Suicide Attempts and Completions in Patients With Bipolar Disorder

May 01, 2007 | Bipolar Disorder [1], Cultural Psychiatry [2], Mood Disorders [3], Panic Attacks [4], Bipolar II Disorder [5], Mania [6], Major Depressive Disorder [7], Addiction [8], Alcohol Abuse [9], Suicide [10]

By Steven C. Dilsaver, MD [11]

According to the CDC, in 2004, suicide was the 11th leading cause of death across all age groups and the 10th leading cause of death for persons aged 14 to 64 years; 32,439 people in the United States took their own lives. Women attempt suicide about 3 times more often than men, although men are 4 times as likely to complete suicide. Anderson and Smith3 reported that suicide was the eighth leading cause of death among men in 2001. Of the 24,672 completed suicides among men, 60% involved the use of a firearm (the use of a firearm was the means of suicide in 55% of all cases).

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Both "static" and "dynamic" factors have an impact on the rates of suicide. Static factors are associated with increased and decreased risks for self-harm. They are not causal but merely increase or decrease the probability of self-harm. Listed in the approximate rank order of risk, the static predictors of risk for a suicide attempt and completed suicide for persons with psychiatric illnesses, as well as some of the more important static protectors, are presented in the Table. Dynamic factors have to do with clinical states, which are subject to dramatic change within narrow time frames—hence, "dynamic."

**TABLE**
Static factors associated with suicide

<table>
<thead>
<tr>
<th><strong>Risks</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>History of a suicide attempt(s)</td>
</tr>
<tr>
<td>History of a psychiatric disorder, particularly a mood disorder</td>
</tr>
<tr>
<td>History of alcohol and/or drug abuse</td>
</tr>
<tr>
<td>Family history of suicide or exposure to the suicide of another person, especially a person to whom one is emotionally attached</td>
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<tr>
<td>Family history of childhood verbal,</td>
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physical, or sexual abuse
Feelings of hopelessness
Barriers to accessing mental health services (including poverty)
Loss of a significant relationship (including bereavement), one's job, financial status, "face" (ie, humiliation)
Easy access to lethal methods
Severe to extreme stressors
Unwillingness to seek help because of stigma of psychiatric illness
Social isolation or interpersonal impoverishment

**Protectors**
Effective treatment for psychiatric disorders, including substance use disorders
Easy access to a variety of clinical interventions and the availability of support for those with help-seeking propensities
The existence of an empathic, high-quality doctor/patient relationship
Support of nuclear and extended family
Strong support outside of one's home (eg, deep-seated friendships and support provided through relationships within the structure of one's religious community)
Possession of the skills to solve personal problems, resolve interpersonal conflicts, and handle disputes nonviolently
Cultural values that discourage suicide
Internalized (not merely professed) religious beliefs that affirm the dignity of human life, promote life-preserving
values, attitudes, and
confer meaning on
human existence

In clinical samples, about 50% of persons with bipolar disorder (BD) were found to have a history of a suicide attempt.\(^4\) In the largest epidemiological study on the topic to date, the suicide attempt rate in persons with BD was twice that of individuals with unipolar depression.\(^5\) Estimates of the fraction of unipolar patients who commit suicide are subject to considerable variance. Sources of variance include, for example, whether one focuses on outpatients or inpatients, the type of patient studied (e.g., those with psychotic versus nonpsychotic depression), and the purity of the composition of the sample. It is not at all unlikely that the results of many studies have been contaminated by the inclusion of subjects with unrecognized bipolar illness.

Miles\(^6\) reviewed studies of the prevalence of suicide in patients with various psychiatric disorders and estimated that 15% of those with "primary endogenous" depression committed suicide. Interestingly, the results of this study also indicated that 15% of those with so-called neurotic depression also committed suicide. Avery and Winokur\(^7\) also estimated that 15% of those with unipolar disorder committed suicide.

In 1990, Goodwin and Jamison\(^8\) presented the results of an exhaustive review of the literature on the relationship between manic-depressive illness and suicide. The findings of the review, which included 30 reports published between 1936 and 1988, showed that 19% of the deaths of 9389 persons with BD were caused by suicide.

