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Suicidal Behavior in Mood Disorders: Response to Pharmacological Treatment

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Abstract Suicidal behavior is strongly associated with depression, especially if accompanied by behavioral activation, dysphoria, or agitation. It may respond to some treatments, but the design of scientifically sound, ethical trials to test for therapeutic effects on suicidal behavior is highly challenging. In bipolar disorder, and possibly also unipolar major depression, an underprescribed medical intervention with substantial evidence of preventive effects on suicidal behavior is long-term treatment with lithium. It is unclear whether this effect is specifically antisuicidal or reflects beneficial effects of lithium on depression, mood instability, and perhaps aggression and impulsivity. Antisuicidal effects of anticonvulsant mood stabilizers (carbamazepine, lamotrigine, valproate) appear to be less than with lithium. Further evaluation is needed for potential antisuicidal effects of atypical antipsychotics with growing evidence of efficacy in depression, particularly acute bipolar depression, while generally lacking risk of inducing agitation, mania, or mood instability. Short-term and long-term value and safety of antidepressants are relatively secure for unipolar depression but uncertain and poorly tested for bipolar depression; their effects on suicidal risk in unipolar depression may be age-dependent. Sedative anxiolytics are virtually unstudied as regards suicidal risks. Adequate management of suicidal risks in mood disorder patients requires comprehensive, clinically skillful monitoring and timely interventions.

Keywords Anticonvulsants · Antidepressants · Antipsychotics · Bipolar I and II disorders · Lithium · Major depressive disorder · Suicide

Highlights We review the following topics:
- The epidemiology of suicide in mood disorders.
- Special challenges for the design of studies aimed at testing for antisuicidal effects.
- Findings for and against long-term antisuicidal effects of antidepressants, anxiolytics, antipsychotics, anticonvulsants, and lithium.
- The place of psychotropic drugs in comprehensive clinical management of potentially suicidal patients.
- References of special interest are annotated.

This article is part of the Topical Collection on *Mood Disorders*

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Introduction

Suicide has a strong association with psychiatric disorders, particularly major affective disorders, and might be amenable to medicinal treatment. Here, we review findings pertaining to suicidal risks associated with *long-term* treatment with various types of psychotropic drugs aimed at preventing suicidal *behavior*. In general, scientifically sound therapeutic investigations of treatments for suicide have been uncommon and are very challenging. Only one treatment—the highly effective antipsychotic drug clozapine—has regulatory recognition for the ability to reduce suicidal risk and only for patients diagnosed with schizophrenia [1, 2•]. For bipolar disorder, long-term use of lithium has substantial evidence of an antisuicide effect, whereas other treatments that are inadequately tested or their findings remain inconclusive, even though some interventions are widely employed empirically [3•, 4•].

The average international, general population suicide rate is approximately 11/100,000/year (0.011 %/year) [4•]. The reported ratio of attempts to suicides (A/S), a proposed inverse

index of "lethality," is approximately 30–50 [5]. The ratio of identified instances of "suicidal ideation" to attempts is at least 6 and probably higher. It follows that each suicide arises from perhaps 240 cases involving ideation only in the general population [6•]. However, among mood disorder patients, the A/S ratio is only 5–10, indicating effects of illness or lethality of attempts. The reported ratio of suicidal ideation to attempts among mood disorder patients is approximately 3, and the ratio of ideation to suicides is about 20–25 [7, 8•]. In bipolar disorder (BD) patients, pooled rates of suicide attempts/year among BD-I (4.01 [CI 3.48–4.54]% in 43 studies) and BD-II patients (4.11 [3.23–4.99]% in 30 studies) are very similar [9•].

