

# Pharmacologic Interventions in Suicide Prevention

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Suicide rates vary by country and by mental disorder. What does not vary, though, is that the number of suicides per year is not declining and that a person with a mental disorder is more likely to commit suicide than one without such an illness. Although many pharmacologic interventions have been reported to reduce the risk of suicide among mentally ill patients, especially those with bipolar disorder, the effects of such interventions are inconsistent at best. Lithium is the only medication for which the evidence consistently shows an antisuicidal effect.

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Suicide rates vary from country to country, as does the number of suicides per year.<sup>1</sup> As Table 1 shows, most countries saw an increased number of suicides from 1970 to 1988. In a few, such as Czechoslovakia, Sweden, and West Germany, the suicide rate decreased, and in others, such as the United States and Austria, the rate stayed about the same. These differences might be attributed to climate, temperature, religion, the rate of substance abuse, or the way in which the data were recorded, but no single explanation can account for such a wide variation. Overall, though, the suicide rate increased during those 18 years.

Suicide rate also varies considerably among mental disorders. Most suicides are associated with pathology of some kind (Table 2), and most are seen in patients with affective disorders. Notably, the rates among patients with depressive disorders and bipolar disorders are similar. The ratio of attempted to completed suicides is estimated to be about 18 or 20 to 1 in the general population.<sup>2</sup> However, older estimates of the risk of suicide among patients with psychiatric diagnoses have recently been revised (Table 3).<sup>3</sup> The widely accepted risk of 15% for affective disorders<sup>4</sup> is much too high, according to Inskip et al.,<sup>3</sup> who examined more recent data and calculated a risk of 6%. These authors also found that suicide attempts are more common soon after onset of mental illness, a finding that is confirmed by Baldessarini and colleagues<sup>5</sup> report that half the suicide attempts among a group of patients with bipolar disorder,

followed for up to 40 years from illness onset, occurred within the first 7.5 years after illness onset (Figure 1). Although many pharmacologic interventions have been reported to reduce the risk of suicide among mentally ill patients, especially those with bipolar disorder, the effects of such interventions are inconsistent at best. Lithium is the only medication for which the evidence consistently shows an antisuicidal effect.<sup>2,6–11</sup>

## TYPES OF INTERVENTIONS

What is the effect of pharmacologic interventions and electroconvulsive therapy (ECT) on suicide risk? The ethical and methodological difficulties inherent in exploring this question are many; published reports on the topic are usually derived from studies that focus on affective disorders, not suicide per se. However, these reports provide some insight into the question.

### Antidepressants

Older antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, as well as the newer antidepressants, the selective serotonin reuptake inhibitors (SSRIs), have an inconsistent effect on suicide risk. Isacson and colleagues<sup>12</sup> found that as the use of antidepressants from all classes increased in the Swedish general population by 51%, the number of suicides decreased by 10%. Even though the TCAs can be lethal in overdose, the authors found that, among the suicides in Sweden from 1992 to 1994, only 0.7% were the sole result of antidepressant overdose. A higher risk for suicide was seen in this retrospective study with SSRIs, which dominated the Swedish market during the study period, than with the reference drug, the TCA amitriptyline. The authors suggested that the SSRIs may be less effective than the older antidepressants for severe depression and that desire for efficacy may outweigh concerns about toxic or lethal overdose when dealing with severely depressed patients.

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**Table 1. Suicide in Europe and the United States, 1970–1988<sup>a</sup>**

Country	1970	1975	1980	1985	1988
Hungary	34.8	38.4	44.9	44.4	41.3
Finland	21.3	25.0	25.7	24.6	28.4
Austria	24.2	24.1	25.7	27.7	24.4
Denmark	21.5	24.1	31.6	27.7	26.0
Switzerland	18.6	22.5	25.7	25.0	22.4
Belgium	16.5	16.2	21.7	23.1	22.7
France	15.4	15.8	19.4	22.6	20.7
Czechoslovakia	25.2	21.9	20.0	18.9	17.7
Sweden	22.3	19.4	19.4	18.2	18.9
West Germany	21.3	20.9	20.9	20.7	17.6
Norway	8.4	9.9	12.4	14.0	16.8
Iceland	13.2	10.1	10.5	13.2	14.0
United States	11.2	12.2	12.1	12.0	11.2
Poland	11.2	11.3	10.7	13.3	12.2
Netherlands	8.1	8.9	10.1	11.3	10.3
United Kingdom	7.9	7.5	8.8	9.0	8.7
Portugal	7.5	8.5	7.4	9.7	8.0
Italy	5.8	5.6	7.3	8.3	7.7
Ireland	1.8	4.7	6.3	7.8	7.5
Spain	4.2	3.9	4.4	6.5	7.2
Greece	3.2	2.8	3.3	4.1	4.1
Total	14.5	15.0	16.7	17.4	16.8

