SUICIDAL RISK IN BIPOLAR DISORDER

Leonardo Tondo, and Ross J. Baldessarini

Summary

Bipolar manic-depressive disorder (BPD) is a prevalent, often severe, sometimes disabling illness, with the potential for fatalities due to accidents, complications of comorbid substance-use, increased mortality due to medical illnesses, and particularly due to suicide. Suicide rates in BPD patients average 0.4%/year, or more than 25-times higher than the general population average of about 0.014%/year. Suicidal acts often occur early in the illness, and in association with severe depressive and dysphoric-agitated mixed phases, especially following repeated, severe depressions. Systematic consideration of risk-factors can enhance assessment of potentially suicidal patients. Several short-term interventions are widely employed empirically to manage acute suicidality, ranging from close clinical supervision and rapid hospitalization to electroconvulsive treatment. Surprisingly, however, evidence of long-term effectiveness against mortality risks associated with major psychiatric disorders is lacking for most treatments. A notable exception in BPD and possibly other major affective disorders, is lithium maintenance treatment, which is associated with strong and consistent evidence of reduced suicidal risk that is not found, or remains untested, for a growing range of treatments used to treat acute and long-term illness in BPD patients, including anticonvulsants, second-generation antipsychotics, and modern antidepressants. For now, however, treatment aimed at reducing suicidal risk in patient with BPD or other major affective disorders can be enhanced by applying current knowledge systematically, with close and sustained clinical follow-up of patients.

Key Words: Antidepressants – Bipolar Disorder – Lithium – Suicide

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Introduction

Bipolar manic-depressive disorder (BPD) is a prevalent, often severe, sometimes psychotic, disabling, and potentially fatal major psychiatric illness (Goodwin and Jamison 1990). Worldwide lifetime prevalence bipolar I disorder (with mania) exceeds 1%, and total prevalence of BPD syndromes included in DSM-IV may approach 5% if bipolar II disorder (severe depression with hypomania) and cyclothymia (sub-clinical mood shifts) are included (Kessler et al. 1994, Tohen and Angst 2002). Of particular public health significance, BPD presents elevated risks of premature mortality associated with adverse outcomes of medical disorders, accidents, and complications of commonly comorbid substance use disorders; however, the major source of premature mortality is a very high risk of suicide (Tondo et al. 2003). This brief overview addresses the epidemiology, risk-assessment, and proposed methods of prevention and treatment of suicidal risk in BPD.

Epidemiology

Officially reported international suicide rates vary widely, and recently have averaged (± SD) 0.0143 ± 0.0070 %/year for 21 developed countries (WHO 2003). A comprehensive meta-analysis (Harris and Barraclough 1997) compared suicide risks as standardized mortality ratios (SMR, with 95% confidence intervals [CI]) and was later updated for BPD (Tondo et al. 2003). This method provides estimates of risk relative to segments of the general population of comparable age and sex. SMR estimates for relative suicide risks among BPD patients were similar to, or even slightly greater than, risks for persons diagnosed with severe major depres-