In short, relationships among levels of suicidal risk are not close quantitatively, and even self-injurious acts bear a somewhat distant relationship to suicide. Moreover, suicidal ideation is a self-reported and subjective measure of uncertain reliability that can range from weariness of life to explicit, self-destructive plans. That is, suicidal ideation or attempts, as usually is implied by the broad term "suicidality," may not be adequate surrogate measures for assessing effects of treatments on suicide but are often considered owing to the relative rarity of suicide. Nevertheless, in a hierarchical view, ideation is a first step toward possible suicidal acts and should be considered explicitly in clinical and research assessments of suicidal risk.

Experimental therapeutic research on suicide prevention is particularly difficult conceptually, ethically, clinically, and quantitatively. Even widely employed, seemingly plausible, methods of treating suicidal persons are not adequately supported by empirical research evidence and may not exert critical, long-term risk reduction for suicide. This circumstance leaves tension between the obligation to intervene clinically, often rapidly, despite a dearth of clear empirical evidence about how best to do it [4•].

There is broad agreement that as many as 90 % of suicides occur in persons with a diagnosable psychiatric disorder, nearly half (48.5 %) involving mood disorders, often with precipitating events [10•]. The *standardized mortality ratio* (SMR) for suicide is highest in mood disorders among all psychiatric disorders, averaging 10–20 times above the general population rate (or approximately 0.11–0.22 %/year.) SMR is highest in BD and in major depressive disorder (MDD) severe enough for hospitalization [4•, 10•, 11•]. Depressive phases of BD, and especially mixed (agitated dysphoric) states, are far more likely to be associated with suicidal behaviors than manic or hypomanic periods [12, 13]. Moreover, rates of suicides and attempts (as well as lethality as reflected in their A/S ratio) are at least as high among type II as in type I BD patients [14•, 15•]. Not only is the A/S ratio much lower (greater lethality) among mood disorder patients than in the general population [3•, 6•, 8•], but this ratio in men is half that in women (12 vs. 23), consistent with generally greater lethality of suicide attempts in men [7].

High risk of suicide among mood disorder patients was supported by our study of nearly 3000 outpatients with major mood disorders evaluated and treated at the Lucio Bini Mood Disorders Research Center in Cagliari, Sardinia [8•]. Risk of suicides was similar among types I and II BD patients, averaging 150/100,000 per year, or 23 times greater than the average rate in the Sardinian general population, of 6.6/100,000 [16], and 3 times greater than among 1983 outpatients diagnosed with unipolar MDD (few of whom ever had been hospitalized). Of note, a third of all suicidal acts occurred within the first few years from onset of major mood disorders [3•], as noted by others [17, 18] and underscoring the need for early diagnosis and intervention.

In BD patients, suicide risk remains high despite the growing variety of treatments with putative mood-stabilizing effects [19•]. This disparity almost certainly reflects the great difficulty of effectively treating depressive and mixed manic-depressive states of BD [20–22]. Modern psychiatric treatments, rapid hospitalization, and even ECT may be useful as short-term interventions but lack evidence of reducing *long-term* suicide risk [4•, 10•, 23•, 24•, 25]. In addition, few persons committing suicide were receiving *any* clinical care at the time of their deaths [26, 27].

Effects of available treatments for bipolar depression indicate that suicidal risk can be reduced more effectively by preventing than by treating acute depressive episodes. This proposal is even more relevant knowing that depressive or dysphoric morbidity accounts for three quarters of the 40–50 % of time ill among clinically treated BD patients and virtually all of similar proportions in MDD patients receiving long-term clinical treatments [28, 29, 30•]. In particular, depressive conditions most associated with suicide have been characterized as agitated dysphoric states in both BD and unipolar MDD patients [5, 21, 31].

