

Correlates of Suicidal Behavior and Lithium Treatment in Bipolar Disorder

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Individuals with bipolar and major depressive disorders have considerably higher suicide rates than the general population. However, estimating the risk of suicide is complicated, and there exists a general lack of consensus among researchers regarding whether suicide rates are higher in patients with unipolar, bipolar I, or bipolar II depressive disorders. Isolating the specific factors that contribute to the high risk of suicide in patients with affective disorders can be challenging as well; substance and alcohol abuse, family history of suicide, differences in allele distributions, comorbid anxiety, depression recurrence, seasonal effects, rapid cycling, and a history of hospitalizations for depression all appear to contribute to the likelihood that these patients will engage in suicidal behavior. Research does tend to agree that lithium is efficacious in decreasing suicidal behavior in patients with affective disorders. (*J Clin Psychiatry* 2004;65[suppl 10]:5–10)

Every year thousands of people in the United States take their own lives, and many more make attempts that are severe enough to warrant emergency room treatment. Suicide rates are considerably higher in individuals with bipolar and major depressive disorders than in those without a lifetime history of psychiatric illness.¹ Standard mortality ratios due to suicide in those who have bipolar disorders and major depression compared with the general population have been reported to be as high as 15 to 20.² Tondo et al.³ estimated that approximately 0.4% of women and men diagnosed with bipolar disorder take their lives every year—a rate that is more than 20-fold higher than that in the general population.

However, estimating the risk of suicide is complicated, and research findings are often controversial—a lack of consensus becomes distinctly apparent when considering the many studies that have compared suicide rates in patients with unipolar, bipolar I, or bipolar II depressive disorders. Studies^{4–7} have suggested that patients with bipolar II made more suicide attempts than patients with bipolar I depressive disorders, and the death rate from completed suicides was higher in patients with bipolar II than in

patients with unipolar depression. But, a study by Angst et al.⁸ concluded that patients with unipolar depression had significantly higher rates of suicide than patients with bipolar I or bipolar II depressive disorders. However, Bottlender et al.⁹ reported that apart from a higher frequency of past suicide attempts in patients with bipolar depression (26.6% in bipolar vs. 17.8% in unipolar), there appeared to be no further differences in suicidality between patients with bipolar depression and patients with unipolar depression. The researchers determined that approximately 40% of patients in both groups had suicidal thoughts and that 0.8% completed suicides during hospital stays in both groups.

The lack of agreement among researchers in estimating suicide risk may be attributed to many factors. One might be that suicide attempts and completed suicides are easier to identify than suicidal thoughts; yet, both are relevant in determining exact risk. Another contributing factor may be the variance in criteria used among different studies to define unipolar, bipolar I, and bipolar II depressions. Different sample sizes among trials might also contribute to contradictory findings. Finally, many studies of suicide are conducted in severely depressed inpatients; yet, the vast majority of individuals with depression are treated as outpatients, if they are treated at all. Therefore, data may be slanted toward severely ill patients.

CORRELATIVE VARIABLES IN BIPOLAR DEPRESSION AND SUICIDE

Understanding the causes of suicide is the first step toward prevention. Although accurately estimating suicide rates in specific affective disorders is not easily accomplished, what has been clearly established is that there is a

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substantial correlation between bipolar depressive disorder and suicide.¹⁰ Unfortunately, however, isolating the factors that specifically contribute to the high association between affective disorders and suicide¹¹⁻¹⁴ can be equally challenging. Despite inherent obstacles, considerable research has attempted not only to examine treatment efficacy for suicidal behavior in these patients, but also to identify what variables can help physicians determine which patients are at the greatest risk.

Substance and Alcohol Abuse

Numerous studies^{11,12,14-16} have indicated that substance and alcohol abuse are highly correlated with suicide attempts in bipolar disorder. Dalton et al.¹¹ examined whether affective disorders were associated with suicide attempts and determined that lifetime comorbid substance use disorder (SUD) was associated with an increase in suicide attempts. Researchers administered the Structured Clinical Interview for DSM-IV to 336 patients with a diagnosis of bipolar I, bipolar II, or schizoaffective disorder (bipolar type), and predictors were subsequently examined in nonattempters and attempters. Lifetime comorbid SUD was a significant ($p = .037$) predictor of suicide attempts; patients without SUD had a 23.8% lifetime rate of attempted suicide, while patients with SUD had a 39.5% lifetime rate of attempted suicide.

