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Antisuicidal Effects in Mood Disorders: Are They Unique to Lithium?

Authors
Leonardo Tondo[1, 2, 3], Ross J. Baldessarini[1, 2]

Affiliations
1 Department of Psychiatry, Harvard Medical School, Boston, MA, USA
2 International Consortium for Bipolar Disorder Research, McLean Hospital, Belmont, MA, USA
3 Lucio Bini Mood Disorder Centers, Cagliari and Rome, Italy

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Correspondence
Leonardo Tondo, MD
McLean Hospital, MRC3
115 Mill Street
Belmont MA 02478-9106
USA
ltondo@aol.com

ABSTRACT

Introduction Suicidal behavior is strongly associated with depression in major depressive (MDD) and bipolar (BD) disorders, especially with associated behavioral activation, dysphoria, or agitation. A rare intervention with evidence of suicide risk-reducing as well as mood-stabilizing effects in mood disorder patients is lithium.

Methods We reviewed available research evidence on associations of long-term treatment with lithium with risk of suicidal behavior. We meta-analyzed 12 randomized trials in 10 reports (with at least 1 suicide in either treatment arm) including both BD and MDD subjects, with particular attention to comparisons of lithium with placebo or other pharmacological treatments. We also summarized ecological studies on lithium concentration in local drinking water and reported suicide rates.

Results We found substantial reduction of risks of suicide and attempts with long-term lithium treatment, particularly in depressive phases of BD and in MDD. Risk of suicidal behavior was higher in mixed (agitated-dysphoric) states than in manic or hypomanic periods. Risk of suicide fatality, specifically, was lower with lithium than with placebo and probably with mood-altering anticonvulsants or antidepressants.

Discussion Long-term treatment with lithium has growing evidence of suicide- and attempt-sparing effects, probably greater than with anticonvulsants or antidepressants; antipsychotics remain to be tested adequately. However, the ethical and scientifically adequate design and conduct of trials of treatments aimed at suicide prevention remain challenging and underdeveloped.

Introduction

Suicide has a strong association with psychiatric disorders, particularly the major affective illnesses, bipolar disorder (BD) and major depressive disorder (MDD). A relatively recent discovery is that suicidal risk might be reduced by medicinal treatment [1–3]. However, scientifically sound therapeutic investigations of suicide prevention remain uncommon and very challenging. Indeed, only 1 treatment—the highly effective antipsychotic drug clozapine—has regulatory recognition for ability to reduce suicidal risk, and only for patients diagnosed with schizophrenia [4, 5]. Here, we review findings pertaining to suicidal risks associated with long-term treatment of mood disorder patients with various psychotropic drugs aimed at preventing suicidal behavior. For BD, long-term use of lithium has particularly substantial evidence of association with reduced risk of suicide and attempts. This evidence is reviewed here, focusing on prevention of completed suicide and comparing these effects of lithium to placebo and to other psychotropic drug treatments.

The average international (183 countries), adult, general population, age-standardized suicide rate in 2015 was 10.5 (95 % confidence interval [CI]: 9.56–11.3) per 100,000 per year (0.0105 % per year) overall, 16.1 (14.6–17.5) for men and 5.24 (4.68–5.80) for

women (male/female ratio = 3.07) [6]. The standardized mortality ratio for suicide in clinical groups versus the comparable general population is highest in mood disorders, usually at 10–20-fold [7]. In BD, the reported suicide rate (per 100,000 per year) in 26 studies averaged 164 (CI: 5.0–324), and in 7 studies the rate was 366 in men and 217 in women [8]. These rates are, respectively, 20- and 41-times higher than among men and women in the general population. The rate of suicide attempts among BD patients in 101 studies averaged 4240 per 100,000 per year (CI: 3780–4700) (25.9-times above the suicide rate) and was 1.40-fold higher among women than men [9]. However, these comparisons should be considered with caution as they derive from different geographic populations. 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 [10, 11]. Moreover, rates of suicides and attempts are at least as high among type II as in type I BD patients [9, 12].