Assessment of Treatments for Suicide

Difficulties in conducting therapeutic studies for suicide (Table 1) include clinical and ethical risks involved in withholding treatment, such as in a placebo condition, and seeking outcomes that may include life-threatening or lethal events, difficulties in identifying, recruiting, and retaining subjects, and the rarity of suicide or even attempts as an outcome measure [32]. Alternatively, many studies rely on surrogate outcomes such as self-injurious acts, suicidal plans or ideation, or interventions to avoid suicide, all of which may or may not escalate to a suicide attempt. In addition, definitions and prevalence of nonfatal suicide-related behaviors, and their quantitative predictive association with suicide itself, are matters of intense discussion centered on the distinction of ideation,

Table 1 Methodological challenges for research on medical treatments aimed at reducing suicidal risks

• Need for large subject numbers or observation times for rare event outcomes
•Difficulties of subject recruitment and retention
•Suicidal patients often have concomitant substance use disorders, borderline traits, history of trauma, and multiple psychosocial stressors (e.g., unemployment, financial troubles, divorce, etc.). These characteristics pose challenges to conducting RCTs and may introduce confounding factors if not controlled for in data analysis.
•Nomenclature and classification of suicidal ideation and behavior require further refinement; the ambiguous and misleading term "suicidality" should be avoided in favor of more specific outcomes (ideation, planning, self-injury, attempt with lethal intent, suicide).
•Unambiguous operational definition of suicide risk required
•Incidental and passive reporting of suicide ideation and behavior as adverse effects, rather than explicit assessments
•Specific attention to mixed-depressive or agitated dysphoric states of unipolar and bipolar depression
•Reporting of actual and *matched* exposure times at risk for each treatment compared (event rates per time as highly, inversely related to exposure time)
•Need to optimize dosing or serum concentrations of some treatments
•Need to control for frequency and nature of clinical contact and support
•Ethical constraints of controlled studies (usually comparing similarly plausible active treatments, not placebo)
•Commercial considerations: potentially small market impact versus high costs, reluctance to compare
competing products head to head; clozapine off-patent, small market (toxic); lithium unpatented and lacking commercial sponsorship
•Randomized, controlled treatment trials with suicidal behavior as an explicit outcome are unlikely to be carried out without compelling indications of commercial value
•Innovative trial designs to address some of these challenges are urgently needed

plans, and attempts, including intent and lethality [33]. Even definitions of suicide ideation are problematic. Notably, the predictive value of *passive* ideation (thoughts of weariness of life) probably differs from that of *active* ideation (with planning and preparing for a suicide attempt). In research on suicide ideation and behavior, crucial assessment of *intent* to die often is neglected [34–36].

The relative rarity of suicide requires assessment of large subject samples for extended times to detect a signal in studies of treatment effects or pooling data across multiple studies. In addition, even randomized, controlled treatment trials (RCTs) have shortcomings. They include potential unreliability of essentially incidental and passive reporting of suicidal thoughts or behaviors based on currently typical "adverse event reporting" systems under conditions not designed explicitly to detect and assess suicidal events actively. However, efforts are being made to include regular, standardized assessments of suicidal behaviors in trials of centrally active new drugs, though again largely aimed at improving detection of "adverse events" [36]. In addition, the relatively short duration of most treatment trials is unlikely to yield statistically adequate numbers of suicidal behaviors as rare events. Another technical limitation to assessing suicidal risks in treatment trials is that observed rates of "suicidal events" rarely are corrected for actual and matched exposure times for individuals given specific treatments. For example, earlier dropping out of a trial arm involving placebo treatment can artifactually make active drug treatment *seem* "riskier" than placebo.