Lopez et al.¹⁵ investigated the association between suicide attempts and drug abuse by analyzing sociodemographic, clinical, and family history variables in 169 patients with DSM-III-R bipolar I disorder while using a logistic regression analysis to control for the effects of other variables. Researchers found that 56 (33%) of the patients in the sample had attempted suicide 1 or more times, and the univariate analyses revealed that drug abuse was significantly ($p < .05$) associated with suicidal behavior in these patients.

In a similar study, Potash et al.¹⁶ examined the clinical and familial correlation between comorbid alcoholism and attempted suicide in affectively ill relatives of probands with bipolar I disorder. In 71 families that were evaluated for a separate genetic linkage study, 337 subjects with major affective disorder were identified. These subjects were assessed with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version. Subjects with bipolar disorder and alcoholism demonstrated a 38.4% lifetime rate of attempted suicide compared with a 21.7% rate in those without alcoholism. Additionally, 11 families with probands with alcoholism and bipolar disorder exhibited a 40.7% rate of attempted suicide in relatives with bipolar disorder compared with a 19.0% rate in the other families. Researchers concluded that the association of comorbid alcoholism and attempted suicide among family members with bipolar disorder and the tendency for attempted suicide and alcoholism to cluster in a subset of families may indicate a genetic origin.

Using a stress-diathesis model¹⁷ developed to assist clinicians in determining which patients are at risk for suicidal behavior, Oquendo and Mann¹⁴ conducted a review of the literature and concluded that bipolar patients who attempted suicide had higher levels of substance abuse than nonattempters. Goldberg et al.¹² also reported a correlation between substance abuse and suicidality in patients with dysphoric mania.

Family History of Suicide

In addition to the clinical and familial correlation between comorbid alcoholism and attempted suicide reported by Potash et al.,¹⁶ Leverich and colleagues¹³ found a correlation between suicide and family history. Using patient-rated and clinician-rated questionnaires to assess the incidence and correlates of serious suicide attempts, researchers evaluated 648 outpatients with bipolar I or II disorder. The 220 patients (34%) who demonstrated a history of suicide attempts had a greater positive family history of drug abuse, suicide, and suicide attempts.

Serotonin Transporter Gene

The association of comorbid alcoholism and attempted suicide among family members with bipolar disorder and the tendency for attempted suicide and alcoholism to cluster in a subset of families may implicate the involvement of genes in the serotonin system in suicidal behavior. Some studies^{18,19} have even suggested that genetic vulnerability factors underlying suicidal behavior may be independent of the genetic transmission of psychiatric disorders. In a controlled study, Bellivier et al.²⁰ examined whether the serotonin transporter (5-HTT) gene encoding the protein responsible for serotonin reuptake from the synapse after its release from serotonergic neurons was involved in suicidal behavior. Researchers studied a functional polymorphism of the 5-HTT gene in 237 subjects with unipolar or bipolar disorder and 187 control subjects. Of all the subjects, 99 had attempted suicide at least once and 26 had made a violent attempt. Although no association was found between the "s" allele of the 5-HTT gene and suicide attempts, researchers did report a significant ($p = .023$) difference in allele distributions in patients who made violent suicide attempts compared with control subjects, indicating that a genetic variant of the 5-HTT gene may predispose individuals to violent suicidal behavior.

Comorbid Anxiety

A correlation between panic disorder and suicidal behavior has also been hypothesized, and researchers^{21,22} attempted to elucidate this association. King et al.²¹ studied 346 outpatients with depression who were divided into 3 groups: 216 patients who had no history of panic attacks, 65 patients who had a history of infrequent panic attacks, and 65 patients who met DSM-III criteria for panic disorder. As shown in Table 1, a higher proportion of patients

Table 1. Frequencies (%) of Primary Diagnoses Among Depressed Patients With and Without Panic Attacks^a