Among BD patients, suicide risk remains high despite the growing variety of treatments with effective mood-stabilizing effects [13]. This disparity almost certainly reflects the great difficulty of effectively treating depressive and mixed manic-depressive states of BD [14–21], which represent the majority of residual morbidity with clinically applied long-term treatments [22–24]. Modern psychiatric treatments, rapid hospitalization, and even electroconvulsive treatment (ECT) may be useful as short-term interventions but lack evidence of long-term suicide preventive effects [25–29].

Assessment of treatments for suicide prevention

Difficulties in conducting therapeutic studies to prevent suicide 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, as well as difficulties in identifying, recruiting, and retaining subjects; and the rarity of suicide or even attempts as outcome measures [25, 26, 30, 31]. An additional potential limitation of all studies of any therapeutic effect is that patients who accept, tolerate, and sustain any type of long-term treatment may be favorably self-selected and not entirely representative of all clinically encountered patients. Many studies rely on surrogate outcomes such as self-injurious acts, communicated suicidal plans or ideation, or interventions to avoid suicide—all of which may or may not precede a suicide attempt. In addition, definitions and prevalence of nonfatal suicide-related behaviors, and their quantitative, predictive association with suicide itself, are matters of discussion related to distinctions among ideation, plans, and attempts, including their intent and potential lethality [31]. Definitions and quantification of suicidal ideation are especially problematic. Notably, the predictive value for suicidal behavior of passive ideation, such as thoughts of weariness of life, probably differs from that of active ideation with specific planning and preparing for a suicide attempt. Moreover, in research on suicide ideation and behavior, crucial assessment of intent to die often is neglected [32–34].

The relative rarity of suicide requires assessment of large subject-samples for extended times to detect a signal in studies of treatment effects or involves pooling data across multiple studies. In addition, even randomized-controlled treatment trials (RCTs) have shortcomings for the study of prevention of suicidal behavior. They include potential unreliability of essentially incidental and passive ascertainment of suicidal thoughts or behaviors based on typical "adverse event reporting" procedures under conditions not designed to detect and assess suicidal events actively and explicitly. However, efforts are being made to include regular, standardized assessments of suicidal behaviors and other specified "adverse events" in trials of new, centrally active drugs [33]. In addition, the relatively short duration of most treatment trials is unlikely to yield statistically adequate numbers of suicidal behaviors. Another technical limitation to assessing suicidal risks in treatment trials is that observed rates of events presumed to be related to suicide rarely are corrected for actual and matched exposure times for treatments given, let alone for individual subjects. Such matching for exposure can matter. For example, earlier dropping out of a trial arm involving placebo treatment can artifactually make active drug treatment seem "riskier" than placebo in association with longer exposure and observation. Despite all these limitations, RCTs are the most reliable sources of information about the effect of treatment on even uncommon outcomes including suicidal behaviors. Accordingly, this review emphasizes assessment of long-term clinical trials involving randomization to lithium compared to placebo or to other active agents for the treatment of mood disorder patients.

Methods

Initially, we summarized findings from previous reviews on the topic that could include fatal or nonfatal suicidal behavior and both BD and MDD subjects. In addition we considered studies involving randomized treatments that compared lithium to placebo or other active medicinal treatments and involved suicide as the specific outcome. We included all identified studies reporting on suicides in RCTs with at least 1 suicide or attempt in either arm of the study; studies with no suicidal acts in either trial arm were considered uninformative and not included. Candidate studies for analysis were identified from a recent systematic review and update [35, 36], our own earlier reviews [37, 38], and by an additional, systematic, computerized literature search of the PubMed database for the past 5 years.

We identified 12 trials comparing risks of suicide with lithium versus placebo or other treatments in 10 reports [39–48]. Alternative treatments included 4 studies of lithium versus placebo, 3 versus an antidepressant (amitriptyline), 4 versus 1 of 2 anticonvulsants (carbamazepine, lamotrigine), and 1 versus an antipsychotic (olanzapine). For meta-analysis we used the Peto method to deal with typically small numbers of suicides (numerators) as well as fixed-effects modeling as interstudy heterogeneity was not significant. We pooled all diagnoses and comparison treatments as well as meta-analyzed BD and MDD patients separately and compared lithium versus placebo or versus other agents. Finally, we used meta-regression analysis to address the possible influence of various factors of interest in the outcome of the primary, pooled meta-analysis. Analyses used commercial software (Statview.5, SAS Institute, Cary, NC) for spreadsheets and STATA.13 (StataCorp, College Station, TX) for computations. Data are presented as means ± standard deviation (SD) or with 95 % CI.