Antidepressants

The strong association of depressive and agitated dysphoric morbidity with suicide in mood disorder patients suggests that short-term and long-term treatment with antidepressants might be expected to reduce suicidal risk [37]. Evidence for short-term and long-term efficacy of antidepressant treatment in unipolar MDD is substantial [37–39, 40•, 41, 42, 43•]. However, antidepressant treatment is not explicitly approved for use in bipolar depression and may not be effective or safe long term in BD, in which its prophylactic value versus destabilizing risks is poorly studied but seems unfavorable [44, 45•]. There also may be increased suicidal risk with antidepressants in some cases of either BD or MDD involving agitation, anger, dysphoria, restlessness, irritability, insomnia, or behavioral disinhibition, especially when complicated by substance abuse, and in younger patients [10•, 45•, 46, 47, 48•, 49–52]. Such forms of depression may be considered "mixed states" based on newly broadened Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria [12]. Studies of antidepressant treatment of various designs are limited mainly to MDD and provide inconsistent evidence concerning suicides or attempts, and indeed, suicidal behavior rarely was an explicit outcome measure. There is evidence of lower suicidal risk during trials in adults of treatment with an antidepressant versus placebo based on questionable use of specific items in depression symptom-rating scales (weighted toward suicidal *ideation*) [44, 48•, 53, 54•, 55, 56•, 57, 58].

Lower rates of suicide with greater use of antidepressants were found in some ecological (pharmacoepidemiological) studies, including in some Nordic countries and the USA, but not in many other areas [41, 42, 54•, 59]. However, in the USA and Sweden, at least, similar inverse correlations were found at least a decade before introduction of fluoxetine as the first clinically successful modern antidepressant in the late 1980s [42, 54•].

Additional studies involving largely retrospective observations of large cohorts of depressed patients and case-control comparisons have yielded inconsistent and inconclusive findings [42, 60, 61]. Furthermore, since suicidal thinking or behavior usually is recorded as an incidental event (adverse

effect) in such studies, interpretation of their findings without randomized controls can be confounded if antidepressants are more likely to be given for more severely ill subjects also at presumably greater suicidal risk. In one clinical follow-up study [5], we found an overall rate of suicidal ideation or acts of 16 %, with more than twice higher risk in BD than unipolar MDD patients. During treatment, based on monthly assessments, 81 % of those considered suicidal at intake became nonsuicidal with treatment and time and only 0.5 % of initially nonsuicidal subjects reported new suicidal thoughts, with no new attempts. These observations underscore the difficulty of evaluating interactions of treatment, time, and suicidal behavior, long term.

Randomized controlled trials should provide the best information on effects of antidepressant treatment on suicidal risks, but individual trials are limited in numbers and exposure times, whereas outcome events are relatively rare. Moreover, their identification has been based on incidental and passively acquired, nonexplicit, assessments of suicidal outcomes and typically after having made efforts to exclude potentially suicidal subjects. Despite such efforts, rates of suicidal behaviors may be at least as high in controlled trials (with acutely depressed subjects) as in cohort studies of MDD patients in various clinical states [62, 63]. For example, suicide rates pooled across several recent large meta-analyses of modern and older antidepressants or placebo were similar with all treatments and averaged 0.862 %/year [38, 53, 54•, 64], or 78 times above the approximate average international general population rate of 011 %/year, about 17 times above the rate of 0.050 %/year in outpatients with MDD [8•]. Another caveat is that the high observed rates from the cited meta-analyses of controlled trials may exaggerate rates by annualizing observed rates based on brief exposure times (typically 6–12 weeks) in most trials in acute depression. Most meta-analyses have found only minor differences in rates of suicidal behaviors between depressed patients treated with antidepressants or a placebo, and some have detected indications of somewhat greater risks with antidepressants versus placebo controls. However, such findings have included increased risks in juveniles and young adults but decreased risks in older adults, with an overall outcome of no difference [48•, 56•, 65•, 66]. These analyses assume that the trials considered remained well randomized despite dropouts and that temporal exposures in both drug and placebo arms remained well-balanced throughout the trials. They also assume that surrogate measures of suicidal ideation or even minor self-injurious behaviors, as adverse effects, are fairly and comparably ascertained in different treatment groups and that they have important predictive value for suicide itself. All of these are questionable assumptions.