The reasons for the seemingly higher rate of suicide in persons with BD compared with those who are unipolar are not known. However, new data provide hints. Simon and colleagues\(^9\) studied the relationship between current and lifetime comorbid anxiety disorders and suicidal behaviors. Lifetime anxiety disorders were associated with more than a doubling of the risk of a suicide attempt. Recent research indicates that persons with BD have a much higher comorbid anxiety disorder burden than persons who are unipolar.\(^10-12\) This substantially contributes to the higher rate of attempted and completed suicide among persons with BD compared with those who are unipolar. Individuals with BD are many times more likely to suffer from panic disorder, obsessive-compulsive disorder, social phobia, and posttraumatic stress disorder (PTSD) than individuals with major depressive disorder (MDD).\(^10-12\)

There is a highly significant dose-response relationship between loading for comorbid anxiety disorders and the probability of having had a suicide attempt; the more anxiety disorders one has, the greater the risk for attempted suicide.\(^10,11\)

**Dynamic risk factors**

Dynamic factors can be causally related to suicidal ideation, suicide attempts, and completed suicide. Dynamic risk factors relate to mood state and shifts in mood state. The probability of attempting or completing suicide is related to the amount of time that a person is in a dysphoric state.

Judd and associates\(^13\) published the results of the first prospective study on the natural history of the weekly symptomatic status of patients with bipolar I disorder (BDI). The patients were followed for an average of 12.8 years, and on average, they had depressive symptoms during 31.9% of the total follow-up weeks. They were in cycling or mixed states during 5.9% of the time; manic/hypomanic symptoms predominated only 8.9% of the time.

In another study encompassing 20 years of longitudinal evaluation, patients were depressed much more often than they were manic/hypomanic.\(^14\) Patients with BDI spent about 30% of the year with depressive symptoms and slightly less than 10% in states of mood elevation. In contrast, patients with bipolar II disorder (BDII) spent, on average, 51.9% of the year with depression and only 1.9% with hypomania. The most powerful predictor for risk of suicide may well be the duration of time that persons spend in a depressive/ mixed phase of the disease; therefore, the substantially greater period that patients with BDII spend in dysphoric states likely puts them at higher risk for suicide than patients with BDI.\(^15\)

Of the 2 dysphoric states, mixed states may be more lethal. In 1936, Jameison\(^16\) reviewed the case histories of 100 persons who committed suicide. He found that patients with mixed states were at highest risk for suicide.

Patients in mixed states can easily be mistakenly viewed as being depressed. This error can lead to maltreatment and even fatal treatment decisions.\(^17\) The use of antidepressants may have the capacity to greatly worsen the condition of mixed patients and increase the risk of suicidal behavior.
For this reason, all patients with BD must be carefully screened for the presence of even subtle hints that they are in a mixed phase.

When even subthreshold symptoms of hypomania/mania are present in the context of depressive symptoms, it is critical to avoid the use of antidepressants. In this author's experience, patients with this symptomatology can almost certainly be effectively treated with atypical antipsychotics in combination with divalproex, lithium, or lamotrigine. Atypical antipsychotics have antimanic properties, some of them may stabilize mood, and one (quetiapine) has an FDA indication for depression. Lithium and lamotrigine have confirmed antidepressant properties.

Many patients with BD, in the midst of a major depressive episode (MDE) or even with subsyndromal symptoms of MDE contaminated by hypomaniac/ manic features simultaneously meet the criteria for generalized anxiety disorder, panic disorder, social phobia, or PTSD. These patients can be aggressively treated with benzodiazepines. Alternatively, some clinicians might elect to use gabapentin or valproate, but in this author's judgment, these are second-line drugs. If one asks patients in these states, "What causes you more suffering, the depressive element of your illness or the anxiety?" Essentially all will respond, "The anxiety!" The magnitude of the global severity of anxiety is linked to the risk of completed suicide.18

If the patient is at risk for panic attacks, it is critical to select a benzodiazepine with proven antipanic effects. The drug should be given on a schedule because once a panic attack starts these drugs will not abort the attack. A reasonable initial dosing schedule in a benzodiazepine-naive patient aged 65 or younger who is having panic attacks, is 1 mg of clonazepam every 8 hours. It is important to caution patients not to drive or use potentially dangerous equipment if they experience sedation as an adverse effect.

Patients with severe anxiety must be very carefully monitored. The first task is to determine whether the patient needs to be hospitalized. A highly significant portion of patients require this intervention. Hospitalization allows for very aggressive treatment in a safe environment. However, in patients for whom outpatient treatment is appropriate, a telephone call to assess progress within 24 to 48 hours of the start of treatment demonstrates the physician's concern and provides an opportunity to ascertain whether the anxiolytic/antipanic medication is adequately effective. If it is not, a dosage change is in order—unless adverse effects are limiting, which is extremely rare. Dosages of 1.5 to 2.0 mg of clonazepam every 8 hours may be required.

An alternative to clonazepam is either immediate- or extended-release alprazolam. A reasonable starting dosage for the immediate-release preparation is 1.0 mg every 6 hours or, more practically, 4 times a day. A reasonable initial regimen for extended-release alprazolam is 1.0 to 1.5 mg every 12 hours.