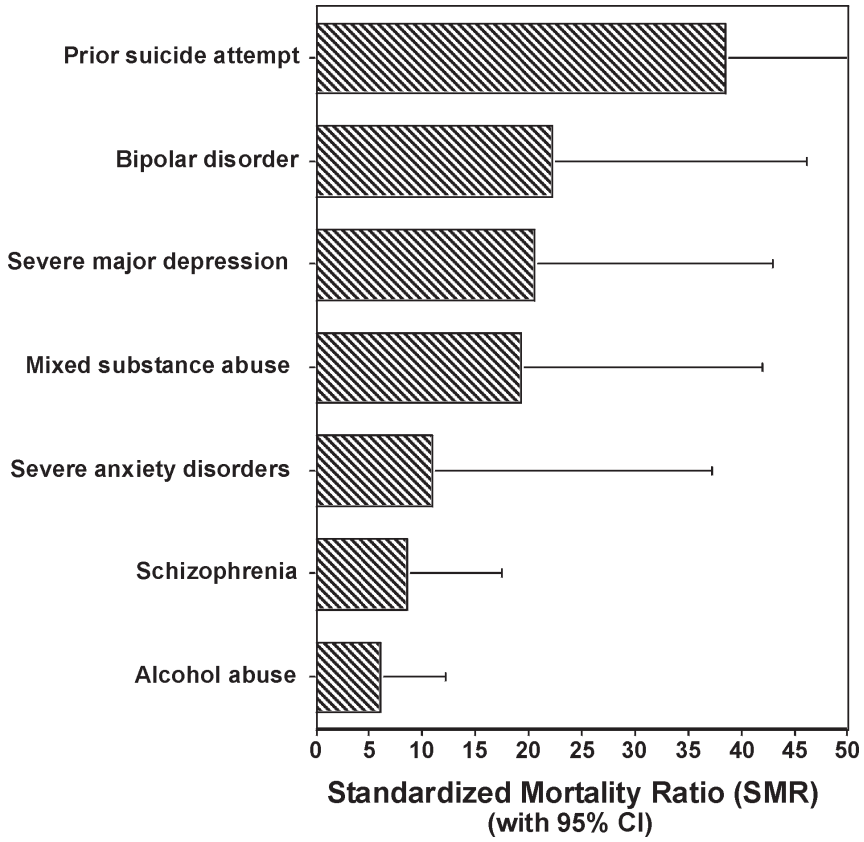

Figure. *Standardized mortality ratios (SMR) with upper 95% confidence intervals (CI) for representative psychiatric disorders compared to bipolar disorder. Studies of severe depression mainly involve patients who have been hospitalized. Severe anxiety disorders include panic disorder and obsessive-compulsive disorder. The data are derived from a comprehensive meta-analysis by (Harris and Barraclough 1997), later updated for bipolar disorder (Tondo et al. 2003)*

sion (usually with hospitalization) or polysubstance abuse (SMR = 15–20), and greater than SMRs for patients diagnosed with alcoholism, severe anxiety disorders (panic or obsessive-compulsive disorder), schizophrenia (SMR = 8.5–11; Figure).

Many studies have estimated suicide risks among persons diagnosed with major affective disorders, including BPD. In an early meta-analysis of 17 long-term studies, Guze and Robins (1970) found that the median proportion of deaths ascribed to suicide among persons considered to have a major affective disorder was approximately 15% (mean, 30.6 ± 18.3%; range, 12%–60%). In a similar analysis of 27 studies Goodwin and Jamison (1990) later found an average of 19% of deaths due to suicide. Recent estimates in samples of never-hospitalized patients with depressive illnesses of moderate severity have suggested lifetime suicide rates of only 6% or less (Inskip et al. 1998, Blair-West et al. 1999, Bostwick and Pankratz 2000, O'Leary et al. 2001). Even this moderate rate is still nearly nine-fold above the estimated lifetime risk in the international general population, of 0.70% ([0.014%/year x 50]; WHO 2003). Moreover, all of these rates almost certainly underestimate suicidal risk, owing to difficulties in determining suicide as a cause of death.

In a recent survey of reported suicide rates associated with BPD (usually type I, with mania), we found an overall average SMR of over 22 (Figure), and a pooled, weighted mean rate of 0.392%/year (based on 823 suicides among 21,484 persons-at-risk for an average of 9.93 years, in 28 studies), which is 27.5 times greater than in the general population (0.392/0.0143). Some of the studies analyzed did not provide adequate information about treatment status, but for studies providing data for treated and untreated patients, we considered only subgroups without ongoing long-term treatment (Tondo et al. 2003).

Another important feature of the epidemiology of suicidal behavior among patients with major affective disorders is that the lethality of suicide attempts, as indicated by the ratio of estimated rates of attempts/suicides, is much higher than in the general population. This ratio among BPD patients may be as low as 3.0 (Carlson et al. 1974), and averages about 5-fold (Tondo et al. 2003). This ratio is much lower than for the general population, in which the ratio of attempts/suicides is typically ≥ 10, may be as high as 25 in the US, and averages about 16-fold internationally (Tondo et al. 2003, WHO 2003).

