

SUICIDE IN BIPOLAR DISORDER: A REVIEW

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SUMMARY

Background: Suicide is a leading cause of death in patients with bipolar disorder. Risk factors and prevention of suicide in this illness are the focus of considerable current research.

Methods: MEDLINE data base was searched for the key words "bipolar disorder" with "suicide", "lithium" with "suicide", "anticonvulsants" with "bipolar disorder", and "anticonvulsants" with "bipolar disorder" and with "suicide". No language or time constraints were applied. The lists of references were searched manually to find additional articles.

Results: It is estimated that 25% to 50% of patients with bipolar disorder will attempt suicide at least once over their lifetime, and that 8% to 19% will complete suicide. Mortality rates from cardiovascular diseases are elevated in bipolar disorder. Risk factors for suicide include younger age of onset of the illness, history of past suicidal behavior, family history of suicide acts, comorbid borderline personality disorder and substance use disorders, and hopelessness. The warning signs calling for immediate action include the patients threatening to harm themselves, or looking for ways to kill themselves (seeking access to pills or weapons), or the patient talking or writing about death.

Robust evidence supports the effects of lithium treatment in reducing suicidal attempts and completions in bipolar disorder. The evidence for antisuicidal effects of anticonvulsants is weaker. Nevertheless, valproate and other anticonvulsants are frequently prescribed as mood stabilizers. There have been controversial suggestions that this treatment may elevate the risk of suicide, but the data supporting this are not convincing. Psychoeducation can reduce the number of suicide attempts and completions.

Conclusions: Suicide in bipolar disorder is a major public health problem. Recent research has expanded our knowledge of risk factors and warning signs. Nevertheless, it appears that the introduction of lithium treatment in the 1970s was the most recent important breakthrough in the prevention of suicide in this illness.

Key words: bipolar disorder – suicide – lithium – anticonvulsants - review

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INTRODUCTION

Patients with bipolar disorder have elevated mortality rates in comparison with the general population (Crump et al. 2013). The excess mortality can be subdivided into deaths from avoidable causes and other deaths that are termed "unavoidable" (Hoang et al. 2013). Suicide is a leading cause of avoidable deaths in bipolar disorder.

In general, a patient's suicide can have a shattering emotional effect on the deceased patient's family as well as on the treating psychiatrist (Gitlin 1999). A survey of therapists for 26 patients who committed suicide revealed their strong emotional reactions including shock, grief, fear of blame, self-doubt, anger, and betrayal (Hendin et al. 2000). We now present a review of the frequency of occurrence, risk factors, biological correlates, and preventative approaches to suicide in bipolar disorder.

METHODS

The MEDLINE data base was searched for articles using the combination of key words "bipolar disorder" with "suicide", "lithium" with "suicide", "anticonvulsants" with "bipolar disorder", and "anticonvul-

sants" with "bipolar disorder and with "suicide". For the treatment searches, generic names were used. No language or publication time constraints were applied. I excluded duplicates, articles dealing with children, articles that commingled diagnostic groups such that data pertaining specifically to bipolar disorder could not be reliably extracted, reports that did not present new data, and repetitive reviews. The lists of references were searched manually to find additional articles.

FREQUENCY RATES AND RISK FACTORS FOR SUICIDAL BEHAVIOR

It is estimated that 25% to 50% of patients with bipolar disorder will attempt suicide at least once in their lifetime, and that 8% to 19% will complete suicide (Marangell et al. 2006). In general, suicide risk factors can be divided into two groups: distal and proximal factors. The distal factors include the following: family history of suicide, early life adversity, epigenetic factors, personality traits and cognitive style, and chronic substance use. The proximal factors include recent life events, psychopathology, suicidal ideation, and hopelessness. The distal factors increase predisposition, whereas the proximal ones act as precipitants (Turecki et al. 2012).

While most research has focused on risk factors for suicidal behaviour, relatively little attention has been given to protective factors (Beautrais 2000). Social supports such as family cohesion or a social peer group as well as marriage and parenthood may reduce the risk of suicide. Cognitive flexibility; active coping strategies and healthy lifestyles are important protective factors (Wasserman et al. 2012). Other potential protective factors include positive and life-affirming beliefs and values, high self-esteem and holding attitudes and moral values against suicide. This area requires more research (Beautrais 2000).

