Bipolar Disorder and Suicide: Research Synthesis and Clinical Translation

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Attempted suicide and suicide are prevalent in individuals with bipolar disorder (BD). Extant evidence indicates that history of suicide attempts, percentage of time spent in a depressed state, and hostility are factors associated with suicide attempts and completed suicide. Childhood adversity (eg, sexual and physical abuse) is emerging as a risk factor for suicide attempts in adults with BD. The pertinacity of medical comorbidity (eg, obesity, metabolic syndrome) in the bipolar population is further underscored by its preliminary association with suicidality. Biomarkers such as cerebrospinal fluid monoamine metabolite levels may be predictive of suicide attempts and lethality in BD. Compelling evidence supports an antisuicide effect of long-term lithium prophylaxis; lithium's salutary effect is mediated primarily by reduced lethality of suicidal acts. Conventional unimodal antidepressants may engender or exacerbate suicidality in susceptible individuals with BD. A nascent database suggests that adjunctive psychosocial interventions may further reduce suicide risk in bipolar individuals.

Introduction

Bipolar disorder (BD) is a prevalent, progressive, episodic, and chronic mood disorder associated with high rates of interepisodic dysfunction. Mortality studies indicate that individuals with BD are at high risk for suicidal ideation, nonfatal suicide attempts, and suicide [1–3]. The suicide rate in BD is approximately 20-fold greater than that of the general population. Devising tactics and strategies capable of lowering mortality from natural and unnatural causes is a primary therapeutic objective in managing BD.

During the past decade, there has been considerable development in delineating factors associated with or predictive of suicidal behavior [3,4]. This growing empiricism provides the basis for more effective risk stratification and resource allocation. Moreover, neurobiological studies have documented several biomarkers associated with suicidality that may help to unravel the complex pathophysiology of suicidal behavior and further inform risk assessment and management strategies.

Disparate somatic therapies and adjunctive manual-based psychosocial interventions have proven efficacy across various phases of BD [5]. Although relatively few studies have closely detailed the antisuicide (or prosuicide) effect of most bipolar treatments, extant evidence strongly supports lithium's mortality-lowering effects, with emerging evidence suggesting that conventional unimodal antidepressants may engender or exacerbate suicidality in susceptible individuals [6].

The objectives of this review are to provide the practitioner with a succinct summary of results from mortality studies in BD, identify prospective predictors of suicide attempts and completion, elucidate biomarkers associated with the lethality of suicidal behavior, and summarize data describing the mortality-lowering effect of somatic and psychosocial treatments. The encompassing aim is to assist the practitioner in evaluating at-risk individuals and to provide direction for effective treatment avenues.

Methods

We conducted a PubMed search of all English language articles published between January 1966 and August 2007. The search terms were "suicide," "mortality," "predictors," and "biomarkers," cross-referenced with "bipolar disorder." The search was augmented with a manual review of article reference lists. Articles were selected for review based on adequacy of sample size, the use of standardized experimental procedures, validated assessment measures, and author consensus regarding overall manuscript quality.

Results from Mortality Studies

Clinical and epidemiological studies have provided compelling evidence that individuals with mood disorders are at increased risk for premature death from natural and unnatural causes. Although the total number of excess deaths among individuals with BD is higher for cardiovascular disease, the standardized mortality ratio (SMR) is highest for suicide in BD [3].

Many of the earlier published studies documenting suicide rates in BD were delimited to inpatients with complex illness presentations. Taken together, the estimated lifetime rate of suicide extracted from the earlier published samples is approximately 10% to 15%, representing an approximately 30-fold increased rate compared with the general population.

A meta-analysis by Harris and Barraclough [7] evaluated SMRs in more than 8000 individuals with major depressive disorder (MDD) and 3700 individuals with BD. They concluded that the SMRs in individuals with MDD and BD were approximately 20 and 15, respectively [7]. Suicide risk was highest in individuals with current alcohol abuse, and most suicide events occurred within the first few weeks after hospital discharge. The SMR for unnatural causes of death (eg, suicide, homicide, accidents) was higher in individuals with BD when compared with individuals with MDD. The same investigators replicated these results in a subsequent meta-analysis [7,8].