Risk factors

Sex differences in suicidal risk parallel those in the general population. Men with BPD average approximately 4-fold greater risk for suicide than women (AAS 2000; WHO 2003). However, among women with BPD, reported rates of suicide *attempts* (median 32%, range: 15%–48%) are about twice higher than among comparable men (median 16%, range: 4%–27%), suggesting somewhat greater lethality of attempts in men (AAS 2000). This conclusion contrasts to the impression that long-term risks of dying by suicide are not lower, and may be somewhat greater among women than men with BPD. Overall, it is clear that suicidal risk is markedly elevated in both men and women with BPD, in whom the risk of the disorder is also largely sex-independent (Tohen and Angst 2002).

Suicidal risk appears to be particularly high early in the course of BPD. Ösby and his colleagues (2001), and we (Tondo et al. 1998) found, among patients with either BPD or unipolar major depression, that suicidal risk was higher at younger ages, and particularly in the first year after the initial diagnosis. Also, among samples of outpatients with either type I or II BPD, high proportions of life-threatening suicide attempts (averaging 16.1% of patients) or suicides (2.60% of subjects) occurred during the first decade of BPD illness that included maintenance treatment with lithium for about half of the time (Dilsaver et al. 1997, Tondo et al. 1998). Nearly one-quarter of these severe suicidal acts occurred within the first year of illness, and half within 5 years; somewhat ominously, the average latency from onset to establishing sustained treatment was nearly 8 years in one of these studies, and latency to maintenance treatment typically has ranged from 5 to 10 years in other studies (Tondo et al. 1998). These findings indicate a high risk for suicidal behavior early in the illness and contrast to with the higher risk of suicide in the elderly in the general population (AAS 2000, WHO 2003). Given growing evidence that at least half of cases of BPD begin before age 20, there is a clear need to identify and treat juvenile cases of BPD much earlier (Faedda et al. 1995, 2004a).

Some comparisons have been reported concerning suicidal risk in BPD subtypes. In general, the risk of suicide associated with BPD is similar to that that found among patients with relatively severe major depressive disorder, particularly for unipolar depression severe enough as to require psychiatric hospitalization. Several studies have reported somewhat higher risks of suicide with major depression than with BPD (Hastings 1958, Tsuang 1978, Black et al. 1988, Newman and Bland 1991, Lester 1993, Høyer et al. 2000, Kallner et al. 2000, Gladstone et al. 2001, Ösby et al. 2001). On the contrary, others found no difference (Carlson et al. 1974), or even higher rates among BPD patients (Morrison 1982, Weeks and Vaeth 1986, Dingman and McGlashan 1988, Sharma and Markar 1994, Ahrens et al. 1995, Koukopoulos et al. 1995, Thies-Flechtner et al. 1996, Angst et al. 1998, Rihmer and Pestality 1999, Bottlender et al. 2000, Tondo and Baldessarini 2001). Risk of suicide is very high in both bipolar and unipolar forms of major affective disorders, and probably higher with greater illness severity.

Soon after introducing the bipolar II subtype concept in the 1970s (recurrent major depression with hypomania, Dunner and Fieve (1974) reported an even greater risk of suicide in association this form of BPD with more prominent depression than hypomania. Moreover, a recent review found particularly high risk of suicide attempts associated with bipolar II disorder (61/253 = 24.1% lifetime risk), with intermediate risk in type I BPD (103/606 = 17.0%), and lower risk in unipolar depression (143/1,214 = 11.8%; Rimher and Pestality 1999).

Depressive and dysphoric-irritable states in BPD are particularly risky for suicide. In a large clinical sample of types I and II BPD outpatients making serious attempts or committing suicide, depression was judged to be present during 73% of the suicidal acts; another 16% involved dysphoric-mixed manic-depressive states; only 11% were manic and none was hypomanic (Tondo et al. 1998). That is, 89% of all suicidal acts were associated with ongoing depression or mixed-dysphoric mood states. Similarly, in other studies, 79%–90% of suicides by BPD patients were associated with a depressive or mixed-dysphoric mood state (Arató et al. 1988, Isometsá et al. 1994, Dilsaver et al. 1997). Previous severe depressions were found to be highly predictive of later suicidal behavior in BPD patients (Dilsaver et al. 1997, Tondo et al. 1998).