PROXIMAL FACTORS

Clinical experience indicates that proximal, near-term risk factors or warning signs are frequent, and can be used by clinicians or patients' families to prevent suicide. The warning signs calling for immediate action such as calling emergency services include the patients threatening themselves, or looking for ways to kill themselves (seeking access to pills or weapons), or someone not professionally involved in the subject talking or writing about death (Rudd et al. 2006).

Warning signs that should prompt a referral to a mental health professional include the following: hopelessness, rage, reckless activities, feeling trapped with no way out, increasing alcohol or drug use, withdrawing from others, anxiety, sleep disturbance, dramatic mood changes, and no sense of purpose in life (Rudd et al. 2006).

These warning signs should prompt action no matter who shows them. However, the elevated risk for suicide associated with bipolar disorder calls for particularly high level of alertness to these signs by clinicians and patients' families.

DISTAL FACTORS

In this section, studies reporting predominantly on distal factors will be reviewed. Some of the studies combine analyses of distal and proximal factors.

Suicidal behavior

The lifetime prevalence of completed and attempted suicides in a large sample of families with bipolar disorder, its relation to family history of major affective disorder and bipolar disorder, and the contribution of clinical and treatment factors to the risk of suicidal behavior was studied in 737 families of probands with major affective disorder (Manchia et al. 2013). Lifetime psychiatric diagnoses and suicidal behavior in first-degree relatives were assessed. The estimated lifetime prevalence of suicidal behavior (attempted and completed suicides) in 737 probands was 38.4±3.0%. Lithium treatment decreased suicide risk in probands ($p=0.007$). In first-degree relatives, a family history of suicidal behavior contributed significantly to the joint

risk of major affective disorder and suicidal behavior ($p=0.0006$). Thus, the liability to suicidal behavior is influenced by genetic factors (particularly family history of suicidal behavior and major affective disorder). Even in the presence of high genetic risk for suicidal behavior, lithium treatment decreases suicide rates significantly (Manchia et al. 2013).

In Finland, 20% (35/176) of bipolar patients attempted suicide during an 18-month follow-up period (Valtonen et al. 2006). Another prospective study determined the clinical predictors of suicidal behavior during a 2-year follow-up of patients with bipolar disorder presenting with a major depressive episode in 64 patients with bipolar disorder (Galfalvy et al. 2006). Twelve of 64 patients had at least one suicide attempt in the follow-up period, five of them attempted in the first 2 months and seven around or shortly after the 1-year follow-up visit. All attempters had a history of past suicide attempts. Most predictors of future suicidal behavior were correlates of past suicidal behavior. Comorbid borderline personality disorder and family history of suicide acts predicted early attempts, while younger age, high hostility scores, number of past attempts, subjective pessimism as reflected in depression and suicidal ideation, and few reported reasons for living predicted suicidal acts during the whole period (Galfalvy et al. 2006).

Studies using similar methods have established that risk for suicidal behavior (attempt or completed suicide) is elevated with a history of past suicidal behavior (Valtonen et al. 2006, Oquendo et al. 2004, Marangell et al. 2006), hopelessness (Leverich et al. 2003, Valtonen et al. 2006), and hostility (Leverich et al. 2003, Volavka 2013). A remarkable demonstration of additive effect of aggression/impulsivity plus pessimism factors on the likelihood of attempted suicide was presented by Oquendo et al. (2004). Early onset of bipolar disorder elevates the risk of suicide (Valtonen et al. 2006, Song et al. 2012). In their retrospective study, Angst et al. noted a significantly elevated suicide risk around the age of onset of 20 years (Angst et al. 2002). A prospective study of 290 bipolar patients in Barcelona found that suicidal risk was similar in Type I and Type II patients. Furthermore, manic-depressive mixed-state recurrences, melancholic depression, and a history of more trials of antidepressants elevated suicide risk (Undurraga et al. 2012).