<sup>a</sup>Adapted from Mäkinen and Wasserman.<sup>1</sup> Rates per 100,000.

**Table 2. Psychopathology in Suicide<sup>a</sup>**

Disorder	Percentage of Suicides
Any psychiatric disorder	90
Depressive disorders	65
Unipolar and bipolar disorders	60
Substance use disorder	40
Schizophrenia	8

<sup>a</sup>Data from Tondo and Baldessarini.<sup>2</sup> Ratio of attempted to completed suicides is 18–20 to 1.

A placebo-controlled study of fluoxetine<sup>13</sup> found that fluoxetine offered no more protective antisuicide effects than did placebo among patients with recurrent brief depression. Teicher et al.<sup>14</sup> reported a case series in which 6 patients developed obsessive suicidal ideation after 2 to 7 weeks of fluoxetine therapy that abated after fluoxetine discontinuation. None of these patients was suicidal before fluoxetine treatment. However, a meta-analysis<sup>15</sup> of studies comparing fluoxetine with placebo or a TCA and fluoxetine plus concomitant medication (usually a sedative) with fluoxetine monotherapy found that fluoxetine-treated patients had a reduced score on the suicide item of the Hamilton Rating Scale for Depression independent of whether sedatives were used. Among patients not taking sedatives, fluoxetine was superior to the TCAs in improvement at endpoint. No other comparisons of suicidality were statistically significant.

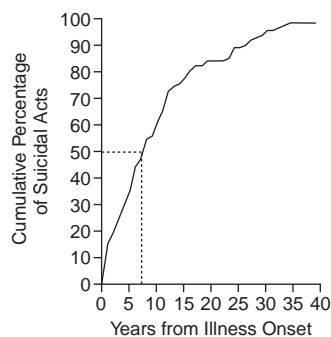
In their review of antidepressants and suicide, Müller-Oerlinghausen and Berghöfer<sup>16</sup> concluded that possible toxicity should be a minor concern compared with efficacy since antidepressants are rarely the means of committing suicide, that drugs with serotonergic mechanisms have not been proved effective in preventing suicide, and

**Table 3. Suicide Rates in Psychiatric Disorders**

Disorder	1977 Estimates (%) <sup>a</sup>	1998 Estimates (%) <sup>b</sup>
Affective disorders	15	6
Alcoholism	15	7
Schizophrenia	10	4

<sup>a</sup>Data from Miles.<sup>4</sup>

<sup>b</sup>Data from Inskip et al.<sup>3</sup>

**Figure 1. Temporal Distribution of 104 Reported Life-Threatening Suicidal Acts Among 346 Bipolar I and II Disorder Subjects<sup>a</sup>**

<sup>a</sup>Reprinted from Baldessarini et al.,<sup>5</sup> with permission.

that drugs with possible excitatory effects should not be used in suicidal patients. They also pointed out that the long-term impact of antidepressant treatment on suicide is unclear.