Risk factors for suicide generally, as well as in BPD, include Caucasian ethnicity and being unmarried (Hirschfeld and Davidson 1988, Sachs et al. 2001, Jacobs 2003). Particularly important clinical predisposing factors in BPD include previous and current depression, previous severe depression, dysphoric-agitated states, hopelessness, previous suicide attempts, and substance or alcohol abuse or dependence (Francis et al. 1987, Goodwin and Jamison 1990, Isometsá et al. 1994, Dilsaver et al. 1997, Fawcett 1998, Móscicki 1997, Tondo et al. 1999, Strakowski et al. 2000, Nierenberg et al. 2001, Sachs et al. 2001, Jacobs 2003). Impulsivity also is a relevant clinical factor in suicidal behavior, and is a common trait of persons with BPD (Corruble et al. 1999, Mann et al. 1999, Goldberg et al. 2001), but it has been tentatively associated primarily with suicide attempts of limited lethality (Baca-García et al. 2001). It is not clear whether relatively high rates of illness recurrence, or presence of rapid cycling (>4 recurrences within a year) increases risk of suicide in mood disorders (Wu and Dunner 1993, Goodwin 1999). There may also be a genetic predisposition to suicide, but it is not clear that this risk is independent of risk for BPD or depressive illness (Baldessarini and Hennen 2004).

Predisposing factors probably interact with some precipitating stressors, but deaths, separations and other major losses, scandals or imprisonment, themselves, may precipitate suicide even in the absence of a psychiatric disorder (Conwell and Henderson 1996). Relevant stressful events identified as suicidal risk factors generally include interpersonal or occupational difficulties, separations and personal or economic losses, retirement, bereavement, social isolation, and limited access to support or clinical services. Holmes and Rahe (1967) ranked particularly stressful life-events as: death of a spouse ≥ divorce ≥ separation ≥ imprisonment ≥ death of a relative ≥ illnesses ≥ weddings ≥ job-loss ≥ conjugal reconciliation ≥ retirement.

Effective assessment of suicide is required to esti-

mate the presence of suicidal thinking, nature of intent, and access to lethal means (Fawcett 1998; Jacobs 2003). Many physicians and even mental health professionals avoid discussing suicide directly and frankly with patients for fear of provoking suicidal behavior or, more likely, because of personal discomfort (Hirschfeld and Russell 1997). Suicidal ideation rarely is new to suicidal persons; many potential victims are willing to discuss their suicidal thoughts, and the topic needs to be investigated, especially when agitation, severe anxiety, anguish, or psychosis is present (Fawcett 1998). It is also important to evaluate for indications of suicidal intent, such as a specific plan or preparation of notes, making a will, giving away possessions or pets, or clearing up business matters pertaining to survivors (Hirschfeld and Russell 1997, Jacobs 2003).

Perlis and Stern (2000) proposed eight key elements in evaluating suicidal risk: (a) assessing the intensity of suicidal ideation; (b) inquiring about details of suicide plans, access to lethal means, and the possibility of rescue; (c) identifying current or recent precipitants for suicidal thinking; (d) screening for the presence of major psychiatric illness, and particularly depression; (e) inquiring about past suicide attempts and plans; (f) screening for risk- and protective factors; (g) evaluating interpersonal and other social supports; and (h) performing an adequate mental status examination. A determination of high acute risk calls for family involvement, and often requires immediate hospitalization, sometimes by legal commitment, especially if the potentially suicidal patient is not already in treatment, or is unwilling to accept help.