A large prospective multicenter study examined the association between baseline clinical and demographic variables and subsequent suicide attempts and completions through 2 years of follow-up of 1,556 patients with bipolar disorder (Marangell et al. 2006). A total of 57 patients (3.66%) attempted or completed suicide. Several variables, e.g. hopelessness, predicted suicidality when considered alone (in bivariate tests), but after controlling for redundant prediction from other baseline characteristics, only history of suicide (odds ratio (OR)=4.52, $p<0.0001$) and percent days depressed in the past year (OR=1.16, $p=0.036$) were significantly

associated with suicidality (Marangell et al. 2006). The authors correctly note that "Multivariate analyses eliminate duplicative" or overlapping relationships that may be significant in bivariate analyses. The existence of overlapping relationships does not indicate that variables eliminated in multivariate analyses are unimportant for understanding suicidal behaviors, but that their potential influence is redundant with the prediction provided by other variables. For example, hopelessness tends to be a reliable predictor of suicidal behavior, but in our sample, the predictive importance of hopelessness was captured by the consideration of previous suicidal behavior" (p. 573).

This caveat is important for at least two reasons. First, it raises the issue of differences between causal attribution and statistical prediction. To say that future suicidal behavior is predicted by past suicidal behavior is statistically meaningful, but not very helpful if we are interested in causal mechanisms. Second, there is nothing we can do about the patient's history, but we can, indeed must, exert intensive therapeutic efforts should hopelessness appear (see below). The fact that hopelessness was not an independent predictor in a multivariate model is clinically irrelevant.

In a prospective study of 3083 bipolar patients, 140 had a suicide event (8 completed and 132 attempted suicides) (Antypa et al. 2013). The strongest predictor of a suicide event was a history of suicide attempt (hazard ratio =2.60, p -value <0.001). Additional predictors were: younger age, personality disorder questionnaire and a high percentage of days spent depressed in the year prior to study entry (Antypa et al. 2013).

Predominant depressive course of illness, comorbid alcohol and substance use disorders, and a history of antidepressant-induced affective episode predicted lifetime suicide attempts in bipolar patients in a Norwegian retrospective study (Finseth et al. 2012).

A large epidemiological study addressed the effects of substance use comorbidities on suicidal behaviors in 1643 bipolar patients who were identified from 43,093 general-population respondents interviewed in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) conducted in the United States (Oquendo et al. 2010). Assessments were made using the National Institute on Alcohol Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV). Lifetime prevalence of reported history of suicide attempt and suicidal thoughts among bipolar disorder respondents with and without DSM-IV lifetime alcohol use disorders (abuse or dependence) was assessed. More than half of the respondents (54%) who met criteria for bipolar disorder also reported alcohol use disorder. Bipolar individuals with comorbid alcohol use disorder were at greater risk for suicide attempt than those individuals without alcohol use disorder (adjusted odds ratio=2.25; 95% CI, 1.61-3.14) and were more likely to have comorbid nicotine

dependence and drug use disorders. However, nicotine dependence and drug use disorders did not increase risk for suicidal behavior among those with bipolar disorder, nor did they confer additional risk among bipolar respondents who also reported alcohol use disorder. Surprisingly, despite greater psychopathological burden, individuals with comorbid bipolar disorder and alcohol use disorder did not receive more treatment or more intensive treatment (Oquendo et al. 2010).

Completed suicide

In a classical Swiss study, 186 unipolar and 220 bipolar depressive or manic patients were followed prospectively for at least 22 years (Angst et al. 2002). At follow-up, mortality was assessed for 99% of them at which time 76% had died. A total of 26 unipolar and 18 bipolar patients died of suicide, yielding standardized mortality rates (SMR) of 26.72 and 12.28 respectively. These rates were significantly different from the general population, and from each other. The SMR of bipolar I and II were not significantly different from each other. Unipolar and bipolar patients who were receiving (uncontrolled) prophylactic treatments had significantly lower mortality rates than those who were not. Elevated SMR for circulatory disorders was observed for both bipolar and unipolar patients; it was significantly higher in the former group (Angst et al. 2002).