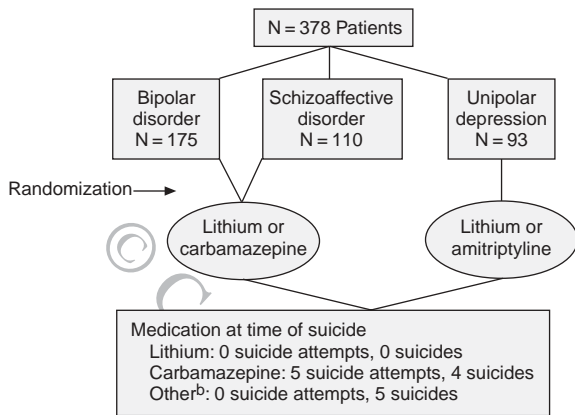
### Electroconvulsive Therapy

ECT appears to be effective in preventing suicide in the short term. In a reanalysis of their previously published data, Prudic and Sackeim<sup>17</sup> found that scores on the suicide item of the Hamilton Rating Scale for Depression decreased after patients received ECT. Although the literature supports their finding, the long-term benefits of ECT on suicide risk are unclear. In a retrospective study of 45 psychiatric inpatients who committed suicide and 45 matched inpatient controls, Sharma<sup>18</sup> found no difference between the 2 groups in the rate of ECT during the last 3 months of hospitalization. In Finland, though, Isometsä et al.<sup>19</sup> found that only 0.14% of all suicides in a 12-month period had received ECT in the 3 months prior to suicide; the authors concluded that this low number may be the result of a preventative effect of ECT but admitted that the results were far from conclusive.

### Antipsychotics

Antipsychotics have an uncertain effect on suicide risk as well. A particularly troubling side effect of older-generation antipsychotics, akathisia, has been reported as the contributing factor in suicide attempts<sup>20</sup>; in that case study of 2 patients, one had received haloperidol and the

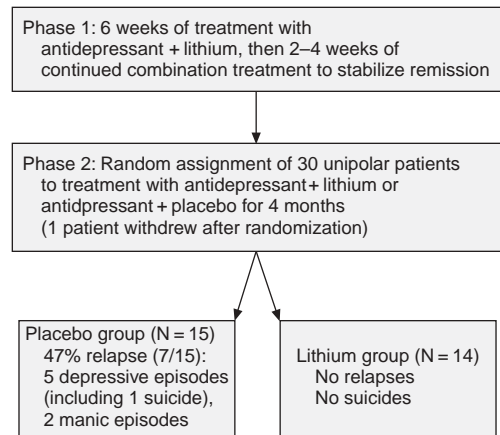
**Figure 2. Effect of Prophylactic Treatment on Suicide Risk in Patients With Major Affective Disorders<sup>a</sup>**



<sup>a</sup>Data from Thies-Flechner et al.<sup>6</sup>

<sup>b</sup>Other category includes antidepressants, neuroleptics, or no medication.

**Figure 3. Double-Blind, Placebo-Controlled Trial of Lithium Augmentation of Antidepressant Continuation Treatment of Unipolar Major Depression<sup>a</sup>**



<sup>a</sup>Data from Bauer et al.<sup>8</sup>

**Table 4. Suicidal Risk in 310 Bipolar Disorder Patients<sup>a</sup>**

Variable	Value
<b>Risk rates</b>	
Persons with suicidal acts	18.7% (58/310)
Suicidal acts per 100 patient-years	1.723
Fatalities per 100 persons	2.581
Fatalities per 100 patient-years	0.301
<b>Fatalities</b>	8.9% (8/90)
Duration of illness at first act, y, mean ± SD	7.95 ± 9.20
Current age, y, mean ± SD	33.6 ± 12.0
<b>Rate of suicidal act (acts per 100 patient-years)</b>	
Before lithium treatment	2.30
During lithium treatment	0.355
After discontinuing lithium	3.51 <sup>b</sup>
1st year after discontinuing lithium	7.11
Later times after discontinuing lithium	2.29

<sup>a</sup>Data from Tondo et al.<sup>7</sup>

<sup>b</sup>9.9-fold higher than during lithium treatment,  $p < .001$ .

other, fluphenazine. However, fluphenazine was recently shown to have a positive impact on suicidal behaviors in patients admitted to a psychiatric emergency service after attempting suicide.<sup>21</sup> In that study, both low-dose and high-dose groups saw a reduction in the number of self-harm actions. Among the atypical antipsychotics, clozapine in particular has been associated with a lower rate of life-threatening suicide attempts with a high probability of success in schizophrenic patients.<sup>22,23</sup>

### Lithium

Lithium has been shown to consistently reduce the risk of suicide in patients with bipolar disorder. In a comparison of lithium with carbamazepine and amitriptyline (Figure 2), 378 patients were followed for 2½ years.<sup>6</sup> Of the 9 patients who committed suicide, none had received lithium or were taking lithium at the time. Six suicides occurred

during the first 6 months of follow-up. The authors concluded that lithium had a prophylactic antisuicide effect that may have been unrelated to its efficacy as a mood stabilizer. Carbamazepine, on the other hand, seemed to afford no such protective effect; the suicide rate of the carbamazepine-treated group was no different from that seen in untreated patients.