About 40% of persons who eventually committed suicide (independent of diagnosis) had made contact with a mental health professional within the several months before dying (Pirkis and Burgess 1998). Some studies found that 75%–80% of suicides had consulted a physician at least once within the year before death, 66% within one month, and 20% in the week before (Anderson et al. 2000, Miller 2001). However, only 46% had seen a psychiatrist within a month, and 36% in the week before death (Pirkis and Burgess 1998). Little is known about utilization of clinical services by suicidal BPD patients specifically. However, in a Hungarian study 74.2% of mainly type II BPD patients who committed suicide were receiving some form of treatment at the time of death (Arató et al. 1998).

The interpretation of such analyses of risk factors associated with suicide, based on case-finding only *after* a suicide, is confounded by lack of knowledge of the proportion of potential suicides that may have been prevented by timely assessment and effective interventions and, therefore, not included in the data considered. The preceding observations strongly suggest that access to care, and very likely also, the quality of care and of close follow-up, may play a crucial role in suicide prevention. Surprisingly, however, very few studies have addressed this question.

Treatment

Evidence that specific medical treatments, notably including use of psychotropic medicines, reduce suicide risk, particularly over the long-term, is very limited and largely inconclusive (Baldessarini and Jamison 1999). Of note, rates of specific psychiatric treatments in postmortem samples of suicides often are remarkably low, on the order of 3%–30% (Isacsson et al. 1994a, 1994b, 1999; Keller et al. 1996; Hirschfeld et al. 1997; Andersen et al. 2000, 2001; Miller and Druss 2001). These findings indicate that access to treatment, whether effective or not, is very limited among suicidal persons.

Antidepressants

Suicidal behavior is strongly associated with acute depressive illness, and antidepressants have been proved effective, at least in the short-term treatment of acute major depression in adults. It follows that antidepressant treatment is a highly plausible intervention to prevent suicide. There has been broad international use of clinically effective antidepressants for more than 40 years, with major improvements in recognition and interventions into mood disorders since the 1960s (Baldessarini 2005). Nevertheless, evidence that antidepressant treatment in either BPD or major depression is associated with lowering of suicidal risk remains inconclusive (Malone 1997, Angst et al. 1998, Salzman 1998, Baldessarini and Jamison 1999, Müller-Oerlinghausen and Berghofer 1999, Khan et al. 2000, Carlsten 2001, Joyce 2001, Baldessarini et al. 2005). Moreover, suicide rates in some countries with high consumption of antidepressant agents have not decreased in the last 50 years though then have in others (Gibbons, et al. 2005, Helgason et al. 2004, Isacsson 2000, Rihmer 2001, Grunebaum et al. 2004). To some extent the lack of demonstrated effectiveness of antidepressant treatment in reducing suicide risk may reflect the remarkably low rates of access to antidepressant treatment, particularly in young men, as well as inadequate dosing and duration of sustained treatment for many depressed patients (Murphy 1998, Baldessarini 2005, Pompili et al. 2005).

Temporal parallels have been noted between falling suicide rates in some countries as modern and safer antidepressants have displaced older, potentially lethal antidepressants since the 1970s (Ohberg et al. 1998, Isacsson 2000, Carlsten et al. 2001, Joyce 2001). During the same era, international suicide rates underwent a moderate, but statistically significant overall decrease, from 0.0172 in 1970–1988, to 0.0143 %/year in the 1990s (paired-t = 3.60, $p<0.001$ for 21 countries; AAS 2000, Tondo et al. 2003, WHO 2003). However, associations between increased use of modern antidepressants and lower suicide rates have not been found consistently (Helgason et al. 2004, Grunebaum et al. 2004, Gibbons et al. 2005). Moreover, all such "ecological" associations are fundamentally limited by the lack of association of the relevant variables at the level of individuals. Deaths ascribed to antidepressant overdose, at least, have become less common with the advent of modern antidepressants, although other lethal means are readily available (Isacsson et al. 1999, Frey et al. 2000).