Disorder	Total N = 346	Infrequent		
		No Panic Attacks N = 216	Panic Attacks N = 65	Panic Disorder N = 65
Major depression	39.3	41.2	33.9	38.4
Bipolar	22.0	20.4	30.8	18.4
Organic mood	17.1	15.3	21.5	18.4
Dysthymia	8.7	9.8	9.2	4.6
Depression NOS	4.0	5.1	3.1	1.5
Cyclothymia	2.3	3.3	0.0	1.5
Panic	2.3	0.0	0.0	12.3
Obsessive-compulsive	0.9	0.5	1.5	1.5
Adjustment	0.6	0.9	0.0	0.0
Somatization	0.6	0.9	0.0	0.0
Schizoaffective	0.6	0.9	0.0	0.0
Psychotic	0.6	0.9	0.0	0.0
Organic anxiety	0.6	0.5	0.0	1.5
Generalized anxiety	0.3	0.5	0.0	0.0
Delusional	0.3	0.0	0.0	1.5

^aAdapted with permission from King et al.²¹

with depression who had infrequent panic attacks or panic disorder had attempted suicide than patients with depression without panic attacks ($\chi^2 = 5.04$, $df = 1$, $p \leq .025$). Researchers also found that depressed patients who had a history of infrequent panic attacks had a significantly ($p < .05$) higher incidence of suicide attempts (32.3%) than patients who had been diagnosed with panic disorder (21.5%). However, further investigation using multiple regression analyses revealed that female gender and history of psychosis most likely contributed to variance in suicide history.

Frank et al.²² examined the potential negative influence of “panic spectrum” conditions (core and most severe symptoms as well as a range of more subtle features) on suicidal ideation in patients with bipolar I disorder. Sixty-six patients with bipolar I disorder completed questionnaires measuring lifetime panic-agoraphobic spectrum symptoms, and researchers compared clinical characteristics between patients who scored above and below a predefined clinical threshold for panic spectrum conditions. Results indicated that the 50% ($N = 33$) of outpatients who reported panic spectrum features above the predefined threshold were substantially more likely than low-scoring patients to report suicidal ideation.

Depression Recurrence

Suicide appears to have a positive association with lifetime episodes of major depression in patients with affective disorders.^{15,23} Oquendo et al.²³ assessed suicidal behavior qualitatively and quantitatively in 44 patients with DSM-III-R bipolar disorder. They reported that patients with bipolar disorder who had attempted suicide experienced more lifetime episodes of major depression, and twice as many were in a current depressive or mixed episode compared with bipolar disorder patients who had not

attempted suicide. Additionally, the Lopez et al. study¹⁵ reported that along with family history of drug abuse, suicide, and suicide attempts, suicide attempts in patients with bipolar disorder were related to severe depressive episodes.

Gender

Although Eaton and Kessler¹ reported that women attempt suicide approximately 2 to 3 times more often than men, a clinical study by Perugi et al.²⁴ of 538 subjects with primary mood disorders reported that men and women did not vary in number of suicide attempts. Men may complete suicide more often than women, as was found in a study by Simpson and Jamison²⁵ of men and women with bipolar disorder. The authors reported that young men who were in an early phase of bipolar illness—especially those who had recently been discharged from the hospital, had made a previous suicide attempt, and abused alcohol—were at the greatest risk for suicide.

Seasonal Effects

The influence of seasonal changes on mood disorders has historically been a controversial topic. In an attempt to elucidate the effect of seasonal changes on mood disorders and suicide, Morken et al.²⁶ examined monthly variations in hospital admissions for mania and depressions and variations in frequencies of suicides. Admissions for mania or depression ($N = 4341$) from 1992 to 1996 were analyzed, as were 14,503 suicides that occurred in Norway from 1969 to 1996. Researchers found that hospital admissions revealed significant monthly variation with the highest peak for women occurring in November ($p < .005$) and for men in April ($p < .05$). However, the times of hospital admissions for men and women were not identical to the onset of the affective episode.

Rapid Cycling

Patients with rapid-cycling bipolar disorder typically have more depressive episodes than do patients without rapid cycling bipolar disorder. In an attempt to determine if rapid cyclers additionally have higher suicide rates than non-rapid cyclers, Wu and Dunner²⁷ compared histories of suicide attempts in 100 rapid cycling patients and 120 non-rapid cycling patients. After evaluation of the patients and their chart information, 7 were excluded from the study either because the history reported by the patient was incomplete or because the history was too complicated and was unsuitable for the purpose of the study. The investigators found no significant differences when comparing suicide attempt histories between the 2 groups.