In addition, we summarized findings from correlational studies that compared lithium concentrations in local drinking water with publicly reported suicide (and homicide) rates in the same regions, based on a recent systematic review [49] as well as literature searching of PubMed for the last 5 years. Findings were summarized descriptively owing to the variety of reported outcomes. Finally, we summarized recent progress with the use of treatments other than lithium aimed at reducing suicidal risk, concentrating on mood-stabilizing anticonvulsants, antidepressants, and antipsychotics.

Results

Previous findings about lithium

We summarized reported findings regarding risks of suicides or attempts among patients given randomly assigned, long-term treatment with lithium or alternative treatments and meeting modern diagnostic criteria for BD or any recurrent major affective disorder or only MDD [37, 50–52]. These studies found highly significantly lower rates of suicidal behavior during treatment with lithium, and similarly against both suicides and attempts, in BD, broad samples of mood-disorder patients, and MDD patients specifically, and in comparison with mood-stabilizing anticonvulsants (▶ **Table 1**). These effects were sustained when corrected for reported exposure times in studies of MDD patients and in comparisons of lithium to carbamazepine, lamotrigine, or valproate (▶ **Table 2**).

Suicide with lithium vs. other treatments in randomized trials

Among the 12 long-term randomized trials, 6 involved only BD subjects and another 6 had mainly MDD patients or both BD and MDD cases. Patients were followed for an average of 92.2 (95 % CI: 67.0–117) weeks, with an average daily trough serum lithium concentration of 0.73 (0.64–0.81) mEq/L (▶ **Table 2**). With lithium treatment, there were 3 suicides among 974 patients (0.31 % [0.06–0.90]), compared to 21 suicides among 1070 subjects treated with placebo or other active agents (1.96 % [1.22–2.98], Fisher's exact p = 0.01). The risk of suicide with lithium treatment was lower among both BD (p = 0.05) and MDD or MDD + BP cases (p = 0.01), and compared only to placebo (p = 0.04) or to other active drugs (p = 0.02) (▶ **Table 2**).

These findings based on simple weighted averages also were sustained by meta-analyses. That is, lithium treatment was associated highly significantly with lower suicide risk than with placebo or with other active treatments, overall (z = 3.65, p < 0.0001), as shown in ▶ **Fig. 1**. This trend was followed in 10/12 trials even though the numbers of suicides per trial was small, as expected (0–1 with lithium, 0–6 with other treatments). Exceptions (lithium apparently less effective) were 1 trial each of lithium versus olanzapine or lamotrigine, in which there was only 1 suicide with lithium and none with the other agents. In addition, suicide was significantly less frequent with lithium versus placebo (z = 2.47, p = 0.01) and versus other drug treatments (z = 2.79, p = 0.005). Meta-regression analysis following the overall meta-analysis indicated that both diagnosis (z = 1.00, p = 0.32) and comparison treatment (placebo or other drugs; z = 0.45, p = 0.65) lacked significant influence on the outcome. In addition, the duration of treatment (20–130 weeks; mean = 1.77 [1.29–2.25] years; z = 1.07, p = 0.28), mean serum lithium concentration (z = 1.67, p = 0.10), and year of publication (z = 0.12, p = 0.90) also lacked influence on the outcome of the meta-analytic comparison of lithium to all other treatments.

Lithium in drinking water

Finally, for lithium, we carried out a systematic search and summarized findings of a growing number of studies that evaluated associations of the low concentrations of lithium in local drinking water with reported suicide or homicide rates in the same communities or regions. We found 18 such reports [53–70]. Several of these reports involved an apparently single set of data from Austria, and their findings are pooled [57–59, 62]. Most of the studies (12/15) found a significant, inverse association between local lithium levels and local rates of suicide or homicide, though sometimes (inconsistently) only in men or women or seemingly modified by local climatic conditions or altitude. One notable study involving a national Danish sample found no such association when individual people were considered rather than relying on group (ecological) associations [63]. Two studies found a protective relationship with

▶ **Table 1** Risk of suicides or attempts with versus without long-term lithium treatment.