To recapitulate, research on effects of antidepressants on suicide risk presents important and difficult methodological problems. However, current data, though based on thousands of subjects treated with antidepressants versus placebo, do not provide sufficiently rigorous and consistent information to support either an increase or a decrease of suicide ideation or behavior in mood disorder patients. They raise the possibility that increased suicidal ideation and possibly also suicidal behaviors may be increased with antidepressant treatment in young patients treated with antidepressants but decreased in older adults. However, it is our clinical impression that antidepressants should be avoided in the presence of depressive states accompanied by "mixed" symptoms including agitation, anger, or insomnia.

Anxiolytics and Sedatives

The limited evidence available does not support the hypothesis that antianxiety agents alter suicidal risk either short term or long term in patients with anxiety disorders or other psychiatric illnesses [67]. However, behavioral disinhibition associated with benzodiazepine use might increase impulsive and aggressive behaviors, especially in combination with alcohol and in personality-disordered patients [68]. Moreover, increased rates of self-poisoning have been noted during treatment with benzodiazepins [69] or zolpidem [70]. On the other hand, discontinuation of benzodiazepine treatment, especially rapidly, is a stressor that may increase suicidal risk [68].

Although it is reasonable to expect beneficial effects on suicidal risk during treatment with anxiolytics, research does not provide strong support for this view, possibly as antianxiety agents typically are used as secondary treatments for mood disorders and rarely investigated as a primary treatment.

Antipsychotics

Most studies of associations between antipsychotic treatment and suicidal risk involve patients with schizophrenia or schizoaffective disorder. First-generation neuroleptic drugs are far less studied for effects on suicidal behavior than modern, atypical antipsychotic agents. A study based on more than 10,000 psychotic patients found no statistical difference in relatively short-term risk of suicides and attempts during treatment with modern or older antipsychotics versus placebo [71]. However, another large study found that mortality from all causes as well as suicide was more prevalent among psychotic disorder patients *not* treated with antipsychotic drugs [72].

The first US FDA-approved treatment of any kind given an antisuicide indication was clozapine for schizophrenia patients [1], based mainly on a large randomized trial (InterSePT) comparing clozapine with olanzapine among schizophrenia patients at high suicidal risk [2•]. The trial found greater prolongation of time to interventions for emerging suicidal risk and reduced rates of suicide attempts, but *not*

reduction of mortality, in patients treated with clozapine, though suicides were rare with either treatment. A subsequent trial in schizophrenia patients found a more beneficial effect of clozapine compared to risperidone, quetiapine, or olanzapine [73].

An emerging approach to treating mood disorder patients, especially with BD, is to employ modern (atypical or second generation) antipsychotic agents [74]. Some of these drugs have substantial and growing evidence for efficacy and safety in the treatment of bipolar depression, which has been notoriously difficult to treat with other medicines, including antidepressants, lithium, and mood-altering mood stabilizers [45•, 75] and is strongly associated with suicidal behavior. Several atypical antipsychotics have demonstrated efficacy in simple bipolar depression [76] and broadly conceived mixed depression that includes hypomanic features, as now defined by DSM-5 criteria [77•]. Most antipsychotic agents also are effectively antimanic, though lurasidone remains untested. Combined efficacy for both mania and bipolar depression indicates an extra degree of safety of such treatments, particularly when used in agitated dysphoric mixed manic-depressive states with very high suicidal risks [13, 45•].

Specific research evidence remains sparse as to whether atypical antipsychotic drugs are associated with reduced risk of suicidal behavior in BD patients. Clozapine has some evidence of effectiveness in BD, including for patients who have not responded satisfactorily to other treatments [78, 79•] and those with psychotic features [80]. However, whether its antisuicidal actions in schizophrenia extend also to BD remains uncertain, this unusually effective but potentially toxic antipsychotic agent requires further testing for effects on suicidal risk in mood disorder patients.

