Treatment of Aggression in Patients With Bipolar Disorder

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Bipolar disorder is generally viewed as a disturbance of mood. However, prominent aspects of behavior that occur during depressive and manic states of bipolar disorder, including psychosis, aggression, and anxiety, are not specific to mood syndromes and occur across many psychiatric states. Severe hyperarousal—beyond that usually associated with classic manic or depressive episodes—could result in a variety of behavioral or symptomatic disturbances including aggression, impulsivity, and anxiety. Since aggression is a well-recognized aspect of mood syndromes, the management of aggression is likely to be an important component of managing bipolar disorder.

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Bipolar disorder is generally viewed as a disturbance of mood. However, prominent aspects of behavior that occur during depressive and manic states of bipolar disorder, including psychosis, aggression, and anxiety, are not specific to mood syndromes and occur across many psychiatric states. Aggression is a well-recognized aspect of mood syndromes, and this article discusses the severity and management of aggression specifically as a component of bipolar disorder.

AGGRESSION AS A COMPONENT OF MOOD SYNDROMES

Kraepelin[1] derived the original dimensional formulation of bipolar disorder. He formulated episodes of depression and mania as permutations of disturbed affect, thought, and behavior. Central to Kraepelin's formulation was the description of mixed states (or depressive-mania) as driven by excessive arousal or "frantic anxiety." More recently, Carroll[2] proposed that bipolar disorder was the result of alterations in neurobiological systems regulating reinforcement and reward, central pain, and motor activity. Without focusing on mood syndromes, van Praag et al.[3] formulated a dimensional system of behavior with dopamine linked to motivation, norepinephrine to pleasure, and serotonin to affect and aggression.

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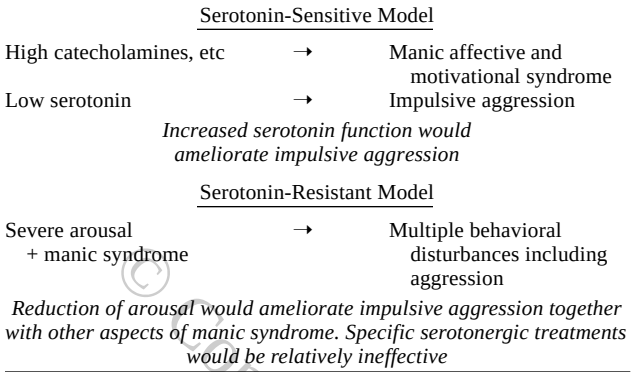
When behavioral states occur across many psychiatric syndromes, they may represent similar neurochemical disturbances over a range of contexts. Serotonergic studies of the mechanisms of behavioral disturbances in mania show that relatively low functional serotonergic activity may result in impaired impulse control and increased aggressive behavior regardless of the context in which it occurs.[4,5] In fact, aggressive behavioral responding increases in normal subjects when serotonergic activity is reduced by tryptophan depletion.[6] Low concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) is specifically associated with impulsive rather than nonimpulsive aggressive behavior.[7] Patients with prominent impulsive aggression, therefore, may differ from other aggressive patients by having lower serotonergic function.[8] Thus, specific behaviors related to aggression might improve during treatment with serotonergic agents, even if other aspects of the patient's illness did not improve.

Alternatively, multiple behavioral problems not specifically related to depressive or manic affect could occur as the result of an underlying disturbance that was not an integral part of bipolar disorder, but which produced similar behavioral problems across different psychiatric states. As an example, severe hyperarousal—beyond that usually associated with classic manic or depressive episodes—could result in a variety of behavioral or symptomatic disturbances including aggression, impulsivity, and anxiety (Figure 1). In this case, the behavioral disturbance would not respond well to specific symptomatic treatment, but would respond to treatment of the underlying arousal disturbance driving the behavior. In other words, rather than serotonergic treatments, strategies that reduced arousal by increasing GABA (γ-aminobutyric acid) or by decreasing excitatory amino acids or noradrenergic transmission might be more effective.

