REVIEW

The Effect of Pharmacotherapy on Suicide Rates in Bipolar Patients

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Keywords

Suicide; Bipolar Disorder; Affective Disorder; Lithium; Antidepressants; Antipsychotics.

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SUMMARY

Suicide is a complex and multicausal human behavior and also a great challenge for psychiatry. We review the evidence available concerning pharmacological prevention of suicide in bipolar disorder patients. Several clinical trials provide evidence that effective acute and long-term treatment of bipolar depression provides a strong protection against suicide, suicide attempts, and probably against other complications of this disorder. Current major mood disorder is the most important risk factor of suicide, and bipolar II patients carry the highest risk. In bipolar patients suicidal behavior is most likely to occur during pure or mixed depressive episodes. Since bipolar disorder is a highly recurrent illness, adequate long-term pharmacotherapy is needed to prevent suicidal behavior.

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Introduction

Prediction and prevention of suicidal behavior among psychiatric patients is a great challenge for the psychiatrists, and could also be among the most reliable indicators of the efficacy of the clinical care. Suicide is very complex, multicausal behavior, involving several psychiatric-medical/biologic, psycho-social, demographic, and cultural components, and history of current major mood disorders (particularly in the presence of previous suicide attempt) constitutes the most important risk factor. Although suicidal behavior is quite frequent among all patients with major mood disorders, the findings strongly suggest that bipolar patients in general and bipolar II patients in particular, might be at highest risk [1–4] (Table 1). In their recent long-term prospective follow up study (average 11 years) on 1983 unipolar major depressives and 843 bipolar (I + II) patients, Tondo et al. [4] found five-times fold higher rate of completed suicide in bipolar I and II than in unipolar patients (0.25% of patients per year vs. 0.05% of patients per year). This study also found that the ratio of attempted to completed suicide in bipolar II, bipolar I and unipolar depression was 5, 11, and 10, respectively, indicating that the lethality of suicide attempts was far highest in bipolar II patients.

As suicidal behavior in bipolar patients occur mostly during severe pure or mixed depressive episodes and less frequently in the frame of dysphoric (mixed) mania, but practically never during euphoric mania and euthymia (i.e., suicidal behavior in bipolar patients is state- and severity-dependent phenomenon) [1,2,5–8],

it is logical to assume that effective acute and long-term treatment has a strong protection against suicide, suicide attempts, and probably against other complications (secondary substance-use disorders, marital instability, loss of job, cardiovascular morbidity/mortality, violent behavior, etc.).

Pharmacological Prevention of Suicide in Bipolar Patients

As bipolar disorder is a highly recurrent illness, successful acute pharmacotherapy of depressive or mixed episodes can only prevent the risk of suicidal behavior connected with a given episode, it is only adequate long-term (prophylactic) therapy that can provide long-term results in patients with bipolar illness. The efficacy of lithium in the treatment of manic states and in prevention recurrences of bipolar patients is well documented [9–11], and some data indicate that combination of lithium (and other mood-stabilizers) with antidepressants reduces the chance of hypomanic or manic switching when bipolar depression is treated with antidepressants [12,13]. However, about 50% of bipolar patients do not show satisfactory prophylactic response to lithium; positive family history of bipolar illness, early onset, mania–depression-interval type of clinical course predicts a good prophylactic response, while higher frequency of episodes (including rapid cycling), depression–mania-interval type of clinical course and comorbid substance-use disorders indicate poor response. The

