treatment of agitation in demented patients. The patients who received divalproex sodium started at 250 or 375 mg/day with 125-mg dose adjustments every 1 to 4 days. Interestingly, the study by Tariot et al.[70,71] designed to examine divalproex sodium in the treatment of the signs and symptoms of mania in dementia showed efficacy in the treatment of agitation without specific improvement in mood symptoms.

CONCLUSION

Patients with bipolar disorder frequently present with agitation. Different points in the life cycle are associated with specific clinical characteristics that guide treatment decisions and outcomes. Therefore, the age of the patient, comorbidities, and the phase of the illness must be considered in deciding how to manage the agitated bipolar patient. Aggressive management to terminate the behavioral emergency as quickly as possible is desirable. Although treatment occurs in a complex relationship that requires weighing the consequences of current decisions for the future as well as the present, a more rapid and complete response may outweigh concerns about tolerability in the acutely manic patient.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lorazapam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproate sodium (Depacon), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of mania.

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