Figure 1. Mechanisms of Behavioral Disturbance in Mania



SEVERITY OF AGGRESSION IN BIPOLAR DISORDER

Aggression is a well-recognized aspect of mood syndromes, but there is surprisingly little direct quantitative data about aggression in patients with affective disorders. The biological component of the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression (NIMH-CDS) examined behavior and symptoms, both specific and nonspecific, relative to the affective state in bipolar (depressed, manic, and mixed) subjects, unipolar depressed, nonaffective psychotic, and healthy comparison subjects. Behavioral measures, including clinician, nurse, and self-ratings, were subjected to factor analysis,[9] and results yielded 9 behavioral constructs, 1 of which was hostility/irritability. Scores for the hostility/irritability construct were similar (i.e., significantly higher than in healthy control subjects)[9] in all psychiatric states except for bipolar mixed states, in which hostility scores were higher than in any of the other groups.[10] In another study,[11] subjects in mixed states did not differ from other subjects (those with pure mania, agitated bipolar depression, and nonagitated bipolar depression) with respect to serotonergic function, but they had markedly higher measures of catecholaminergic activity and hypothalamic-pituitary-adrenocortical axis function. These behavioral and biochemical data suggest that patients in mixed states differed from other psychiatric patients in having more severe hyperarousal, rather than in specifically having lower serotonergic activity with resultant increased aggression.

TREATMENT

Lithium, which has a partially serotonergic mechanism of action, is an effective treatment for mania and for impulsive aggression occurring in nonmanic patients[12]; it is also at least moderately effective in the treatment of bipolar depression. Yet, lithium was completely ineffective in the treatment of NIMH-CDS patients who were in mixed states.[13] These results were consistent with the above formulation that in some patients—regardless of specific mood states—behavioral disturbances may occur as a result of extreme hyperarousal. In such cases, the usually specific treatments for mood state or behavioral symptoms would be ineffective. One would expect, however, that treatment of the underlying hyperarousal state would result in resolution of the associated behavioral problems.

My colleagues and I recently completed a comparison of lithium, divalproex, and placebo in a series of 179 subjects hospitalized for manic episodes.[14] Comprehensive evaluations of behavior and symptoms were carried out before and during 3 weeks of treatment. The primary outcome measure—a change in mania factor scores derived from the Schedule for Affective Disorders and Schizophrenia-Change version—was compared in patients with and without depressive symptoms at baseline according to nurse- or physician-rated scales. Overall response to lithium and divalproex was similar in patients with acute mania, but divalproex was more effective in patients having combined depressive and manic states. Lithium was relatively ineffective, which was similar to the results of the NIMH-CDS study. Factor analysis of behavior yielded a factor for hostile, impulsive, or aggressive behavior. Cluster analysis showed that the hostility factor was highest in the group of dysphoric manic patients, who responded well to divalproex but less well to lithium. Divalproex, unlike lithium or placebo, significantly reduced anger factor scores in manic patients. These data suggest that the hyperarousal associated with depressive, anxious, and aggressive symptoms in mixed states responds to treatment with divalproex.

Approach to Management

Patients with mania are susceptible to overstimulation, and they fear the loss of control. To manage aggression in these patients, it is important to recognize impending overstimulation and immediately establish consistent behavioral limits and environmental structure.[15] Table 1 summarizes contributing factors to and countermeasures of aggressive behavior in manic episodes. Internal and external overstimulation can be countered by reducing environmental noise, providing a safe and predictable setting, and promoting an internal stimulus barrier with antiarousal medication. Fear of loss of control and impulsivity can be countered by controlling overstimulation and providing consistent behavioral limits.

Pharmacologic treatment helps to create an internal barrier against overstimulation. Benzodiazepines may be useful in relatively mild manic episodes, but are less likely to be effective in severe episodes or those with severe impulsive aggression; furthermore, benzodiazepine treatment can cause behavioral disinhibition.[16] Antipsychotic treatments are often used for rapid treatment of behavioral

Table 1. Factors Contributing to Aggression in Patients With Mania

Contributing Factors	Countermeasures
Overstimulation (internal and external)	Reduce environmental noise Provide safe and predictable setting Promote internal stimulus barrier with anti-arousal medication
Fear of loss of control and impulsivity	Control overstimulation Provide consistent behavioral limits

manifestations of mania, but their effectiveness compared with vigorous treatment with anticonvulsants or combination mood-stabilizer regimens is not established.[17] Combinations of low doses of antipsychotic and benzodiazepine treatments may produce synergistic effects, with resultant lower dose requirements for each drug.[18]