Table 1 Clinically explorable suicide risk factors in bipolar disorders

Diagnostic subtype
Bipolar II depression > bipolar I depression > mixed affective episode, dysphoric mania.
Prior suicide attempt
Violent > nonviolent
High lethality > low lethality
Clinical features
Severe depression with hopelessness/insomnia/guilt
Mixed depressive episode (major depression + 2 or more hypomanic symptoms)/agitated depression
Mixed affective episode (mania and major depression simultaneously)
Dysphoric (mixed) mania or hypomania
Early onset of bipolar disorder
Comorbid anxiety/anxiety disorders, substance-use, and personality disorders
Cyclothymic/irritable affective temperament
Family history of suicide in first- and second-degree relatives
History of childhood physical and/or sexual abuse
Permanent adverse life situations, acute psychosocial stressors
Lacking social support, no adequate acute, and long-term treatment/care
Recent hospital discharge
Availability of lethal suicide methods (guns, pesticides, etc.)
Noncompliance with the treatment

place of antiepileptics (valproate, carbamazepine, and lamotrigine) in the acute and long-term treatment of bipolar disorders is also well established. Predictors of better response to anticonvulsants than to lithium are mixed episodes, rapid cycling, comorbid substance-use disorders, and previous lithium nonresponse [9–11].

Lithium and Antiepileptic Mood Stabilizers

In a comprehensive review of 45 randomized, controlled, and open clinical studies (including 34 studies also providing data without lithium treatment) involving a total of 85,229 person-years of risk exposure, Baldessarini et al. [14] reported over 80% risk reduction for attempted and completed suicides either in unipolar or in bipolar patients with long-term lithium treatment. The risk reduction was similar for suicide attempts and for completed suicides and for bipolar and unipolar patients. The incidence-ratio of attempts-to-suicides increased 2.5 times with lithium treatment, indicating reduced lethality of suicidal acts. Baldessarini et al. concluded that the robust reduction of suicidal behavior with lithium maintenance in bipolar and unipolar patients to overall levels was close to general population rates. The marked antisuicidal potential of lithium seems to be more than the simple result of its episode-prophylactic effect, as it has been demonstrated that during the long term lithium prophylaxis of 167 recurrent bipolar or unipolar affective disorder patients with at least one prior suicide attempt, a significant reduction in the number of suicide attempts was found not only in the excellent responders (92%), but also in moderate responders (78%) and in poor responders (70%) [15]. The clinical im-

portance of this finding is that in the case of lithium nonresponse, when the patient has one or more suicide risk factor, instead of switching lithium to another mood stabilizer, the clinician should retain lithium (even on a lower dose) and combine it with another mood stabilizer. Other studies also show that lithium treatment prevents suicidal behavior in patients with recurrent unipolar depression [16] and with affective spectrum disorders [17].

Interestingly, the definite antisuicidal potential of lithium has been also supported recently from an epidemiological perspective: investigating the lithium levels in tap water in 18 municipalities in Japan in relation to the suicide mortality in each municipality, the authors found that lithium levels were significantly and negatively associated with suicide rate averages for 2002–2006 [18].

In a 34- to 38-year-long naturalistic follow-up study including 220 formerly hospitalized bipolar I and bipolar II patients, Angst et al. [19] found that patients who received long-term pharmacotherapy (lithium, neuroleptics, and antidepressants) tended to live longer and to have significantly (2.5-fold) lower suicide rate (13.1% vs. 5.2%) than untreated bipolars. In addition, they also found significantly lower rates from all natural deaths among treated versus untreated bipolars.

In a prospective, randomized, open-label 2.5-year follow-up study Thies-Flechtner et al. [20] investigated the number of suicide events in 175 bipolar, 110 schizoaffective, and 93 recurrent depressive patients. The patients were randomly assigned to lithium, carbamazepine, or amitriptyline. There were 14 serious suicide events (9 completed suicides and 5 serious attempts) during the study, and 7 out of the 14 events (6 suicides and 1 attempt) were among the bipolar patients. Most of the 14 suicide acts happened in the carbamazepine group (4 suicides and 5 attempts), and none of the 14 suicidal patients were taking lithium. These results also show that lithium has a strong antisuicidal potential which markedly exceeds its episode-prophylactic effect that may be related to the well-known antiaggressive and serotonin-agonistic activity of lithium [11,15].