Other recent studies of hospitalized BD and MDD individuals also have reported high SMRs from suicide in both MDD and BD [3,9]. Evaluating a Swedish national registry, Osby et al. [3] reported that the SMR was highest in younger individuals within several years of receiving a BD diagnosis. The BD group also had a higher rate of death from natural causes, notably cardiovascular and respiratory diseases, underscoring the illness burden attributable to somatic disorders.

Rihmer and Kiss [10] reviewed six studies documenting suicide rates in individuals with MDD and BD (ie, bipolar I disorder and bipolar II disorder). They reported that the rate of past suicidal behavior in the bipolar group was 19% higher than that of individuals with MDD.

Rihmer et al. [11], reporting on the psychiatric diagnosis in individuals (n = 100) who completed suicide during a depressive episode, found that 53% of their sample met criteria for MDD, whereas 47% met criteria for BD (46% bipolar II, 1% bipolar I). Taking into account that most BD individuals met criteria for bipolar II disorder, these data underscore that the hazard posed by BD is not exclusive to bipolar I disorder and belies a common perception that bipolar II disorder represents a milder phenotype of BD. Tondo et al. [12] also reported a higher suicide rate in bipolar II disorder and a significantly higher annual rate of suicide in bipolar II disorder and MDD versus bipolar I disorder. It has been conjectured that the higher overall mortality rate in bipolar II disorder may be partially mediated by higher relative rates of multiaxial comorbidity [13].

Taken together, the estimated all-cause SMR in BD is 1.5 to 2.0, whereas for suicide, the SMR is estimated to be 20 to 30 [3]. The premature and excess deaths reported in the bipolar population have important public health, economic, and treatment implications [14,15].

Variables Predictive of Suicide Attempt and Completion in BD

Research attempting to elucidate risk factors associated with suicide documents numerous heterogeneous and often-conflicting variables. The disparity in the variables reported and their uncertain predictive value often leave practitioners uncertain as to how to ascribe meaningful clinical translation (ie, risk stratification). Potential influencing factors such as age, race, or other demographics may be applicable toward understanding population behavior, but they are not conclusively helpful for the practicing clinician with the individual patient. Human suffering has been described as the single common denominator associated with suicide, making detection and management of patient suffering of paramount importance when trying to prevent suicide [16].

Various factors have been associated with suicidal behavior and suicide in the BD population; however, few have been subject to multivariate analyses (Table 1) [17••,18,19]. Marangell et al. [17••] prospectively assessed the relationship between baseline variables (eg, sociodemographic, clinical) and correlates of suicide attempts and suicides in BD individuals treated for up to 2 years in the Systematic Treatment Enhancement Program for BD (STEP-BD). Unlike most existing studies evaluating factors associated with suicidal behavior in BD, the STEP-BD used multivariate statistics to control for redundant predictions. Moreover, the STEP-BD sample is the largest clinical cohort of BD individuals evaluated in a clinical study.

The results indicated that 57 patients (3.7%) attempted (n = 50) or died by suicide (n = 7) over the 2-year follow-up period. Individuals who attempted or died by suicide reported a greater history of previous suicide attempts; more

Table 1. Factors associated with suicide and serious suicide attempts in individuals with bipolar disorder

Course of illness variables
Early onset of bipolar disorder
Early sexual abuse
History of frequent prior psychiatric hospitalizations
History of recurrent severe depressive episodes
Phenomenology
Mixed or depressive mania
Hopelessness
Low self-esteem
Presence of suicidal thoughts during depressive episodes
Severity of anxiety or depression
Aggression/impulsivity
Comorbidity
Current or lifetime history of comorbid alcohol or substance use disorders
Cluster B personality disorder
Obesity
Cigarette smoking
Family history of suicide
Stressors
Occupational problems
Recent psychosocial stress
Prior history of sexual/physical abuse
Interpersonal conflicts with spouse/partner
Lack of confidant before illness onset

(*Adapted from* Marangell et al. [17••].)

suicidal ideation at baseline; and more days spent depressed, anxious, or irritable over the past year when compared with those who did not experience an event. With a pattern-mixture analysis to control for redundant prediction, a history of suicide attempt and percentage of days spent depressed in the past year were the only variables associated with suicide attempt or death by suicide. The results of the detailed STEP-BD analysis cohere with other published studies and underscore the hazard posed by depressive symptoms that dominate the BD longitudinal course [20–22].