Hospitalization

Although a paucity of studies has been conducted examining the relationship between prior hospitalizations and suicide attempts in patients with bipolar disorder, the

study by Leverich et al.¹³ reported that patients with a history of suicide attempts had more hospitalizations for depression compared with patients without such a history. The study by Lopez et al.¹⁵ further verified this finding in a univariate analysis, citing that history of hospital admission was significantly ($p < .05$) associated with suicide attempts. Morken et al.²⁶ also found that among men, suicide was highly correlated with a history of hospital admission.

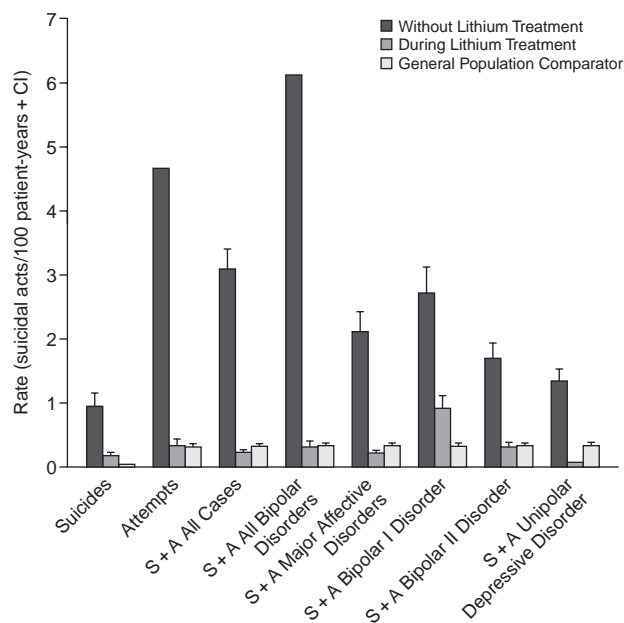
EFFECTS OF LITHIUM

One area of research agreement is that lithium effectively decreases suicidal behavior in patients with bipolar disorder. In a review of the literature concerning the efficacy of lithium in treating affective disorders, Muller-Oerlinghausen²⁸ reported that lithium should be considered a first-line mood stabilizer in affective disorders—particularly in patients with a history of suicide attempts. In fact, Muller-Oerlinghausen stressed that psychiatrists and other physicians should exercise extreme caution when discontinuing lithium treatment or switching to another mood stabilizer, because a patient might have been protected against suicidal impulses despite an incomplete response in the number and quality of depressive and manic episodes.

Baldessarini et al.²⁹ conducted a recent meta-analysis in which lithium was shown to have a profound effect on reducing suicidal behavior in patients with bipolar depression. Data from 34 studies comprising 42 groups receiving an average of 3.36 years of lithium maintenance treatment and 25 groups with no lithium treatment were followed for 5.88 years. A total of 16,221 patients were included with a gross experience of 64,233 person-years. As illustrated in Figure 1, rates for suicide attempts were 4.65 without lithium treatment versus 0.31 with treatment (a 93% difference). For completed suicides, rates were 0.94 without lithium versus 0.17 with treatment (an 82% difference), versus approximately 0.02 for the general population. Risk for all suicidal acts was reduced for unipolar depressive disorder by 100%, for bipolar II disorder by 82%, and for bipolar I disorder by 67%.

In another meta-analysis, Tondo et al.³⁰ compared suicide rates in patients with major affective disorders who were given long-term lithium treatment with those who were not. Their investigation reviewed 22 studies that provided suicide rates during lithium maintenance treatment (13 of these studies also provided rates without such treatment). After scoring study quality, testing between-study variance, and examining suicide rates between patients receiving and not receiving lithium maintenance treatment using random-effects regression methods to model risk ratios, researchers found that in all studies suicide risk was consistently lower during long-term treatment of major affective illnesses with lithium. Of the 5647 patients included in the 22 reviewed studies, suicide was 82% less frequent during lithium treatment than without it, and the

Figure 1. Rates of Suicides (S) or Attempts (A) or Both (S + A) Without Lithium Maintenance Treatment, With Lithium Treatment, and Approximately Equivalent Rates for the International General Population^a



^aReprinted with permission from Baldessarini et al.²⁹

computed risk-ratio in the 13 studies with rates for patients receiving and not receiving lithium was 8.85 (95% CI = 4.12 to 19.1; $p < .0001$).