Outcome	Studies	RR (95 %CI)	*z*-score	*p*-value
All suicidal acts[a]	34	0.241 (0.176–0.331)	8.82	< 0.0001
Suicides	26	0.252 (0.169–0.377)	6.71	< 0.0001
Attempts	19	0.211 (0.132–0.337)	6.52	< 0.0001
BD only	14	0.187 (0.126–0.279)	8.28	< 0.0001
MDD only[b]	17	0.215 (0.158–0.292)	9.82	< 0.0001
Acts: lithium vs. anticonvulsants[c]	6	0.350 (0.254–0.437)	5.24	< 0.0001

[a] Includes suicides and attempts among BD and MDD patients not considered separately. Studies with no suicidal events in either treatment arm (both numerators = 0) are excluded.

[b] Adjusted for exposure time (rates: lithium, 0.174 % per year vs. no lithium, 1.48 % per year) incidence rate ratio (IRR) = 8.71 (CI: 2.10–77.2); exact p = 0.0005; MDD subjects only.

[c] Adjusted for exposure time (rates: lithium, 0.278 % per year vs. anticonvulsants [carbamazepine, lamotrigine, or valproate], 0.884 % per year) IRR = 2.96 (CI: 2.32–3.79); exact p < 0.0001; BD subjects only.

Data are adapted from previous meta-analytic studies [37, 50–52].

▶ **Table 2** Suicide risk in randomized trials of lithium vs. other treatments for major affective disorders.

Trial	Year	Lithium			Other Rx			Dx	Follow-up (wk)	Age	[Li^+] (mEq/L)	Other Rx
		Suicide	No Suicide	Risk (%)	Suicide	No Suicide	Risk (%)					
Prien et al.	1973	0	45	0.00	1	38	2.56	MAD	104	39	0.80	PBO
Prien et al.	1973	0	101	0.00	1	103	0.96	BD	104	39	0.70	PBO
Glen et al.	1984	0	57	0.00	1	49	2.00	MDD	128	45	0.90	AMI
Greil et al.	1996	0	40	0.00	1	40	2.44	MDD	128	41.5	0.60	AMI
Thies-Flechtner et al.	1996	0	46	0.00	1	46	2.13	MDD	130	41.5	---	AMI
Thies-Flechtner et al.	1996	0	87	0.00	6	82	6.82	BD	130	41.5	---	CBZ
Greil et al.	1997	1	86	1.15	5	83	5.68	BD	128	41.5	0.60	CBZ
Bauer et al.	2000	0	14	0.00	1	14	6.67	MDD	20	≥ 18	0.75	PBO
Calabrese et al.	2003	0	121	0.00	1	220	0.45	BD	78	≥ 18	0.58	LTG
Tohen et al.	2005	1	213	0.47	0	217	0.00	BD	52	≥ 18	0.75	ONZ
Lauterbach et al.	2008	0	84	0.00	3	80	3.61	MDD	52	≥ 18	0.70	PBO
Licht et al.	2010	1	77	1.28	0	77	0.00	BD	52	≥ 18	0.90	LTG
Weighted means (95 % CI)	**n = 12**	**3/974 0.308 % (0.06–0.90)**			**21/1070 1.96 % (1.22–2.98)**			**6 BD 6 MDD or MAD**	**92.2 (67.0–117)**	**≥ 18**	**0.728 (0.645–0.811)**	**5 Rxs**

Some MDD trials include a minority of BD. Studies with no suicides with lithium or other treatments are not included.

Overall Fisher's exact p = 0.001; with active treatments only, p = 0.02, and vs. placebo, p = 0.04; for BD subjects, Fisher's exact p = 0.05; for MDD subjects, p = 0.01.