An important epidemiological study examined the effect of bipolar disorder and major comorbid disorders on mortality in a population-based longitudinal cohort sample in Taiwan (Chang et al. 2012). This study compared all-cause and unnatural (suicides and accidents) mortality rates between 1542 subjects with bipolar depression and 17480 patients with other types of depression. The study had three major findings:

- Bipolar depression was associated with a significantly greater increase in all-cause mortality than were other types of depression (hazard ratio 1.3);
- Patients with bipolar depression faced twice the risk for suicide and approximately twice the risk for accidental death compared with those with other types of depression;
- Patients with bipolar depression and cardiovascular diseases were 4-times more likely to die from suicide than were those with other types of depression and cardiovascular diseases. (Chang et al. 2012). In our view, this comorbidity finding is the most important contribution of the study.

A list of additional suicide risk factors in bipolar patients can be found elsewhere (Latalova 2011).

Clinical implications of risk studies in bipolar disorder

Comorbid alcohol and drug abuse must be identified and treated since it elevates the risk for suicide (Oquendo et al. 2010). The same applies to comorbid cardiovascular diseases. Interventions to promote

healthy lifestyles and to deliver medical screening and care may prove valuable for patients with bipolar disorder (Chang et al. 2012).

PREVENTION AND TREATMENT OF SUICIDAL BEHAVIOR

Pharmacotherapy

The introduction of lithium was initiated by the publication of Cade's findings (Cade 1949) and Schou's studies (Schou et al. 1954). Lithium and anticonvulsant maintenance treatments have been the mainstays of suicide prevention in patients with major affective disorders (Malhi et al. 2012). A retrospective cohort study conducted at 2 large integrated health plans in California and Washington aimed to compare risk of suicide attempt and suicide death during treatment with lithium with that during treatment with divalproex. (Goodwin et al. 2003). The patients were comprised in a population-based sample of 20,638 health plan members who had at least 1 outpatient diagnosis of bipolar disorder and at least 1 filled prescription for lithium, divalproex, or carbamazepine. Suicide attempt and completion rates were greater during treatment with divalproex than during treatment with lithium.

A study using a similar design arrived somewhat similar conclusions. The subjects were 12,662 Oregon patients diagnosed with bipolar disorder (Collins & McFarland 2008). Divalproex was the most common mood stabilizer followed by gabapentin, lithium, and carbamazepine. There were 11 suicide deaths and 79 attempts. Adjusted hazard ratios (versus lithium users) for suicide attempts were 2.7 for divalproex users ($p < 0.001$), and 1.6 for gabapentin users (not significant). For suicide deaths, the adjusted hazard ratios were 1.5 for divalproex users (not significant), and 2.6 for gabapentin users ($p < 0.001$). Thus, lithium showed superior effects against suicide attempts and completions in comparison with anticonvulsants (Collins & McFarland 2008).

A meta-analysis of 31 studies involving a total of 85,229 person-years of risk-exposure, the overall risk of suicides and attempts was five times less among lithium-treated subjects than among those not treated with lithium (RR=4.91, 95% CI 3.82–6.31, $p < 0.0001$). The reduction of overall suicidal risk during long-term treatment with lithium was only slightly greater in 14 studies of patients diagnosed with bipolar disorder (RR=5.34, 95% CI 3.59–7.93) than in 17 studies including a mix of patients with major affective or schizoaffective disorders (RR=4.66, 95% CI 3.43–6.33; $p = 0.34$ for the comparison). The incidence-ratio of attempts-to-suicides increased 2.5 times with lithium-treatment, indicating reduced lethality of suicidal acts (Baldessarini et al. 2006).

There were only 5 randomized controlled trials among the 31 studies included in the Baldessarini meta-analysis. Randomized, double-blind design considered

gold standard in clinical trials is difficult to apply in studies of high-risk individuals because of the ethical and logistical obstacles involved.

Such obstacles interfered with the enrollment of sufficient number of patients in a randomized double-blind trial testing the hypothesis that lithium offers bipolar patients with a history of suicide attempt (N=98) greater protection against suicidal behavior compared to valproate (Oquendo et al. 2011). During the 2.5 years trial, there were 45 suicide events in 35 participants, including 18 suicide attempts made by 14 participants, six from the lithium group and eight from the valproate group. This trial detected no statistically significant difference between lithium and valproate in time to suicide attempt or suicide event. However, the small number of subjects limited statistical power. Consequently, clinically significant differences between the two drugs could not be ruled out (Oquendo et al. 2011). Thus, strong evidence indicates effects of lithium treatment in reducing suicidal attempts and completions in bipolar disorder. Lithium decreases suicide rates significantly even in the presence of high genetic risk for suicidal behavior (Manchia et al. 2013). The evidence for antisuicidal effects of anticonvulsants is weaker.