In a 1998 report, Tondo et al.<sup>7</sup> prospectively followed 310 patients with bipolar disorder (types I and II were included) for a mean of 6.4 years during lithium treatment. The time from illness onset to start of lithium treatment (mean = 8.3 years) was also evaluated. The authors found that the risk of suicide before lithium treatment was 6.5-fold higher than that during lithium treatment; lithium discontinuation increased the risk 9.9-fold. Suicidal acts were sharply reduced during lithium treatment (Table 4). In another review of 22 studies of persons with bipolar or related affective disorders, Tondo and Baldessarini<sup>2</sup> noted that the protective effect of lithium reduced the rate of suicide 5.4-fold.

Bauer and coworkers<sup>8</sup> recently conducted a double-blind, placebo-controlled trial of lithium as augmentation of antidepressant treatment in patients with unipolar depression (Figure 3). Thirty patients stabilized for 2 to 4 weeks on combination treatment were randomly assigned to continued lithium augmentation or to have lithium replaced by placebo for 4 months. Those patients assigned to placebo had lithium gradually discontinued over a 1-week period. As Figure 3 shows, no relapses occurred in the lithium group; instead, all relapses, including 1 suicide and 2 first-onset manic episodes, happened in the placebo group. Of note, acute suicidal ideation and history of mania were among the exclusion criteria for the study. Relapses occurred an average of 27 days after double-blind treatment

began, and the relapse rate was statistically significant between the 2 groups, even if the 2 manic patients are excluded from analysis. All 5 of the patients with relapse of depression were immediately restarted on lithium augmentation treatment; 4 of these remitted within 2 weeks (the other was the suicide).

This study<sup>8</sup> allowed a week for the gradual discontinuation of lithium, which may have been too abrupt. The authors, though, discounted any "rebound" effect of lithium withdrawal as the cause of the relapses. Instead, they concluded that to prevent relapse, patients should receive lithium augmentation for longer than the 2 to 4 weeks that their study design allowed.

Other studies have also found that lithium provides protection against suicide. Schou and Weeke,<sup>9</sup> for example, examined 92 case records of patients diagnosed with manic depression at hospital admission, April 1969 to December 1983, who had committed suicide before July 1, 1986, to determine how many were receiving prophylactic or continuation treatment. Only 9 were on treatment with lithium, either alone or in combination with an antidepressant. Six of those 9 had received lithium for less than a year, and 3 of 9 had previously attempted suicide. The majority of patients were not in treatment at all (32/92) or were receiving treatment for a current episode (28/92). The rest of the patients (23/92) were on antidepressant monotherapy; 13 of those were receiving what the authors considered to be an inadequate dose of an antidepressant. Adequate prophylactic treatment, especially with lithium alone or as the augmenting agent, reduced the risk of suicide in these patients.

In a group of patients who attended a mood disorder clinic, received lithium maintenance therapy, and were followed for 18 years, Coppen and Farmer<sup>10</sup> found a suicide rate of 1.3 per 1000 patient years. This population included 60 patients with unipolar depression, 30 with bipolar disorder, and 6 with schizoaffective disorder. Patients were followed from January 1977 to January 1995; average time on lithium treatment was 4.5 years. By the end of the follow-up period, 24 patients were still enrolled with the clinic, 43 had left while still on lithium therapy, and 12 discontinued treatment altogether. Twenty-four patients had died, 2 of whom committed suicide: 1 was still taking lithium, and 1 had discontinued lithium the year before. Although this suicide rate is higher than that seen in the general population, the authors found that it is lower than that seen in other long-term studies of patients with mood disorders who did not receive maintenance therapy. The average suicide rate for those studies was 5.5 per 1000 patient years.