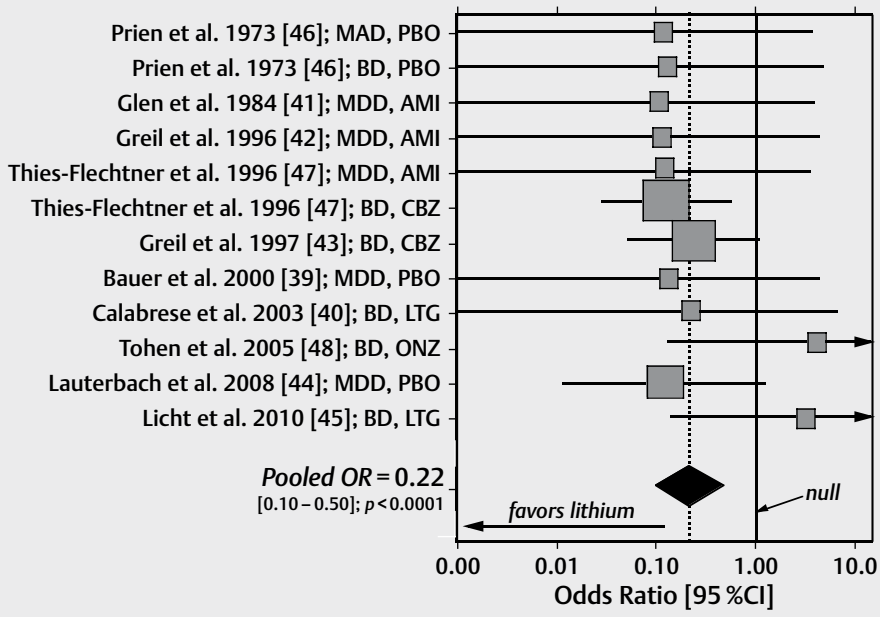
AMI: amitriptyline; CBZ: carbamazepine; LTG: lamotrigine; MAD: major affective disorders; ONZ: olanzapine; PBO: placebo; Rx: treatment.

Data are derived from previous reviews [35, 36].

homicide rates in addition to suicide rates [54, 55]. Although these findings are not entirely consistent, they are suggestive that a favorable relationship might exist between higher local concentrations of lithium in drinking water and less violent behavior (suicide or homicide). Notably, concentrations of lithium in ground water were low (averaging 2–83 µg/L or 6–18 µEq/L) and far below serum concentrations considered to be therapeutic in BD (600–1200 µEq/L) [13]. Nevertheless, it might be that years of exposure to even such low concentrations of lithium can have biological effects (▶ **Table 3**).

Other treatments: anticonvulsants

There is little research that directly compares suicidal risks during treatment with proved or putative mood-stabilizers other than lithium [47, 71–74]. However, several studies found substantially lower average risks of suicidal behavior with lithium than with carbamazepine or valproate among BD or schizoaffective patients [47, 71, 75–79]. In a meta-analysis [75], we compared protective effects against suicidal behavior of lithium versus several mood-stabilizing anticonvulsants (mainly valproate and some use of carbamazepine or lamotrigine) in 6 direct comparisons (half involved randomized assignments to treatments) including more than 30,000 patients. Subjects were at risk longer with lithium than with an anticonvulsant (31 vs. 19 months), which may tend to increase risk of suicidal events with lithium. Nevertheless, the observed rate of suicidal acts averaged 0.3 % per year during treatment with lithium versus 0.9 % per year with anticonvulsants, yielding a highly significant meta-analytically pooled risk ratio of 2.86 (CI: 2.29–