Elucidating factors that predict suicidality early in treatment have implications for identifying at-risk patients and informing the urgency of clinical intervention. Suicidal risk appears to be higher in BD populations characterized by mixed states and rapid cycling [23,24]. Simon et al. [25] reported that anxiety disorder comorbidity, especially generalized social anxiety disorder, is associated with suicidal ideation and behavior in BD individuals enrolled in the STEP-BD program.

Galfalvy et al. [26] reported on clinical predictors of suicidal behavior during a 2-year follow-up period in BD individuals (n = 64). Twelve patients (19%) attempted suicide during the observation period. The nonparametric survival curve estimates revealed two clusters of suicide attempts (within the first 2 months after baseline and after 1 year of follow-up). Family history of suicide acts and comorbid borderline personality disorder predicted early attempts; younger age, high hostility scores, number of past attempts, subjective pessimism, and few reported reasons for living were significant predictors of suicide acts throughout the observation period. Hostility was the strongest risk factor of all identified variables [26].

Prior suicide attempt status and associated variables may suggest differential vulnerabilities to suicide in BD. Using logistic regression models to examine correlates of suicidal ideation among patients with BD who had attempted (vs those who had not attempted) suicide in the past, Allen et al. [27] reported differential variables impacting suicidality. Among prior suicide attempters with BD, poor psychosocial adaptation and the personality factor "openness" were stronger contributors to suicidal ideation, whereas anxiety and extraversion appeared to be protective. Depression, anxiety, and neuroticism were the predominant influences on suicidal ideation in patients with BD without past history of suicide attempt.

Stress endured early in life (eg, maternal separation) has been demonstrated in preclinical models to have persisting effects on behavior, neurochemistry, and neuroendocrine dynamics [28,29]. Extant preclinical evidence affords a hypothesis that distal stressors such as childhood abuse (CA) may exert a detrimental effect on the course of adult BD [4,30]. Preliminary studies indicate that CA is associated with several indices of bipolar illness severity (eg, comorbidity, psychosis) [4,30–33]. Surprisingly, putative links between CA and suicidality in BD have been reported infrequently relative to MDD [4,34]. Nevertheless, emerging links between distal stressors and suicidality and BD are documented.

For example, Leverich et al. [30] reported on the association between a childhood/adolescent history of physical or sexual abuse and course-of-illness variables, comorbidity, and prior suicide attempts in a large clinical sample of individuals (n = 631) with *DSM-IV*–defined bipolar I/II disorder. A total of 49% (n = 185) of female patients and 36% (n = 99) of male patients reported ever being abused during childhood or adolescence. No significant gender differences in physical abuse incidence were reported; however, significantly more females reported a history of sexual abuse. Physical and sexual abuse were strongly associated with an increased incidence of suicide attempts; the physically abused group reported increased suicidal ideation when manic, and the sexually abused group reported increased suicidal ideation when depressed [30].

A subsequent analysis by Leverich et al. [4] reported a linear relationship between the percentage of patients

reporting past suicide attempts and the reported frequency of physical abuse occurring in childhood, adolescence, or adulthood. Any amount of sexual abuse as a child was associated with an increased percentage of patients having attempted suicide. An additive effect of physical and sexual abuse as opposed to either alone also was reported [4].

Goldberg and Garno [32] reported that 51% of adult patients with *DSM-IV*–defined BD (n = 100) reported a history of severe CA. A history of childhood sexual abuse was significantly associated with a lifetime suicide attempt. However, no association was noted between a history of physical abuse, physical neglect, emotional abuse, or neglect and suicidality [32].

Epidemiological, clinical, and familial comorbidity studies indicate that individuals with BD are differentially affected by several general medical disorders. Likewise, most multiple-episode BD patients have an active medical comorbidity at the time of psychiatric hospitalization [3]. A compelling database suggests that medical comorbidity in BD is prevalent and associated with several indices of illness severity, slower rate of recovery, quality-of-life impairment, and premature mortality [35•].