Similarly, Müller-Oerlinghausen et al.<sup>11</sup> found a lower suicide rate among patients compliant to lithium therapy than in noncompliant patients. In their study, 68 patients receiving lithium prophylactic therapy were followed for an average of 8 years. All patients had been diagnosed

with an affective disorder, and all had attempted suicide at least once before beginning lithium treatment. Thirteen patients discontinued lithium treatment; of those, 11 showed suicidal behavior 2 weeks to 44 months after stopping treatment, and 4 of those committed suicide. Of the 55 patients who were compliant with lithium treatment, 2 committed suicide, but in 1, the most recent serum lithium value was zero, implying that the patient had discontinued the treatment. Most of the patients who committed suicide (4/6) were considered nonresponders to lithium. The authors found a statistically significant increase in suicidal behavior in patients who stopped taking lithium. In a meta-analysis involving 22 studies and more than 5000 subjects, Tondo et al.<sup>24</sup> found that suicide was 82% less frequent during lithium treatment.

As prophylactic treatment for patients with mood disorders, especially bipolar disorder, lithium appears to have a beneficial, preventative effect on suicide rate. Although still higher than that of the general population, the suicide rate among patients taking lithium as continuation therapy is lower than that among patients who have discontinued lithium. Lithium works; the question is how.

#### ANTISUICIDAL ACTION OF LITHIUM

Although lithium seems to strongly protect against suicide attempts and fatalities in patients with bipolar disorder, its mechanism of action remains to be elucidated. For example, lithium's antisuicide action may be a result of its effectiveness as a mood stabilizer. In other words, the rate of suicide may be lower simply because patients feel better and have reduced levels of aggression and hostility. However, Müller-Oerlinghausen and associates<sup>11</sup> found that suicide attempts dropped in both responders and nonresponders to the drug, and Thies-Flechtner et al.<sup>6</sup> found that lithium appeared to be more effective in preventing suicide than another mood stabilizer, carbamazepine. This finding implies that lithium's preventative effect may be specific and separate from its mood-stabilizing effect. This specific antisuicidal action may be mediated by the serotonergic system, which is implicated in aggression and violence. Another argument in favor of a specific antisuicidal effect is the sharp and sudden increase of suicide attempts and suicides seen in patients who have recently stopped taking lithium, especially if the discontinuation is rapid.<sup>7,8,11</sup>

Some inconsistencies exist in the argument that lithium's antisuicidal effect is specific, though. For example, if this effect is due to lithium's action on the serotonergic system, then other drugs with serotonergic action, such as some antidepressants, would be more effective in preventing suicide. In fact, clozapine, which seems to reduce suicidality in schizophrenic patients, is an antagonist of some serotonin receptors. Lithium's antisuicidal properties may occur via a neuromodulating system other than



the serotonergic, but this has not yet been demonstrated. In addition, even though lithium seems to exert its preventative effect on responders and nonresponders, it is primarily nonresponders who commit suicide—Tondo and colleagues<sup>7</sup> found that all suicidal acts occurred during a depressive or mixed episode. Moreover, the lithium-related reduction of suicide risk may be associated with a decrease in aggressiveness and impulsiveness commonly experienced during lithium treatment. Lithium's protective action may also be a consequence of the interpersonal therapeutic relationship between patient and psychiatrist that results from a consistent schedule of drug monitoring. The patient might benefit from the psychiatrist's attention and care, and the psychiatrist may be able to respond immediately to early signs of a relapse that might be missed otherwise. Clearly, more studies are needed to determine how lithium treatment reduces the risk of suicide and if other mood stabilizers have the same impact.

### CONCLUSION

The study of suicide is by definition a problematic one because of the ethical concerns. In addition, most published prospective studies were not originated with suicide in mind, but gathered data on it after the fact. Other studies are epidemiologic and retrospective in nature. Some limitations of published studies of suicide include the diagnostic heterogeneity and lack of specific diagnostic rates, the lack of information about the intent and severity of suicide attempts, the lack of independent parallel groups randomly assigned to treatment, the lack of control over treatment, and the inclusion of high-risk subjects, i.e., those with previous suicide attempts. In addition, many of these studies do not take the role of comorbidity and treatment discontinuation into account, and many use a limited number of subjects and standardized mortality ratios that are uncontrolled for psychiatric disorders in the general population. However, despite these limitations and problems, lithium is consistently associated with a lower risk of suicide and even appears to prevent it in patients with affective disorders who are compliant with the medication regimen. What is responsible for this impact on suicidality is still unknown and merits further examination.

*Drug names:* amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clozapine (Clozaril and others), fluoxetine (Prozac), haloperidol (Haldol and others).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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