For some other atypical antipsychotics, including aripiprazole, asenapine, lurasidone, olanzapine, and ziprasidone, there is emerging evidence that they are effective alone or used adjunctively with lithium or a mood-altering anticonvulsant to treat BD, with beneficial effects on bipolar depression as well as mania, and perhaps the ability to reduce rapid cycling [81]. There also is some evidence that they may reduce suicidal risk in schizophrenia, or at least not increase it [82], as well as reducing all-cause mortality [73, 83–85]. Evidence of reduced risk of suicidal ideation or behavior in schizophrenia patients has been associated with sertindole [86–88], olanzapine, and risperidone [87, 89, 90]. However, such benefits may not be associated with long-acting, injected preparations of risperidone or paliperidone [91]. Olanzapine added to lithium or divalproex led to lower rates of suicidal ideation in mixed-state BD-I patients than did placebo, based on one item of a depression rating scale [92], although specific effects of olanzapine plus fluoxetine (effective in bipolar depression) on suicidal risk are not known.

Of note, discontinuing atypical antipsychotic drugs in schizophrenia patients was followed by markedly increased rates of suicide attempts in one study [93]. In addition, antipsychotic agents have risks of akathisia and agitation, which also have been associated with some atypical antipsychotics, including aripiprazole, ziprasidone, and even clozapine, and may contribute to suicidal risk [94, 95].

In summary, treatment with antipsychotic drugs, especially clozapine, has been associated with substantial reduction of suicide-related behaviors in schizophrenia patients. In mood disorder patients, several modern antipsychotic agents can improve bipolar depression, with low risks of inducing agitation or mood switches, and may facilitate treatment of unipolar depression, though they require specific testing for antisuicidal effects in mood disorders.

Anticonvulsants

There is little research that directly compares suicidal risks during treatment with proved or putative mood stabilizers other than lithium [96•, 97]. However, several studies found substantially lower average risks of suicidal behavior with lithium than with carbamazepine or valproate among BD or schizoaffective patients [98, 99, 100•]. In a meta-analysis [101], we compared protective effects against suicidal behavior of lithium versus several mood-stabilizing anticonvulsants (mainly valproate and some use of carbamazepine or lamotrigine) in six direct comparisons (half involved randomized assignments to treatments) including more than 30,000 patients who were at risk longer with lithium than with an anticonvulsant (31 vs. 19 months). The observed rate of suicidal acts averaged 0.3 % per year during treatment with lithium versus 0.9 %/year with anticonvulsants, to yield a meta-analytically pooled risk ratio of 2.86 (95 % CI 2.29–3.57; $p < 0.0001$), or nearly 3-fold superiority favoring lithium over the few anticonvulsants that have been tested in this way. Nevertheless, anticonvulsants may have some beneficial effects on suicidal behavior [67, 102].

The FDA [103] conducted a meta-analysis of placebo-controlled trials involving 11 anticonvulsants. This analysis found *more* prevalent suicidal ideation and behavior with anticonvulsants than with placebo in patients with epilepsy but not in psychiatric patients [103]. The lack of effect among psychiatric patients was further supported by other studies [104–109]. Addition of valproate as well as lithium yielded lower suicidal risks than treatment with only antipsychotics in a Danish study of over 16,600 persons sampled for 6 years [110], whereas lithium and valproate had similar associations with suicidal behavior [96•, 106, 111]. In conclusion, research on anticonvulsants and suicidal risk remains inconsistent and inconclusive.