Higher rates of overweight, obesity, and abdominal obesity are consistently reported in individuals with BD in epidemiological and clinical samples [32,36]. Emerging evidence suggests that obesity affects BD's clinical presentation, course, and outcome. For example, the co-occurrence of these conditions is associated with a multiple-episode course of BD, suicidality, depression severity, decreased probability of symptomatic remission, and shorter time to episode recurrence when compared with healthy-weight individuals with BD [17,37].

An increased prevalence of the metabolic syndrome in BD compared with the general population has been preliminarily reported [18]. For example, the University of Pittsburgh group reported an overall 30% prevalence of National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III–defined metabolic syndrome in their cohort (n = 171) of BD individuals [18]. The reported prevalence of the metabolic syndrome's individual components was as follows: diabetes mellitus (8%), abnormal high-density lipoprotein cholesterol (23%), hypertension (39%), hypertriglyceridemia (48%), and abdominal obesity (49%). The percentage of patients reporting a history of at least one suicide attempt was higher in BD individuals with comorbid metabolic syndrome compared with those without this comorbidity (55% vs 36%; P = 0.05).

Taken together, suicidal behavior in BD is presaged by a confluence of interacting sociodemographic, clinical, anamnestic, iatrogenic, and environmental factors. Depressive symptom burden clearly emerges as a common risk factor for suicide attempts and deaths by suicide in BD. Emerging evidence also indicates that medical comorbidity (eg, obesity, metabolic syndrome) is associated with increased suicide risk. Future research needs to parse out the mediating and moderating role imparted by somatic illness. Taken together, clinicians are encouraged to provide guideline-concordant care for patients with BD emphasizing improved treatment for depression and somatic comorbidity given the associated elevated suicide risk for these patients.

Biomarkers of Suicidality in BD

Although disparate, probabilistic clinical factors predictive of suicide attempt and death by suicide have been documented, no single factor is deterministic, emphasizing the need for other factors to inform risk assessment. Biomarkers associated with suicidality frequently have been reported in individuals with MDD. For example, a substantial body of evidence has documented alterations in cerebrospinal fluid (CSF) monoamine levels. Postsynaptic serotonin receptors (5-HT_{1A}, 5-HT_{2A}) also have been upregulated in the prefrontal cortex of suicide victims, possibly reflecting serotonergic system underactivity [38].

Sher et al. [38] were the first to prospectively evaluate the predictive value of CSF concentrations of 5-hydroxyindolacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) for lethality of suicide attempts in BD. They repeatedly evaluated CSF concentrations of 5-HIAA, HVA, and MHPG in BD individuals (n = 27) during an observation period of up to 2 years [38].

Six patients attempted suicide during the study, all of whom had previously attempted suicide as indicated by the baseline measures. Individuals who attempted suicide during the follow-up period had higher aggression and hostility scores compared with BD patients who did not attempt suicide. Individuals who attempted suicide during the follow-up period also had a higher prevalence of first-degree relatives who attempted or died by suicide. A positive correlation existed between CSF, 5-HIAA, and HVA levels (r = 0.71; P < 0.001), 5-HIAA and MHPG concentrations (r = 0.54; P = 0.004), and HVA and MHPG levels (r = 0.62; P = 0.001). No differences were seen in monoamine metabolite levels between BD patients who did and did not attempt suicide during the follow-up period. A negative correlation also was observed between CSF 5-HIAA, HVA, and MHPG levels and the maximum lethality of suicide attempts.

Results from family, twin, and adoption studies indicate that genetic factors may be relevant to suicidal behavior. In his review of more than 20 family studies, Turecki [36] noted that first- and second-degree relatives of suicide attempters and those who died by suicide had higher rates of suicidal behavior when compared with relatives of controls. Moreover, an affective disorder often was present but did not entirely explain suicidal behavior in the first-degree relative [39].