My colleagues and I conducted a study [D.L.D.; F. Stallone, Ph.D.; R.R. Fieve, M.D.; unpublished data] examining the efficacy of lithium in decreasing suicidal behavior in patients with bipolar disorders who had been admitted to the New York State Psychiatric Institute clinic. Our findings were in agreement with other studies that have supported lithium as an antisuicide drug. After treating patients with bipolar disorder with lithium for approximately 2 years, we discovered that there were no suicide attempts during the entire study period—an unusual outcome since we were observing several hundred patients who had made numerous suicide attempts before treatment.

Kleindienst and Greil³¹ conducted a randomized clinical trial with a 2.5-year observation period to compare the differential efficacy of lithium with that of carbamazepine in 171 patients diagnosed with bipolar disorder according to DSM-IV criteria. A series of subgroup analyses was performed to investigate the efficacy of the 2 agents in treating bipolar disorder in clearly defined subsamples. Overall, in patients with bipolar I disorder ($N = 114$), lithium was superior to carbamazepine in efficacy against symptomatology. In patients with bipolar II disorder or otherwise unspecified bipolar disorder ($N = 57$), carbamazepine was at least equally as efficacious as lithium. In

a second part of the study, the entire sample was analyzed to determine the efficacy of each agent in decreasing suicidal behavior, and a trend in favor of lithium was found. In the sample of patients diagnosed with either bipolar I or bipolar II disorder, 4 suicide attempts were observed during the treatment period, and all the patients were receiving carbamazepine. No patients in the lithium treatment group attempted suicide during the study period.

Conversely, in their private practice study of 140 patients with bipolar disorder receiving maintenance treatment for a minimum of 6 months during a 23-year period, Yerevanian et al.³² found no difference in the protective effect of lithium or anticonvulsant mood stabilizers against non-lethal suicidal behavior. Researchers compared patient charts for incidence of completed suicides, number of suicide attempts, and number of hospitalizations for suicidal ideation or behavior per 100 patient years of either "on" or "off" lithium or anticonvulsant mood stabilizer monotherapy. Results indicated that only 1 completed suicide occurred (the patient was in an "off" period of lithium treatment at the time) and that incidence of nonlethal suicidal behavior was not different during treatment with lithium compared with anticonvulsant treatment.

Recently, Goodwin et al.³³ conducted a retrospective chart review of 638 patients with bipolar disorder who were members of 2 West Coast health plans and were treated with lithium, divalproex, or carbamazepine. The suicide death risk was 2.7 times higher during treatment with divalproex than during treatment with lithium, and other suicidal behaviors (nonfatal attempts resulting in hospitalization and attempts diagnosed in the emergency department) were also reduced during lithium treatment.

Rucci et al.³⁴ compared lifetime suicide attempts among patients with bipolar I disorder during a 2-year period of intensive pharmacotherapy and 1 of 2 adjunctive psychosocial interventions. Subjects entered the study during an acute mood episode and were treated with primarily lithium pharmacotherapy and either psychotherapy specific to bipolar disorder, which included help in systemizing daily routines, or nonspecific, intensive clinical management involving regular visits with empathetic clinicians. Results indicated that all patients experienced a 3-fold reduction in suicide attempts during the acute treatment phase and a 17.5-fold reduction during maintenance treatment. Additionally, no patient who had attempted suicide 1 or more times before entering the trial attempted suicide during the protocol. Researchers concluded that a treatment program in a maximally supportive clinical environment could substantially reduce suicidal behavior in patients with bipolar I disorder.

CONCLUSION

The issue of suicidal behavior needs to be considered in all patients with depression and particularly those with

bipolar disorders. Suicidal behavior is an unfortunate part of the illness and risk factors have been difficult to pin down. However, appropriate treatment can substantially reduce the rate of suicide in this population.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder and divalproex is not approved for the maintenance treatment of bipolar disorder.

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