In some vulnerable patients, mixed dysphoric-agitated states in BPD can be induced by antidepressant treatment, and may not be recognized as such clinically. Such states, as well as other adverse behavioral responses to antidepressant treatment in mood disorder

patients may well increase the risk of aggressive-impulsive acts, perhaps including suicidal behavior, in some adults and children (Pompili et al. 2005). Though plausibly related to suicidal risk, the quantitative contribution of such effects of antidepressant treatment to suicidal behaviors, specifically, remains uncertain (Beasley et al. 1991, Mann and Kapur 1991, Rothschild and Locke 1992, Tollefson et al. 1994, Healy et al. 1999, Faedda et al. 2004b, Pompili et al. 2005). Such associations with serotonergic antidepressants, in particular, are counter-intuitive in view of substantial evidence indicating a deficiency of central serotonergic functioning in association with violent acts including suicide (Mann et al. 2001).

Lithium salts

Based on present knowledge about pharmacological interventions and risks of suicide and attempts, prophylactic treatment with lithium provides the strongest available evidence of reduced suicidal risk during any psychopharmacological treatment (Müller-Oerlinghausen et al. 1992, Baldessarini et al. 2001, Tondo et al. 2001, Goodwin et al. 2003). Studies reporting on the association of lithium treatment and suicide in bipolar and other major affective disorder patients consistently have found lower rates of suicides and attempts during lithium maintenance treatment than without it, including several prospective, randomized, and controlled trials (Tondo et al. 2001, 2003; Baldessarini et al. 2003, 2005).

In our initial meta-analysis of 22 studies involving a total of 5,647 patients with BPD or other types of manic-depressive disorders (mainly recurrent major depression, and some cases of schizoaffective disorders) and 33,473 patient-years of risk, long-term treatment with lithium, essentially as a monotherapy, was associated with a nearly six-fold reduction of the crude average rate for completed suicide, and a computed reduction of 8.85-fold, or 85%, based on multivariate modeling (Tondo et al. 2001). Our more recent updated meta-analysis provides even stronger support for such effects of long-term lithium treatment (Baldessarini et al. 2005). In one of these studies, involving 360 Sardinian BP I and II patients evaluated before, during, and following discontinuation of maintenance lithium treatment, again as a monotherapy, we found that rates of suicide and life-threatening attempts were reduced by 6.4-fold, or 83% (Tondo et al. 1998). Moreover, in that study, the risk of suicidal acts increased by 20-fold within 12 months after discontinuing lithium maintenance treatment, and later fell back to the same level encountered before lithium treatment started.

Most of these studies may be open to the hypothetical criticism of possible self-selection bias if patients who accept a stable, long-term treatment regimen *also* have lower suicidal risk. Some studies of lithium and suicidal risk involve comparisons of patients without vs. during treatment (Baldessarini et al. 2001, 2003, 2005; Tondo et al. 2001, 2003). Even though the same persons are involved under two conditions of treatment, those who accept, tolerate, and continue the treatment might differ from randomly selected patients, perhaps in subtle ways not readily identified by considering their morbid histories alone. Several randomized, controlled trials also indicate a reduced risk of suicidal and attempts with lithium vs. placebo or alternative treatments (Baldessarini et al. 2005). However, even randomized trials, with typically limited long-term adherence and retention, are not necessarily free of such potential selection or retention biases. On the other hand, it simply is not feasible to evaluate any long-term treatment without substantial acceptance, tolerance of, and adherence to the treatment being investigated. Therefore, we suggest that the available findings with lithium treatment, at a minimum, reflect substantial and consistent reductions in suicidal risk among those who accept, tolerate, and adhere to long-term prophylactic treatment with lithium salts.

The effectiveness of lithium treatment in preventing suicide in broadly defined manic-depressive syndromes is likely to operate through reduction of risk or severity of recurrences in depression or mixed dysphoric-agitated states (Baldessarini et al. 2001, 2003, 2005). However, some experts have suggested that lithium may have specific effects against suicide independent of its mood-stabilizing actions (Müller-Oerlinghausen 2001, Ahrens et al. 2001). Specific contributions of lithium treatment of particular interest may include reduction of impulsivity or of aggressive and hostile behavior, possibly mediated through enhanced functioning of the central serotonin system (Müller-Oerlinghausen 1992, Young et al. 1994, Wickham & Reed 1997). Finally, additional support for relatively selective effects of lithium treatment are arising from comparisons to alternative active treatments, such as use of anticonvulsant or antipsychotic agents (Baldessarini et al. 2005).