The Effect of Somatic and Psychosocial Treatment on Suicidality

Antidepressants

No antidepressant agent has an established safety and efficacy record (ie, replicated, adequately powered registration trials) in any phase of BD. In the largest effectiveness study to assess adjunctive unimodal antidepressants' role in BD, neither paroxetine nor bupropion provided an advantage over placebo in achieving durable recovery (or higher switch risk into mania) [40]. Nevertheless, antidepressant monotherapy appears to be a common treatment in real world settings [41]. Antidepressant treatment is associated with treatment emergent affective switching (TEAS) and cycle acceleration. Although TEAS risk is decreased with concomitant mood stabilizer therapy, it is not eliminated [42].

Furthermore, no antidepressant agent has demonstrated an antisuicidal effect in BD populations. During the past decade, there has been renewed interest in the possibility that antidepressants may engender or exacerbate various aspects of suicidality. The US Food and Drug Administration issued a public health advisory in October 2004 requiring a black box warning for all antidepressants [42]. This pronouncement originally was delimited to pediatric populations, but it was later extended to adult populations. Several aspects of the "activation syndrome" described in association with antidepressants phenotypically overlap with mixed states and other complex bipolar presentations (ie, characterized by severe irritability and aggression) [42].

Extant studies are largely naturalistic and methodologically diverse, precluding a firm conclusion regarding antidepressant-associated suicidality. Nevertheless, many studies suggest that antidepressant treatment may increase suicidality in a subset of BD patients. Further characterization of individuals evincing suicidality in response to antidepressants reveals that they often are cases of unrecognized BD and are infrequently receiving a concomitant mood stabilizer (ie, likely exposed to antidepressant monotherapy).

Lithium

Results from most contemporary investigations and meta-analyses indicate that long-term lithium treatment lowers suicide attempts and deaths by suicide in BD patients [43–45]. Baldessarini et al. [46] conducted a meta-analysis of 31 studies with a total of 33,340 patients and 85,299 years of lithium exposure. The risk ratio reduction favoring lithium was 4.7 based on crude pooled risks of 0.563% per year versus 2.640% per year in lithium-treated and nontreated BD patients, respectively [46].

The crude rates for suicide attempts in individuals treated with lithium versus those treated without were 1.08% per year versus 3.63% per year, representing a 3.4-fold higher risk in non–lithium-treated individuals. For suicides, the corresponding rates of 0.155% per year versus 1.030% per year represented a larger (8.4-fold) difference. The ratio of attempts to completed suicide, conceptualized as the "lethality index" of suicidal behavior, was 2.5-fold higher during lithium treatment (6.94% per year vs 2.79% per year). The higher ratio of attempts to suicide indicates that reduced lethality may be a therapeutic benefit associated with lithium treatment. Taken together, this analysis suggests that lithium reduces the frequency and lethality of suicidal acts [38].

Cipriani et al. [47] conducted a systematic review of randomized trials investigating lithium's suicide protective effects in patients with mood disorders. Across 32 trials, 1389 patients were randomized to receive lithium, and 2069 to placebo or other active compounds. Patients who received lithium were approximately 60% less likely to die by suicide. Similarly, lithium resulted in a nearly 70% reduction in the composite measure of suicide and deliberate self-harm [47]. However, uncertainty remains as to lithium's specific suicide protective effects. Much of this uncertainty relates to there being no prospective, randomized trial in BD to evaluate suicidality as an *a priori* outcome measure. Several reports have failed to detect a mortality-lowering effect of lithium [48].

Offering further opportunity to shed light on this important issue, the newly initiated LiTMUS (Lithium Treatment in Moderate Dose Use Study) trial, conducted under the auspices of the Bipolar Trials Network, will investigate lithium's suicide protective effects when administered to a real world population with BD. Intended to enroll 264 patients over the course of 2 years, LiTMUS will assess lithium's effectiveness as a component of treatment as usual over 6 months.

Several studies have evaluated lithium discontinuation's effect on suicidal risk and completion. For example, Baldessarini et al. [49] evaluated 165 patients who discontinued lithium treatment due to medical reasons, side effects, or electively after a lengthy period of illness stability. They reported that the rates of suicidal acts increased 14-fold, especially during the first 12 months of discontinuation. Similarly, the risk of fatalities increased 13-fold after lithium discontinuation. The rates of suicidal acts were reduced by approximately 50% when lithium was discontinued gradually [49]. These observations point out the need for careful attention to gradual lithium discontinuation strategies for patients who require treatment change or who are likely to be noncompliant.