▶ **Fig. 1** Forest plot of comparative risk of suicide during long-term, randomized-controlled treatment (mean: 92 [67–117] weeks) with lithium carbonate versus placebo (PBO) or a psychotropic drug (AMI: amitritpyline; CBZ: carbamazepine; LTG: lamotrigine; or ONZ: olanzapine) among 1070 subjects with mood disorders (BD: bipolar; MAD: major affective; or MDD: major depressive disorder). Studies with no suicides in any treatment-arm are omitted; due to low numerators, Peto's method for meta-analysis was employed. In 10/12 comparisons, lithium was associated with fewer suicides (in the 2 exceptions with lithium vs. olanzapine [48] or lamotrigine [45], the numerators [suicides] differed by only 1 vs. 0). The overall, pooled odds ratio (OR with 95 % CI) = 0.222 [0.099–0.497]; z = 3.65, p < 0.0001. Meta-regression found no effect of the comparison treatment, diagnosis, weeks of treatment, or year of publication. Separate meta-analyses found significant superiority of lithium versus placebo (pooled OR = 0.132 [CI: 0.026–0.656]; z = 2.47, p = 0.013) or other drugs (OR = 0.264 [0.104–0.674]; z = 2.79, p = 0.005), and in both BD (OR = 0.290 [0.108–0.784; z = 2.44, p = 0.015) and MDD or MDD cases (OR = 0.131 [0.033–0.524]; z = 2.87, p = 0.004).

3.57; p < 0.0001). This finding indicates a nearly 3-fold superiority favoring lithium over the few anticonvulsants tested in this way. However, addition of valproate as well as lithium yielded lower suicidal risks compared to treatment with only antipsychotics in a Danish study of over 16,600 persons sampled for 6 years [80]. In other studies valproate and lithium had similar associations with suicidal behavior, suggesting that both may reduce suicidal risk [73, 81–83]. Taken together, these studies suggest that anticonvulsants may have some beneficial effects on suicidal behavior, including patients with major affective disorders, though possibly less than lithium.

A contrasting perspective arose from a U.S. Food and Drug Administration (FDA) meta-analysis of placebo-controlled trials involving 11 anticonvulsants, submitted for regulatory review [76]. This review found more prevalent, incidentally reported suicidal ideation and behavior with anticonvulsants than with placebo, at least among patients with epilepsy, though not in psychiatric patients [76]. The lack of such adverse effects among psychiatric patients was supported by several other studies [80, 82, 84–86]. In conclusion, research on anticonvulsants and suicidal risk remains limited, inconsistent, and inconclusive, although lithium appears to be superior in preventing suicidal behavior, based on direct comparisons (▶ **Table 1** and ▶ **Table 2**).

Other treatments: antidepressants

The strong association of depressive morbidity with suicide in mood-disorder patients would suggest that treatment with antidepressants might reduce suicidal risk. Evidence for short- and long-term efficacy of antidepressant treatment in unipolar MDD is substantial [13, 19, 87–93] but not universally accepted [93]. 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 remains insufficiently studied [19, 94, 95]. Antidepressant response in BD may be better among patients without agitated-dysphoric forms of depression or mixed features [95] and without previous rapid-cycling [97]. Conversely, suicidal risk is likely to increase with antidepressant treatment 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 juvenile patients [28, 98–109]. An emerging view is that agitated-dysphoric depression can include "mixed-features" based on DSM-5 diagnostic criteria [11, 110]. Studies of associations of antidepressant treatment and suicidal behavior vary widely in design, are limited mainly to MDD, and provide inconsistent evidence concerning suicides or attempts, which have usually been noted incidentally as adverse effects rather than as an explicit outcome measure.

▶ **Table 3** Studies of lithium in drinking water and risk of suicide or homicide.

Reports	Location	Regions Sampled	[Li^+] (µg/L)	Findings
Dawson et al. 1972	Texas	24	0–139	Less suicide & homicide with higher [Li]; urine [Li] correlated with water [Li]
Schrauzer & Shrestha 1990	Texas	27	0–160	Less suicide with higher [Li], only ≥ 70 ug/L
Ohgami et al. 2009	Japan	18	0.7–59	Less suicide with higher [Li]
Kabacs et al. 2011	East England	47	1–21	No association
Kapusta et al. 2011; Helbich et al. 2012, 2013, 2015	Austria	99	11–27	Less suicide with higher [Li], only at lower altitudes, not in women
Blüml et al. 2013	Texas	226	2.8–219	Less suicide with higher [Li]
Sugawara et al. 2013	Japan	40	0–13	Nonsignificantly less suicide with higher [Li], especially in women
Giotakos et al. 2013	Greece	34	11–21	Less suicide with higher [Li]
Giotakos et al. 2015	Greece	34	11–21	Less homicide with higher [Li]
Ishii et al. 2015	Japan	274	0–130	Less suicide with higher [Li], only in men
Pompili et al. 2015	Italy	145	0.1–61	Less suicide with higher [Li], mainly in women in 1980 s
Shiotsuki et al. 2016	Japan	153	0.1–43	Less suicide with higher [Li], only in men, but also with more sunshine, higher ambient temperature & less rain
Knudsen et al. 2017	Denmark	3.7 M individuals	0.6–31	No association
König et al. 2017	Chile	12	1.0–207	Less suicide in high-[Li] region (high Atacama Desert)
Liaugaudaite et al. 2017	Lithuania	22	0.5–36	Less suicide with higher [Li], only in men
Totals/averages	**9 countries**	**1121 regions**	**2.06 (0–4.29) to 83.4 (41.5–125)**	**12/15 inverse correlation 4/12 in men only 2/12 in women mainly**