In order to effectively treat aggressive behavior in manic episodes, it is necessary to resolve the underlying manic episode. In a prospective study that compared the antimanic response of divalproex with that of haloperidol in the initial treatment of acute psychotic mania, the rate of resolution of manic and psychotic symptoms was similar using a divalproex oral loading dose of 20 mg/kg/day and haloperidol 0.2 mg/kg/day.[19] Combination mood-stabilizer (carbamazepine plus lithium) treatment also appears to be as effective in psychotic manic episodes as combination mood-stabilizer/antipsychotic (lithium plus haloperidol) treatment.[20] Vigorous early use of mood stabilizers is therefore a vital measure in the resolution of behavioral problems in patients with manic episodes.

In general, when an antimanic treatment is ineffective for mania, it is also ineffective for associated aggressive behavior. For example, lithium is effective in treating impulsive aggression outside of manic episodes and is effective in manic episodes when excessive arousal is absent (i.e., pure manic episodes of mild-to-moderate severity),[12,13] but it is ineffective—at least as monotherapy—against either aggression or mania in severe mixed episodes.[13,14] Within this latter context, other treatments, particularly anticonvulsants, may be more effective than lithium.[21,22]

Some basic principles of management are useful to remember in treating aggressive behavior in manic patients. Treatment strategies must be presented to patients in a way that respects, as much as possible, their pervasive fear of loss of control. The message should be that "this medication will help you to regain control of yourself" rather than "this medication will control you." If the decision has been made to give medication, the clinician should simply inquire whether the patient prefers oral or injectable medication rather than offering the patient an opportunity to reject the treatment plan.

Other aspects of managing aggressive behavior in patients with mania are listed in Table 2. Assessment of the patient should include a history of previous aggressive behavior and threats, the patient's legal situation and personal problems, trauma history, medical problems including substance abuse and/or withdrawal, and previous treatment response. The treatment team should strive to ensure the patient's safety and provide consistent environmental boundaries in which overstimulation is reduced. Clear interpersonal communication should be established with consistent personal boundaries and avoidance of provocation, splitting, and other interpersonal distortions. Pharmacologic treatment approaches should include rapid mood stabilization and establishment of an internal stimulus barrier. In summary, successful treatment of behavioral disturbances in manic patients requires integrated environmental and pharmacologic treatment that provides an externally coherent environment and internal resolution of the hyperarousal state that accompanies severe manic episodes.

Table 2. Management of Aggression in Mania

Assessment	Previous aggressive behavior and threats Legal situation and personal problems Trauma Medical problems including substance abuse/withdrawal Previous treatment response
Environment	Reduce overstimulation Provide consistent environmental boundaries Ensure safety
Interpersonal	Establish clear communication and consistent personal boundaries Avoid provocation, splitting, and other interpersonal distortions
Pharmacologic	Provide rapid mood stabilization and establish internal stimulus barrier

CONCLUSION

Prominent aspects of behavior that occur during depressive and manic states of bipolar disorder are not specific to mood syndromes and occur across many psychiatric states such as psychosis, aggression, and anxiety. Behavioral and biochemical data suggest that patients in mixed states differ from other psychiatric patients in having more severe hyperarousal, rather than in specifically having lower serotonergic activity and resultant increased aggression. In behavioral disturbances that occur as a result of extreme hyperarousal, the usually specific treatments for mood state or behavioral symptoms may be ineffective. Successful treatment of behavioral disturbances in manic patients requires integrated environmental and pharmacologic treatment that provides an externally coherent environment and internal resolution of the hyperarousal state that accompanies severe manic episodes.

Drug names: carbamazepine (Atretol, Tegretol, and others), divalproex (Depakote), haloperidol (Haldol and others).

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DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their knowledge, the following agents mentioned herein are not approved for these respective uses: divalproex at an initial dose of 20 mg/kg/day, combination of antipsychotic and benzodiazepine, haloperidol 0.2 mg/kg/day for mania, anticonvulsants other than divalproex for mania, lithium carbonate for aggression outside of mania, anticonvulsants for aggressive behavior.