Little is known about the extent to which delay of initiation of treatment may influence suicidal behavior in bipolar patients. A retrospective study investigated the association between delay of mood stabilizer treatment in bipolar patients and lifetime history of suicide attempts (Nery-Fernandes et al. 2012). A consecutive sample of 268 bipolar I outpatients from two teaching hospitals in Brazil was recruited. The mean time from the first episode until the first mood stabilizer medication was 8.6 years (SD 9.8 years). The patients who received their first mood stabilizer later than 5 years after the first episode showed a significantly higher lifetime prevalence of suicide attempts than the other patients. This finding supports the importance of early diagnosis and early intervention for bipolar disorder in order to limit the potentially lethal impact of the disease (Nery-Fernandes et al. 2012).

Anticonvulsants and suicide in bipolar disorder: a controversy

As noted above, anticonvulsants have been used widely as a maintenance treatment for patients with bipolar disorder, and evidence for their effects in reducing suicidal behavior has been published. However, in 2008, the Food and Drug Administration (FDA) in the United States issued an alert to health care providers warning of increased risk of suicidal thoughts and behavior related to anticonvulsants. This warning was based on a meta-analysis of 199 placebo-controlled trials that included 43,892 patients (27,863 in drug-treatment groups and 16,029 in placebo). A total of 0.43% of the patients in drug treatment groups exhibited suicidal behavior or ideation compared with 0.22% of the patients in placebo groups. The FDA meta-analysis and its conclusions

have been criticized. The analysis was based on adverse event reports rather than on systematically collected data. Furthermore, 11 anticonvulsants were treated as a single group, despite individual differences in mechanisms of action and adverse effects profile (Hesdorffer & Kanner 2009, Hesdorffer et al. 2010).

In this context, a study was launched to determine if anticonvulsants increase the risk of suicide attempt in patients with bipolar disorder. The study compared suicide attempt rates before and after treatment and with a medication-free control group (Gibbons et al. 2009). Analyses were restricted to anticonvulsant and lithium monotherapy. A medical claims database was used to study the relationship between the 11 anticonvulsants identified in the FDA alert, and lithium, to suicide attempts. A cohort of 47,918 patients with bipolar disorder with a minimum 1-year window of information before and after the index date of their illness was studied.

Overall, there was no significant difference in suicide attempt rates for patients treated with an anticonvulsant compared with patients not treated with an anticonvulsant or lithium. In anticonvulsant-treated subjects, the rate of suicide attempts was significantly higher before treatment than after. In patients receiving no concomitant treatment with an antidepressant, other anticonvulsant, or antipsychotic, anticonvulsants were significantly protective in comparison with no pharmacologic treatment. Thus, contrary to the FDA alert, anticonvulsants were not found to increase risk of suicide attempts in patients with bipolar disorder relative to patients not treated with an anticonvulsant or lithium. Use of anticonvulsants reduced suicide attempt rates both relative to patients not receiving any psychotropic medication and relative to their pretreatment levels (Gibbons et al. 2009).

However, the Gibbons analyses were criticized by several authors affiliated with the FDA (Mentari et al. 2010). Reduced rates of suicide attempts after the start of treatment could have been due to episodic fluctuations of the course of bipolar disorder rather than to treatment. There were several other criticisms relating to the composition of the patient groups and unreliable nature of medical claims data. Gibbons et al. (2010) responded cogently to these criticisms. A recent re-analysis of the Gibbons data indicated that suicide attempts in patients with bipolar disorder tend to precede, not follow, initiation of anticonvulsants (Marcus et al. 2013). Subsequent efforts to resolve the controversy regarding the role of anticonvulsants in suicidal behavior have not been completely successful. A review of the literature concerning the possible relationship of antiepileptics and suicide-related clinical features and behaviours suggested that there are no convincing data concerning a "class effect" of antiepileptics in inducing any type of suicide-related behaviors (Fountoulakis et al. 2012).