Lithium

Suicidal risk, including life-threatening attempts and suicides, has been found to be reduced during long-term treatment of BD patients with lithium in several [3•, 110–113, 114•] but not all studies [96•, 116]. Supporting this association are meta-analyses and reviews, as well as several randomized, placebo-controlled efficacy trials not specifically designed to test for effects on suicidal risk [3•, 39, 112, 116, 117•]. A rare RCT found a substantial but statistically nonsignificant difference in rates of suicidal acts over 12 months among patients randomized to lithium versus placebo, in which all of three suicides were associated with placebo [118]. In meta-analyses of data from 34 trials, we considered suicidal behavior in patients treated long term with lithium, usually for mood disorders, and involving more than 110,000 person-years of risk. The results indicated much lower risks of suicides and attempts during treatment with lithium among patients with recurrent mood disorders (5-fold) or BD specifically (6-fold) [3•, 113]. We estimated a number needed to treat (NNT) at 23 (CI 21–25) patients treated with lithium to avoid one life-threatening or fatal suicidal act; this relatively large NNT probably reflects the low prevalence of suicidal acts. We also found that rates of suicidal acts increased by 20-fold within several months after discontinuing lithium maintenance treatment and were twice greater with abrupt or rapid versus gradual (over ≥2 weeks) discontinuation, later returning to levels encountered before lithium treatment had started [119]. In addition, in eight studies of patients diagnosed with recurrent, unipolar MDD (at risk a total of 2434 patient-years), there was a 4-fold lower of risk of suicide and attempts with lithium versus alternatives that included anticonvulsants [120]. Based on these studies, a recent European Psychiatric Association review recommended use of long-term lithium treatment to reduce risk of suicidal behavior in BD patients [121•]. Details about an antisuicidal effect of lithium treatment are provided in two recent book chapters [4•, 9•].

With the exception of clozapine for schizophrenia [2•], no other treatment has regulatory approval of an indication for an antisuicidal effect, including lithium. A limitation, even in RCTs that appear to support such an effect, is that available studies rely on incidental findings from trials designed to test for clinical efficacy but not explicitly for suicidal risks. An additional potential limitation of all studies of therapeutic effects is that patients who accept, tolerate, and sustain long-term treatment with any method may be favorably self-selected and not entirely representative of all clinically encountered patients. A common feature of patients who appear to benefit from long-term treatment with lithium or clozapine is that they require and receive especially close monitoring which may provide added support and facilitate early identification of emerging symptoms that might lead to suicidal behavior. This possibility was not supported in the InterSePT trial for schizophrenia patients, in which clinician contact time was similar between treatment options [2•]. However, we reported previously that various measures that can be considered indices of access to clinical care were closely correlated with state suicide rates in the USA [122].

The effectiveness of lithium treatment in preventing suicide is likely to be associated with reduced impulsivity and aggressiveness associated with depression or dysphoric agitated, mixed states which are particularly associated with suicidal acts [123–126, 127•]. Alternatively, lithium may have specific effects against suicide independent of its mood-stabilizing actions [127•, 128], as suicidal risk has been found to be reduced even among patients whose primary mood symptoms had not

Table 2 Summary of findings from studies of pharmacological treatments aimed at reducing suicidal risks

Treatment	Timing	Findings	Limitations
Antidepressants	Short-term and long-term effects on suicide risk not established	Inconsistent findings in controlled and uncontrolled trials in unipolar depression; little research in bipolar disorder; may increase risk of nonlethal suicidality at ages <25 years, but decrease it in older adults	Lack of actual, matched exposure times. Suicidal status usually assessed passively and incidentally as an adverse effect rather than explicit outcome measure
Antipsychotics	May have short-term benefits; clozapine may be effective long term.	Clozapine: only FDA-recognized "antisuicidal" treatment (schizophrenia only). Modern antipsychotics require further study.	Clozapine's status based on one controlled trial with no effect on mortality
Anxiolytics and sedatives	May be beneficial short term	Very limited, inconclusive research	Potential disinhibition with increased suicidal risk. Risk of abuse/dependence
Anticonvulsants	Short-term and long-term effects not established	Valproate most studied. Anticonvulsants may be less effective versus suicide than lithium.	Suicidal behaviors incidental, not explicit outcomes
Lithium	Probably effective long term, not short term	Mainly consistent decrease of suicide risk in nonrandomized studies and placebo-controlled trials	Incidentally identified outcomes. Risk of self-selection by acceptance and tolerance of treatment