On the other hand, however, in a retrospective chart review study of 140 out-patients with bipolar disorders treated continuously for a minimum of 6 months during a 23-year-period of private practice, Yerevanian et al. [21] found more than 2-fold reduction in nonlethal suicidal behavior during, compared with after discontinuation of mood stabilizer pharmacotherapy (lithium, valproate, or carbamazepine). The frequency of nonlethal suicidal behavior was not different during treatment with lithium, compared with valproate or carbamazepine. It is also important to note that only one completed suicide (several days after stopping lithium) occurred in this sample in a case of a middle-aged bipolar II male patient.

In their naturalistic, retrospective chart review study of 405 bipolar patients seen in a large US Veterans Administration health-care system Yerevanian et al. [22] analyzed the risk of suicidal behavior of the patients followed for a mean of 3 years. As there was only one completed suicide in this study the analysis was restricted only to suicide attempts and serious suicidal ideation resulting in hospital admission. This study showed that mood stabilizer monotherapy (lithium, divalproex, and carbamazepine) reduced the risk of suicidal behavior by more than 90%. Lithium

and antiepileptic mood stabilizers showed similar benefits in this respect.

In a population-based retrospective “real word” cohort study on more than 20,000 patients with bipolar I or bipolar II disorder Goodwin et al. [23] compared the risk of suicide and suicide attempts during lithium treatment with that of during divalproex or carbamazepine treatment. There was no exposure to lithium, divalproex or carbamazepine during 45% of all person-years of the follow-up (mean: 2.9 years). In this observational study, where milder or nonsuicidal cases were probably overrepresented among patients who had never been treated with any mood stabilizer, it has been found a 42% reduction in suicide death among patients taking lithium compared to those who were not treated with any mood stabilizers. After adjustment for age, sex, comorbid disorders, and concomitant use of other psychotropics, the authors found that the risk of suicide deaths and suicide attempts resulting in hospitalization were 2.7 times and 1.8 times higher during treatment with divalproex and 1.5 times and 2.9 times higher during treatment with carbamazepine than during treatment with lithium. These findings are in good agreement with the results of Thies-Fletcher et al. [20], who reported that among patients treated for bipolar disorders the risk of suicidal behavior was lower during lithium treatment than during treatment with carbamazepine.

Using linkage of national registers, Sondergard et al. [24] investigated the association between continued mood stabilizing treatment and suicide among all patients discharged nationwide from hospital psychiatry as an in- or outpatient during 1995 and 2000 in Denmark with an ICD-10 diagnosis of bipolar disorder ($n = 5926$). The results showed that bipolar patients who continued treatment with mood stabilizers (lithium, divalproex, lamotrigine, oxcarbazepine, and topiramate) had a significantly decreased rate of suicide compared to patients who purchased mood stabilizers once only and the rate of suicide decreased consistently with the number of additional prescriptions. The authors also found that a switch to or augmentation with lithium to patients initiated on antiepileptic mood stabilizers was associated with a significantly reduced suicide rate whereas a switch to or augmentation with antiepileptics to patients first started on lithium showed no additional effect on suicide mortality. Although long-term treatment with lithium and antiepileptic mood stabilizers was associated with similar reduction in the suicide mortality, these findings show that lithium may have some superiority over antiepileptic mood stabilizers in preventing suicide.

Analyzing the 12,662 Oregon Medicaid patients diagnosed with bipolar disorders and treated with mood stabilizers between 1998 and 2003 Collins and McFarland [25] found that the adjusted hazard ratios (versus lithium) for suicide attempts were 2.7 for divalproex users ($P = 0.001$), 2.8 for carbamazepine users (not significant) and 1.6 for gabapentine users (not significant). For completed suicides the hazard ratios were 1.5 for divalproex users (not significant), 2.6 for gabapentine users ($P = 0.001$), and not available for carbamazepine users.