An expert consensus statement by epileptologists noted that since the FDA warning, a number of retro-

spective cohort and case-control studies have been published that are trying to address this issue, but gathered results are contradictory. Although some (but not all) anticonvulsants can be associated with suicidal ideation and behavior, the actual suicidal risk is yet to be established. In any event, it seems to be very low (Mula & Sander 2010, Mula et al. 2013). A recent review found no evidence supporting the notion that anticonvulsants as a group elevate the risk of suicidal behavior in bipolar patients (Yerevanian & Choi 2013), and the guidelines of the European Psychiatric Association cite work indicating antisuicidal effects of valproate and carbamazepine (Wasserman et al. 2012).

Previous work broadly confirms that anticonvulsants do not achieve the antisuicidal efficiency of lithium (Wasserman et al. 2012). However, in clinical practice, anticonvulsants (particularly valproate) are used more frequently than lithium as mood stabilizers. The reasons can be found in easier optimization of anticonvulsant dose, and greater safety in case of overdose.

Better therapeutic response to anticonvulsants in patients with bipolar disorder- II type (depressive, hypomanic, but not manic episodes) as well as their greater safety in cases of comorbid abuse of psychoactive substances should also be taken into account.

Psychotherapy

In recent years, there has been growing evidence that psychosocial interventions, added to basic pharmacological treatment, can significantly contribute to the stabilization of bipolar disorder. The evidence supports the efficacy of cognitive behavioural therapy (CBT), in combination with pharmacological treatment for the prevention of relapse and of suicidal behavior (Wasserman et al. 2012). Some other psychological treatments are promising. Randomized controlled trials support the efficacy of adjunctive CBT (Lam et al. 2005, Miklowitz et al. 2007) family-focused treatment (FFT) or similar forms of family psychoeducation (Miklowitz et al. 2006, Rea et al. 2003, Fristad et al. 2003), interpersonal and social rhythm therapy (IPSRT) (Frank et al. 2005), and group psychoeducation (Colom et al. 2003, Simon et al. 2006) in preventing depressive and manic recurrences, stabilizing symptoms, or enhancing functioning in 1- to 2-year periods. Well-designed studies that directly examined the impact of psychotherapy on suicidality in bipolar patients are not available. In a review article (Fountoulakis et al. 2009), the authors concluded that although studies researching the effect of psychosocial interventions on suicidal behavior are virtually non-existent, some hard data concerning the effectiveness of psychosocial interventions in bipolar disorder are emerging, but still suffer from methodological drawbacks. Most studies are focused on psychotherapy in preventing further episodes. The treatment of patients with suicidal risk is a challenge for psychotherapists. Psychoeducational approaches are promising interventions for the long-term control of bipolar disorder (Lam et al. 2005).

Psychoeducation and social skills improvement go beyond classical psychotherapy. The most crucial goal of the psychoeducation in bipolar patients is relapse prevention by increasing compliance with pharmacotherapy regime, supporting social rhythms activities, reduction of emotional expression in the family, and increase of coping skills against stress (Lam et al. 2009). It is assumed that adjuvant psychoeducation, training of communication skills and active problem solving reduce patients' suicidal ideation.

Finally, psychosocial approaches aim to help alleviate depressive symptoms, improve patient personal relationships by learning of some interpersonal strategies, and improve the overall quality of life. The results of the above studies suggest that psychoeducation may reduce the number of suicide attempts and suicides.

CONCLUSIONS

Suicide in bipolar disorder is a major public health problem. Recent research has expanded our knowledge of risk factors and warning signs. Robust evidence for the importance of comorbidity with substance use disorders in the development of suicidal behavior has emerged. Furthermore, the relationship between impulsive aggression and suicidal behavior has been clarified. Nevertheless, it appears that the introduction of lithium treatment in the 1970s was the most recent important breakthrough in the prevention of suicide in bipolar disorder. Early and proper treatment of bipolar disorder has an important role in suicide prevention.

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