Many of these studies were reviewed by Vita et al. (2015). Lithium concentrations in drinking water (usually based on mass spectroscopy assays) ranged from 0 to 219 and averaged 2–83 µg/L or 0.30 [0–0.62] to 12.0 [6.0–18.1] µEq/L. Note that 2 studies found less homicide with higher concentrations of lithium in drinking water [55, 68]. Knudsen et al. [63] found no association of exposure to lithium in drinking water in Denmark and risk of suicide in bipolar disorder.

There is some evidence of lower suicidal risk during trials of treatment with an antidepressant versus placebo, mostly among adult MDD patients. Most of this evidence is based on questionable extraction of data from specific items in depression symptom-rating scales, which are weighted toward suicidal ideation [104–106, 109, 111–113].

Lower rates of suicide with greater use of antidepressants have been reported in some pharmacoepidemiological studies based on finding inverse correlations between use of antidepressants and suicide rates in some regions or countries, particularly following the introduction of modern antidepressants in the 1990 s [114]. However, such ecological-correlational studies have not yielded consistent findings across countries or regions. Correlations of interest have largely been limited to Nordic countries and the United States but appear to be randomly distributed across the world [19, 98, 113–115]. Moreover, in the United States and Sweden, at least, declining suicide rates were noted at least a decade before introduction of fluoxetine as the first clinically successful modern antidepressant in the late 1980 s [19, 113, 114]. In general, such correlational analyses are fraught with potential confounding by uncontrolled factors [114, 116].

Additional studies involving mainly retrospective observations of large cohorts of depressed patients and case-control comparisons have yielded inconsistent and inconclusive findings [19, 100, 102]. In one clinical follow-up study, during treatment, monthly assessments indicated that 81 % of subjects 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 [117]. Not all patients who had started treatment were followed-up, and details of suicidal status during the initial days of treatment were limited. 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, reducing their ability to identify relatively rare suicide-related outcome events. Moreover, as their identification usually has been based on incidental and passively acquired nonexplicit assessments of suicidal outcomes, some events may be missed, even after having made efforts to exclude potentially suicidal subjects. This situation may change as the FDA makes efforts to require explicit rating of suicidal status in trials of centrally active substances [34]. Despite