On the other hand, however, a recent analysis of STEP-BD study data [26] found no suicide-protective effect of lithium and other mood-stabilizers (such as valproate, carbamazepine, lamotrigine, and certain antipsychotics) in patients with bipolar disorders. However, the methodology of this case-control prospec-

tive follow-up study has been criticized, since the authors could not control for the medication status (compliance) in the last 1–4 weeks before the suicide event, therefore it is very likely that bipolar patients, who stopped the mood stabilizer relapsed and become suicidal more frequently (“suicidal cases”) than those who did not stop the drug and remain well (“nonsuicidal controls”) [27].

Antidepressants and Antipsychotics

The role of typical and atypical antipsychotics in the acute treatment of mania, mixed states, and psychotic depression is well considered [9,11]. Recent results suggest that some atypical antipsychotics (olanzapine, quetiapine, and aripiprazole) have long-term mood-stabilizing effect in patients with bipolar disorders [28–30], but their putative specific antisuicidal effects need further studies. Antidepressants have very limited value in the long-term treatment of bipolar disorders because of their mood-destabilizing effects [9,31,32]. However, rates of hypomanic or manic switches during treatment with SSRIs are much lower than with TCAs, and mood stabilizers further reduce the risk of the mood switch [9,12,13]. The study by Yerevanian et al. also showed that during the long-term pharmacotherapy of bipolar patients the risk of suicidal behavior is highest in patients with antidepressant and antipsychotic monotherapy [33,34], lowest in patients with mood stabilizer monotherapy [22] and the risk of patients with combination therapy (mood stabilizers + antidepressants or antipsychotics) showed an intermediate position with similar risk of suicidal behavior to bipolar patients during the period “off” mood stabilizer [22,33,34]. This suggests that combination of antidepressants or antipsychotics with mood stabilizers substantially reduces (but does not eliminate) the elevated risk of suicide seen in patients on antidepressant or antipsychotic monotherapy, and only mood stabilizer monotherapy provides the best result in this respect. These findings have important clinical implications: clinicians who add antidepressants or antipsychotics to mood stabilizers to treat breakthrough depression or mania during the long-term treatment of their bipolar patients should consider that antidepressants and antipsychotics may increase the risk of suicidal behavior; therefore, they should keep their patients on these supplementary medications as short a time as possible and the main component of the long-term pharmacotherapy should be the mood stabilizer monotherapy. While the antisuicidal effect of clozapine in schizophrenia is well established, and the recent sertindole cohort prospective study (SCoP) showed promising antisuicidal effect of sertindole in schizophrenic patients, at least in comparison with risperidone [35], these results suggest that the use of atypical antipsychotics like clozapine and sertindole in the treatment of bipolar patients is more safe in this respect.

The Role of Psycho-Social Interventions

Recently some effective psychosocial interventions in the field of bipolar disorders were developed primarily for patients who show insufficient response to acute and long-term pharmacotherapy, who cannot tolerate drugs or who are noncompliant with the

treatment [36,37]. The main goals of these interventions are: preventing medication noncompliance with psychoeducation or with cognitive-behavioral therapy, lifestyle modification, modification of family and other interpersonal conflicts, teaching patients and relatives to identify early symptoms of relapse/recurrence, and obtain treatment as early as possible [38,39]. These psychosocial interventions specifically designed for relapse/recurrence prevention in bipolar patients are effective either alone, but mostly in conjunction with mood stabilizers [36,38]. Psychosocial interventions, mentioned above, while reducing relapse/recurrence may indirectly reduce the risk of suicide. The only one published study concerning the effect on suicidality of intensive psychosocial treatment that specifically targeted suicidality in bipolar disorder in addition to mood stabilizer pharmacotherapy showed that patients experienced a 18-fold reduction of the frequency of suicide attempts during the 2-year maintenance phase [40].

Of course, we are unable to prevent all suicides. However, our present pharmacological and psychosocial interventions are effective enough to minimize the chance of suicidal behavior in patients with bipolar disorder.

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Author Contribution

Zoltan Rihmer conceived the paper, and wrote the paper. Xenia Gonda collected the studies and literature and wrote the paper.

Conflict of Interest

The authors have no conflict of interest.

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