Shifts from states of euthymia, or relative euthymia, to subsyndromal and syndromal states of depression or into subthreshold or veritable mixed states, greatly increase the risk of suicidal behavior. The term "mixed state" includes not only MDE features as defined in DSM-IV but also the amalgam of an MDE and a full-hypomanic syndrome. The term also includes subsyndromal mixed states—an MDE contaminated by features of hypomania/mania. An MDE with any degree of contamination by hypomaniac or manic features may constitute the most lethal of all clinical states.

**Substance use disorders**

The active abuse of alcohol and/or drugs is an independent risk factor for suicide in patients with BD. Patients with a substance use disorder may be particularly impulsive and can be assumed to have greater impairment of judgment than they would without current substance abuse. It is now the standard of practice, in contradistinction to years past, to treat the substance use disorder and BD simultaneously.

Physicians are advised to have a particularly low threshold for hospitalizing patients with BD who are heavily abusing alcohol or extensively using dangerous substances—certainly if detoxification is necessary. Patients who habitually abuse alcohol or drugs and cannot be relied on to refrain from substance abuse constitute a highly nonadherent population. Even if medications are used as prescribed, it is wholly unreasonable to presume that these patients will respond well as outpatients. Persons with BD have higher lifetime rates of alcohol and drug abuse than patients with any other Axis I disorder (other than patients with histories of primary substance use disorders). In the Epidemiologic Catchment Area (ECA) database, persons with BD have about 3 times the relative rate of alcohol and drug abuse than those with MDD. The ECA database revealed that 46% of the patients with BD had lifetime histories of alcohol abuse, 42% had histories of drug abuse, and 62.5% had histories of alcohol and/or drug abuse.8,19 (Please note that these are lifetime—not point prevalences.)