efforts to limit suicidal risk in treatment trials, rates of suicidal behaviors may be at least as high in antidepressant RCTs (usually involving acutely depressed subjects) as in cohort studies of MDD patients in various clinical states [98, 103, 107]. For example, suicide rates pooled across a large number of trials of modern and older antidepressants or placebo were similar with all treatments, averaging 0.862 % per year, or 57 times above the approximate average international general population rate of 015 % per year and 17 times above the reported rate of approximately 0.050 % per year in outpatients in various phases of MDD [89, 98, 108, 111, 113]. Another caveat is that the high observed rates from the cited meta-analyses of controlled trials may be exaggerated by annualizing observed rates based on brief exposure times (typically 6–12 weeks) in most trials in acute depression (for example, the apparent, annualized rate of 1 suicidal event among 100 subjects in a 12 week-trial [1.0 %] would be 4.3 % per year). An additional concern is that, short of well-matched exposure times, it is possible that suicidal risk may vary artifactually between shorter and longer exposure times, for example, obscuring potential benefits of active treatments if early dropout rates are more likely with placebo. Most studies and meta-analyses have found only minor differences or somewhat lower rates of suicidal behaviors in depressed patients treated with antidepressants versus a placebo [118–120]. Others have detected indications of somewhat greater risks, mainly of suicidal ideation, with antidepressants versus placebo controls, particularly in juveniles and very young adults, but decreased risks in older adults, with an overall outcome of no difference [101, 105, 112, 121, 122]. These analyses assume that the trials considered remained well randomized despite potentially dissimilar dropout rates and that temporal exposures in both drug and placebo arms remained well balanced over time. They also assume that such surrogate measures as suicidal ideation or even minor self-injurious behaviors, identified 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 suicidal 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. At this time, it is not possible to compare effects on suicidal behavior with antidepressants versus lithium, in particular. Most of the evidence regarding suicidal risk in association with antidepressant treatment pertains to MDD patients, whereas long-term research on antidepressant treatment in BD remains far less well developed, although innovative treatments for depressive phases of BD are emerging and should be evaluated for potential antisuicidal effects [20, 123, 124]. Finally, 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, in which suicidal risks are elevated.

▶ **Table 4** Summary of findings from studies of pharmacological treatments aimed at reducing suicidal risks other than lithium.

Treatment	Timing	Findings	Limitations
Anticonvulsants	Short- and long-term effects are not established.	Valproate most studied. Anticonvulsants may be less effective vs. suicide than lithium.	Suicidal behaviors incidental, not explicit outcomes. FDA proposal that anticonvulsants may increase suicidal risk is not supported for mood disorders.
Antidepressants	Short- and long-term effects on suicide risk not established.	Inconsistent findings in controlled & uncontrolled trials in MDD; little research in BD; may increase risk of nonlethal suicidal behavior at ages < 25 years but decrease risk in older adults.	Studies lack of data for actual, matched exposure times. Suicidal status usually assessed passively and incidentally rather than explicit outcome measure.
Antipsychotics	Short- and long-term effects on suicide risk are not adequately tested in mood disorders.	Clozapine: only FDA-recognized "antisuicidal" treatment (schizophrenia only). Modern antipsychotics require further study, especially those with antidepressant effects in BD.	Clozapine's status based on one controlled trial with no effect on mortality (surrogate outcome measures only).

Adapted from Tondo and Baldessarini [28].

Other treatments: antipsychotics

With the exception of clozapine for schizophrenia [4, 5], no other treatment has regulatory approval of an indication for an antisuicidal effect, including lithium. 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 clinical monitoring that 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 [5]. Nevertheless, 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 United States [125].

In the past several years, several epidemiological studies have added to the conclusions that long-term antipsychotic treatment is associated with reduced all-cause mortality rates, and risk of suicide in particular, and that clozapine is probably more effective against suicidal risk than other older or newer antipsychotic agents [126–129]. However, almost all of this work involves patients diagnosed with schizophrenia rather than mood disorders.

Impressions arising from the preceding overview of effects of treatments other than with lithium on risk of suicidal behavior are summarized in ▶ **Table 4**.

Discussion

The findings reviewed here illustrate many difficulties for the design, conduct, and interpretation of studies aimed at testing for antisuicidal effects of specific treatments. The ethics of studies with suicide as a potential outcome are daunting and make use of placebo-controlled conditions in randomized trials 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, even 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. It is 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. Such trials are rare, probably reflecting 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 drug. 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 BD and in mixed, dysphoric-agitated states, and perhaps also with anger, aggression, or impulsivity and insomnia—all of which are particularly prevalent in BD patients, but also occur in MDD, and contribute to suicide risk. In such conditions, antidepressants can 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 BD or MDD patients calls 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, based on clinical observations, although this clinical impression required experimental testing.

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 [35, 52, 130–133]. Alternatively, lithium may have specific effects against suicide independent of its mood-stabilizing actions, as suicidal risk has been found to be reduced even among patients whose primary mood symptoms had not responded well to lithium [134–136]. 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 of lithium with modern antipsychotic drugs are needed.

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 ECT 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.

Conflict of Interest

The authors declare no conflict of interest.

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