During the past decade, the evidentiary base supporting adjunctive, manual-based psychosocial interventions' effectiveness in BD has increased substantially [50]. Psychosocial interventions mitigate depressive symptoms and improve interpersonal coping strategies and quality of life. This therapeutic profile provides a framework for hypothesizing that psychosocial interventions may reduce nonfatal suicide attempts and suicide.

Rucci et al. [51] reported on the effect of adjunctive psychosocial treatment (ie, interpersonal and social rhythm therapy, intensive clinical management) on rates of suicide attempts among patients (n = 175) with bipolar I disorder

prospectively evaluated for an average of 1.4 years. Most individuals (n = 166) were treated with lithium (mean plasma lithium level = 0.83 mEq/L; SD = 0.22; range = 0.32–1.21 mEq/L) during the studied period. Most patients (n = 92) were treated for depression or mixed/cycling (n = 43). The computed rates of prior suicide attempts from the estimated date of illness onset to entry into the acute treatment phase were compared with the rates during the treatment phase. A base rate of 1.05 attempts per 100 patient months was computed for the period before study entry. During the acute and maintenance phases, the rates of suicide attempts per 100 patient months were 0.31 (threefold reduction) and 0.06 (17.5-fold reduction), respectively. The reductions noted during the acute and maintenance phases were highly significant.

In their review of family-focused treatment (FFT) in suicidal BD patients, Miklowitz and Taylor [37] described FFT's adaptation to managing suicidal behavior in BD. They hypothesized that adding psychoeducation, communication skills, and problem-solving training to patients and their family members may decrease suicidal thoughts and behavior. They also proposed that the learning skills of distress tolerance, mindfulness, emotion regulation, and interpersonal effectiveness of dialectical behavioral therapy be adapted for treating suicidal BD patients.

Taken together, guideline-concordant care (eg, long-term lithium prophylaxis) and adjunctive psychosocial interactions decrease the high risk of suicidal behavior in BD. Conventional antidepressants have not been shown to mitigate suicide risk in BD, and their use is associated with increased suicidality in susceptible individuals. A disquieting chasm exists between the antisuicide effect of several treatments for BD, in particular lithium, and their underuse in real world settings.

Conclusions

Attempted suicide and deaths by suicide are prevalent in individuals with BD. Extant evidence indicates that history of suicide attempts, percentage of time depressed, and hostility are associated with suicide attempts and death by suicide. Childhood adversity (eg, sexual and physical abuse) and medical comorbidity are emerging risk factors for suicide attempts in adults with BD. Compelling evidence supports an antisuicide effect of long-term lithium prophylaxis; lithium's salutary effect is mediated primarily by reduced lethality of suicidal acts. Conventional unimodal antidepressants may engender or exacerbate suicidality in susceptible individuals with BD. A nascent database suggests that adjunctive psychosocial interventions may further reduce suicide risk in bipolar individuals.

A chronic disease management model that is informed by evidence-based treatment guidelines targeting BD and common comorbid symptoms and that provides timely access to psychoeducation and available psychosocial interventions is warranted. Particular attention and facile screening for risk factors for medical comorbidity and suicidal behavior should be a routine component when managing the bipolar patient.

Disclosures

Dr. McIntyre has received research grants from the Stanley Medical Research Institute, the National Alliance for Research on Schizophrenia and Depression, and Eli Lilly and Co.; has served on advisory boards for AstraZeneca Pharmaceuticals, LP, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Inc., Janssen-Ortho, Inc., Solvay/Wyeth, Eli Lilly and Co., Organon, Inc., Lundbeck, Biovail Pharmaceuticals, Pfizer, Inc., and Shire, PLC; has served on the speakers' bureau for Janssen-Ortho, Inc., AstraZeneca Pharmaceuticals, LP, Eli Lilly and Co., Lundbeck, and Biovail Pharmaceuticals; and has participated in continuing medical education–related activities in conjunction with AstraZeneca Pharmaceuticals, LP, Bristol-Myers Squibb, France Foundation, I3CME, Solvay/Wyeth, and the Physicians' Postgraduate Press.

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No further potential conflicts of interest relevant to this article were reported.

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