Anticonvulsants

A growing number of anticonvulsants have demonstrated antimanic efficacy and are used empirically for possible long-term mood-stabilizing effects in BPD patients, but remain largely unexamined for possible beneficial effects on suicidal behavior. Specifically, effects of carbamazepine, lamotrigine, and valproic acid on suicidal behaviors are not established, but there is some evidence that they may be less effective than lithium (Dardennes et al. 1995, Thies-Flechtner et al. 1996, Denicoff et al. 1997, Greil et al. 1997, Greil & Kleindienst 1999, Bowden et al. 2003, Calabrese et al. 2003, Goodwin et al. 2003, Baldessarini et al. 2005). The evident superiority of lithium over other agents with antimanic or putative mood-stabilizing properties may reflect selective effects beneficial for suicidal behaviors that are specific to lithium, such as against impulsivity and aggressive tendencies. Alternatively, lithium may simply have superior mood-stabilizing properties, particularly against BP depression or mixed-states (Dardennes et al. 1995, Thies-Flechtner et al. 1996, Denicoff et al. 1997, Greil & Kleindienst 1999, Tondo et al. 2003). Potential beneficial effects of anticonvulsants against suicidal risk in conditions other than BPD have not been investigated.

Antipsychotics

A particularly important finding is evidence of reduced risk of some suicidal behaviors in several studies

of clozapine (Meltzer et al. 2000, Sernyak et al. 2001, Hennen and Baldessarini 2005), including an important randomized trial against olanzapine (Meltzer et al. 2003). Despite inconclusive evidence of proof of reduction in mortality, and limitation only to the treatment of patients with chronic psychotic disorders (schizophrenia or schizoaffective disorders), this drug is the first treatment of any kind to receive regulatory approval by the US FDA for the indication of reducing risk of suicidal behaviors. As such, this appears to be an historically important, and precedent-setting development. Interestingly, like lithium, but in contrast to standard clinical practice in the use of antidepressants, clozapine is employed with unusually close medical supervision and regular blood testing to minimize the risk of potentially lethal side effects. On the other hand, the level of patient contact and follow-up with clozapine and olanzapine were closely matched in the pivotal randomized trial by Meltzer and his colleagues (2003). A growing number of modern antipsychotic agents other than clozapine, including amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are employed internationally for the treatment of BPD and schizoaffective disorders (Tohen et al. 2003, McCormack and Wiseman 2004, Bourin et al. 2005). However, their potential for limiting risks of suicidal behavior in patients diagnosed with BPD or major depression remains unknown (Baldessarini and Tarazi 2005).

Electroconvulsive treatment

Electroconvulsive therapy (ECT) has the clinical reputation of being the most effective and rapid treatment for emerging or ongoing suicidality in severe depressive illness (Avery & Winokur 1978, Metzger 1998, Weinger 2000). An earlier US National Institute of Mental Health (NIMH) consensus report considered ECT the treatment of choice in emergency situations involving high suicidal risk (Rose et al. 1985). Nevertheless, effectiveness of ECT for sustained suicide prevention has not been proved, and requires further study, including in BPD patients (Jacobs 2003).

Psychosocial interventions

There is widespread agreement that specific and comprehensive suicide prevention strategies are needed. In several countries, public and professional educational programs have been developed with the aims of increasing awareness of suicide risk and of the treatability of BPD, major depression, psychotic disorder, substance abuse, and other psychiatric illnesses that are strongly associated with suicide (Sachs et al. 2001, Taylor et al. 1997, Grandin et al. 2001, Gray and Otto 2001, Pearson et al. 2001).