Sample populations in epidemiological studies might be expected to be less severely ill than those
Observations made in lithium clinics led investigators to suppose that this drug could have potential antisuicidal effects of lithium improvement over 4 to 6 weeks. With this regimen, there is typically substantial improvement within a week and progressive patients have comorbid anxiety disorders, a high-potency benzodiazepine with antipanic properties. produces nice antidepressant effects in many patients with bipolar disorder, and, because many long-term), along with the anticonvulsant lamotrigine titrated to 200 mg over 3 weeks because it I might, for example, prescribe a weight-neutral atypical (since it is assumed that treatment will be treatment with antidepressants in the absence of an antimanic and mood-stabilizing agent. addition of an antidepressant, if necessary, may be effective. antipsychotic agent with mood stabilizing properties followed, a few days to a week later, with the The concept of DMX may be relevant to the debate over the capacity of antidepressants to induce mania. patients meeting the criteria for DMX must be screened with care for a history of hypomania or episodes of hypomania. Some patients have also had episodes of mania. The DMX3 is a good indicator for BDII. Sensitivity and specificity increase in proportion to the number of symptoms of hypomania. Benazzi reported that there is a dose-response relationship between the number of hypomanic symptoms occurring in the context of DMX and a family history of BD. All patients meeting the criteria for DMX must be screened with care for a history of hypomania or mania. The concept of DMX may be relevant to the debate over the capacity of antidepressants to induce suicidal ide- ation in children and adolescents. One can reasonably hypothesize that these drugs have the capacity to induce suicidal ideation in youths who have mixed depression or bipolar spectrum disorders. Children and adolescents must be screened for the presence of DMX and a history of hypomania, even if it is only of 2 or 3 days' duration. The DSM-IV stipulation that a hypomanic syndrome must be of at least 4 days' duration is arbitrary. Empirically derived evidence indicates that episodes of only 2 days' duration are clinically significant. Two-day periods of hypomania are closely linked to a family history of bipolarity and a bipolar course is defined as episodes of hypomania that may induce rapid cycling or otherwise adversely impact their course. These patients typically also suffer psychosocial damage that may be permanent. Consequently, because of the delay in making a correct diagnosis, the average person with BD is much more difficult to treat than he or she would have been if the proper diagnosis had been made at initial presentation. Incorrect diagnosis, maltreatment, and a delay in effective treatment greatly increase the risk of suicidal behavior and completed suicide. The literature indicates that at least 40% of persons presenting with depressive symptoms have an illness that is bipolar in nature. This is consistent with well-designed studies indicating that the prevalence of BDII and other bipolar spectrum disorders with clinical presentations that clinicians may misdiagnose as simple depressive or anxiety disorders, are up to 2.4% for BDI, 4.8% for BDII, and 6.3% for cyclothymic disorder. The bipolar spectrum includes a minimum of 6% of the population, and some experts suggest that the percentage is much higher. Clinical significance of depressive mixed states or mixed depression Depressive mixed state (DMX) is an MDE combined with manic/hypomanic symptoms. MDE with 3 or more features of hypomania other than euphoria or inflated self-esteem is expressed as DMX. DMX is associated with a higher risk of suicidality than nonmixed depression. One contributing factor may be impulsivity associated with hypomanic activation. According to DSM-IV and the International Classification of Disease, 10th revision criteria, a patient with DMX has MDD. Particularly common symptoms in a DMX are irritability, distractibility, racing/crowded thoughts (often to the point of producing distress), psychomotor agitation, and increased activity. The DMX is a nosological orphan. As a consequence, few psychiatrists have heard about it. Akiskal and Benazzi have presented validating findings indicating that patients with DMX tend to have family histories of BD and episodes of hypomania. Some patients have also had episodes of mania. The DMX3 is a good indicator for BDII. Sensitivity and specificity increase in proportion to the number of symptoms of hypomania. Benazzi reported that there is a dose-response relationship between the number of hypomanic symptoms occurring in the context of DMX and a family history of BD. All patients meeting the criteria for DMX must be screened with care for a history of hypomania or mania. 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A regimen of a sedating atypical antipsychotic agent with mood stabilizing properties followed, a few days to a week later, with the addition of an antidepressant, if necessary, may be effective. This regimen spares patients treatment with antidepressants in the absence of an antimanic and mood-stabilizing agent. I might, for example, prescribe a weight-neutral atypical (since it is assumed that treatment will be long-term), along with the anticonvulsant lamotrigine titrated to 200 mg over 3 weeks because it produces nice antidepressant effects in many patients with bipolar disorder, and, because many patients have comorbid anxiety disorders, a high-potency benzodiazepine with antipanic properties. With this regimen, there is typically substantial improvement within a week and progressive improvement over 4 to 6 weeks. Potential antisuicidal effects of lithium Observations made in lithium clinics led investigators to suppose that this drug could have
antisuicidal effects. Cipriani and colleagues\textsuperscript{34} conducted a meta-analysis of randomized trials assessing the efficacy of lithium relative to placebo and active treatments on the risk of suicide and intentional self-harm using the Cochrane Collaboration Depression, Anxiety and Neurosis controlled trials register. Thirty-two trials that included 1389 patients who received lithium and 2069 patients who received other agents provided data for the analysis. Patients who received lithium were less likely to commit suicide (odds ratio [OR] = 0.26; $P = .01$; 95% confidence interval [CI], 0.09 to 0.77). A composite measure of suicide and deliberate self-harm was also lower in patients treated with lithium (OR = 0.21; $P = .0005$; 95% CI, 0.08 to 0.50) and lithium was associated with a lower rate of death from all causes (OR = 0.42; $P = .02$; 95% CI, 0.21 to 0.87).

The authors concluded that the evidence "seems unequivocal that patients [treated] with lithium were much less likely to die of suicide or of another cause than patients given an alternative to lithium, whether the alternative was placebo or another compound." Lithium was associated with a reduction in the rate of suicide of about 60%, and risk of a composite measure of suicide and deliberate self-harm of about 70%.

It is important to recognize that the results of this key study strongly suggest, but do not prove, that lithium has mitigating effects on suicidal behavior. A study designed to prove that lithium has antisuicide effects relative to other treatments cannot be done for ethical reasons. It is also critical to appreciate that a great many more subjects have been treated with lithium in clinical trials than any other drug. Suicide has a low event rate in these trials. A large number of subjects is required to attain sufficient statistical power necessary to obtain data indicating that a drug has antisuicide effects. Other effective treatments could have the same effect, but the composite number of subjects treated with these agents is too low to conduct a meta-analysis.

**Summary**

Nearly 19% of all patients with BD commit suicide in the absence of effective treatment. There are static factors that increase the risk of suicide and others that decrease it. However, the most important factors are dynamic in nature—those that have to do with mood state and change in mood state.

The erroneous diagnosis of BD as MDD, an anxiety disorder, or a personality disorder places patients at an increased risk for suicide because it may lead to the use of potentially harmful treatments and a delay in the institution of effective treatment. On the other hand, overlooking and withholding treatment for comorbid anxiety disorders and substance use disorders can also greatly increase the risk of suicide attempts and completed suicide.

Changes in nosological schemata occurring over the next decade, such as the redefinition of hypomania and the official recognition of the DMX, stand to positively affect clinical practice and decrease the rate of suicide associated with BD.

**References:**


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