Used with free permission of authors' material by Oxford University Press as a modification of Table 37.2 in Tondo L and Baldessarini RJ: Clinical Management of Suicidal Risk. In: Yildiz A, Ruiz P, Nemeroff C (editors) *The Bipolar Book: History, Neurobiology, and Treatment*. London: Oxford University Press, 2015, p. 524 [4•]

responded well to lithium [121•, 127•]. The apparent, major beneficial effect of lithium treatment on risk of suicides and attempts may be superior to any such effect of anticonvulsants proposed as mood stabilizers, and comparisons with atypical antipsychotic drugs are needed. The current state of evidence concerning specific treatments aimed at reducing suicidal risk is summarized in Table 2.

Concluding Considerations

The findings reviewed here illustrate many difficulties in designing, conducting, and interpreting studies aimed at testing for antisuicidal effects of specific treatments (Table 1). The ethics of studies with suicide as a potential outcome are daunting and make use of placebo-control conditions highly problematic. Also, the infrequency of suicidal behaviors, even in high-risk samples, makes it difficult to reach sound conclusions from samples of modest size followed for limited times, with well-matched exposures in parallel groups randomly assigned to alternative treatments. In addition, suicidal risk appears to vary with age, the type, duration and severity of affective illnesses, and the timing of interventions in different phases of illness. At the very least, such variations call for randomizing subjects to specific treatments and avoiding "mirror image" comparisons of subjects with versus without a particular test treatment. It is also possible that patients who accept, tolerate, benefit from, and continue to take a treatment for any purpose may differ in unknown but critical ways from those who refuse or discontinue the treatment. Clearly, randomized and prospective trials involving explicit outcome measures relevant to risk of suicidal behavior are required. That such trials are very rare may reflect the ethical, clinical, and liability challenges of efforts to test for reduction of suicidal risks, as well as the lack of clear commercial advantages of such an achievement. For example, there is little commercial interest in lithium as an unpatentable mineral and having an antisuicide indication for clozapine appears to have had little effect on the already small market of this important but potentially toxic substance [1]. Moreover, ethically feasible, head-to-head comparisons of similarly plausible experimental treatments aimed at preventing suicide are not likely to be favored by manufacturers of only one of the products. More generally, the low frequency of suicide, itself, severely constrains market interest in a treatment aimed at preventing it.

Mood disorders are associated with major increases of suicidal behavior in association with depressed mood. Risks are especially high in mixed, dysphoric agitated states and perhaps also with anger, aggression, or impulsivity and insomnia—all of which are particularly prevalent in BD patients and contribute to high suicide risk. In such conditions, antidepressants may risk worsening arousal and agitation, potentially even increasing suicidal risk, at least temporarily, especially early in treatment of young patients and without close, initial clinical follow-up. In general, and particularly during new use of antidepressants in bipolar or unipolar mood disorder, patients call for thoughtful and responsive clinical monitoring, especially in the initial days of treatment, seeking early detection of worsening or emerging agitation, dysphoria, restlessness, insomnia, anger, and psychotic symptoms, including mixed manic-depressive states. Use of mood-stabilizing or antipsychotic agents in depressed patients with agitation is probably a safer and more rational option and may reduce conditions conducive to suicide.

Finally, the preceding overview underscores the conclusion that research support for specific therapeutic interventions aimed at reducing suicidal risk in mood disorder patients remains limited. Treatments with evidence of value, including clozapine for schizophrenia or lithium for major mood disorders, seem to be most useful for long-term reduction of suicidal risk, whereas electroconvulsive treatment and rapid hospitalization probably are effective short term in acute suicidal crises but are not known to have long-term preventive effects. Nevertheless, the need for effective clinical management of suicidal patients makes it essential to rely on clinical experience, with skillful and sensitive application of direct and supportive personal interventions in an environment as protective as possible.

Compliance with Ethical Standards

Conflict of Interest Leonardo Tondo and Ross J. Baldessarini declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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