Despite their widespread clinical application, there are remarkably few experimental studies of the effectiveness of psychosocial interventions aimed specifically at reducing either morbidity or mortality in BPD (Huxley et al. 2000). Nevertheless, several investigations of psychotherapeutic treatments and clinical management techniques, including some studies involving randomization and controls, have considered suicidal behavior as an outcome measure (Gray and Otto 2001). Psychotherapeutic techniques based on problem-solving, rehearsal, and use of cognitive and behavioral methods appear to be effective in reducing suicidal risk in various types of patients, particularly when applied in combination with appropriate pharmacotherapy (Hawton et al. 1987, Salkovskis et al. 1990, Linehan et al. 1993, McLeavey et al. 1994). A specific and evidently widely employed management tactic, involving "contracts for safely" between clinicians and patients who agree to report impending loss of control of suicidal impulses, has evidence of frequent failures, and has not been tested in a scientifically appropriate manner, including for use with BPD patients (Egan 1997, Gray and Otto 2001, Jacobs 2003).

A recent meta-analysis considered studies of suicidal risk-reduction in association with psychosocial treatments and interventions, including intensive community services and rapid hospitalization, as well as specific types of psychotherapy. The findings did *not* indicate significant reductions of suicidal behavior in broad samples of psychiatric patients (Gray and Otto 2001). A possible reduction of suicide attempts was found only among four methodologically variable studies involving cognitive-behavioral psychotherapy (CBT), mainly in depressed patients but not specifically applied to patients with BPD (Gray and Otto 2001).

Conclusions

This brief update supports the emerging conclusion that BPD is, internationally, a highly prevalent, often severe, sometimes disabling, and potentially fatal illness. It is associated with a very high risk of suicide, especially early in the illness when sustained clinical interventions, and even the diagnosis, may not have been established, and suicidal risk continues over many years, eventually accounting for perhaps 15% of causes of death. The epidemiology of suicide risk in BPD, specifically, is methodologically limited and has often been confounded by a lack of separation of types I or II BPD from each other, or from recurrent major unipolar depressive illnesses.

The depressive and dysphoric-agitated mixed phases of BPD, particularly following repeated episodes of severe depression, appear to be especially dangerous and life-threatening, as well as being particularly challenging to diagnose and to treat effectively and safely (Marneros et al. 2004). BPD also is associated with very high rates of comorbid substance-use and anxiety disorders (Krishnan 2005), as well as impulsivity, lack of insight, and poor treatment-adherence—all further complicating the effective clinical care of such patients and probably adding to suicidal risk.

Short-term interventions that are widely accepted empirically for managing acute suicidality include close clinical supervision, rapid hospitalization, and use of ECT. However, various types of clinical interventions, including specific mood-altering medical treatments and widely accepted psychosocial therapies, have little evidence of long-term effectiveness in reducing suicidal risk in BPD patients. Lithium maintenance treatment appears to be a unique exception in having considerable research support for association with sustained re-

duction of suicidal risk in persons with BPD and possibly other forms of major affective illnesses, including demonstrated sparing of mortality. Anticonvulsant and atypical antipsychotic agents, as well as the less toxic modern antidepressants, all require specific research assessment of their long-term ability to limit premature mortality from all causes in BPD and other major affective disorders, and to reduce suicidal risk specifically.

Finally, despite major advances in psychiatric therapeutics in recent years, the short-term efficacy and long-term preventive effectiveness of available and emerging new treatments for BPD against depression, mixed affective states, sustained dysthymia, rapid-cycling, comorbidity with anxiety and substance-use disorders, demoralization and dysfunction, in addition to mania and psychosis, largely remain to be demonstrated and compared critically. Even treatments that are effective against some symptomatic and functional expressions of BPD may have a limited impact on suicide and other mortal risks. This paradoxical impression reflects still-remarkably low rates of diagnosis of BPD, of use of adequate doses of effective pharmacological agents, and of sustained, systematic, and comprehensive, long-term treatment with adequately close and supportive clinical supervision. As additional research is pursued, efforts to reduce suicidal risk in patients diagnosed with BPD can usefully include optimized clinical management based on available knowledge that requires further dissemination and systematic application in mental health services, as well as improved access to care and to clinicians skilled in the care of complex major psychiatric illnesses.

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