

Suicide and suicide prevention in patients with bipolar disorders

Zoltán Rihmer, MD, PhD, DSc.

Department of Clinical and Theoretical Mental Health,
and Department of Psychiatry and Psychotherapy,
Semmelweis University, Faculty of Medicine,
Budapest, Hungary
Tel: (36-1) 325-1498
Fax: (36-1) 355-8498
E-mail: rihmerz@kut.sote.hu

Abstract

Bipolar disorders are quite prevalent but frequently underdiagnosed and undertreated. The early recognition and appropriate treatment is particularly important, since out of all psychiatric illnesses, (untreated) bipolar disorders carry the highest risk of both attempted and completed suicide. Studies show that suicidal behaviour in patients with bipolar disorders is state and severity dependent; that means that suicidality markedly decreases or vanishes after clinical recovery. However, since the majority of mood disorder patients never commit suicide and more than half of them never attempt suicide, special clinical characteristics of the disorder as well as some familial and psychosocial factors should also play a contributory role. Considering the clinically explorable suicide risk factors in patients with bipolar disorders (family and/or personal history of suicidal behaviour, early onset, severe depressive episode/hopelessness, agitated/mixed depression, bipolar II diagnosis, rapid cycling, comorbid Axis I and Axis II disorders, adverse life situations, lack of social and medical support, cyclothymic temperament, impulsive aggressive personality features, etc.), there is a good chance that suicidal behaviour is predictable. There is also much evidence that (successful) acute and long-term pharmacotherapy of bipolar patients reduces the risk of attempted and completed suicide by more than 80 percent, even in this high-risk population. Recent studies also show that supplementary psychosocial interventions (psychoeducation, and targeted psychotherapies) further improve the results.

Key words: bipolar disorders, suicidal behaviour, suicide prevention, antidepressants, mood stabilizers, suicide risk factors, psychosocial interventions

Suicidal behaviour, particularly completed suicide, which is the most dangerous complication of untreated major psychiatric illness, is one of the most tragic human events. Although suicide is very complex, multi-causal behaviour, involving several medical-biological, psychosocial and cultural components, a history of untreated major mood disorders (particularly in the presence of previous suicide attempt) constitutes the most important risk factor. However, because the majority of mood disorder patients never complete (and about 50% of them never attempt) suicide, other familial-genetic, personality and psychosocial risk factors also play a significant contributory role (1, 2, 3, 4).

Psychological autopsy studies from several different countries of the world have consistently shown that around 90% of consecutive suicide victims have one or more Axis I (mostly untreated) major psychiatric disorders at the time of their death, and major mood disorders (59-87%), schizophrenia/schizoaffective disorder (10-12%) and substance-use disorders (10-15%) are the most common principal diagnoses (4, 5, 6, 7, 8). On the other hand, it has been estimated that 15-19% of severe (mostly hospitalized) patients with major depression would die by suicide (6, 9). In their meta-analysis of studies on suicide risk in psychiatric disorders, Harris and Barraclough analysed separately the risk of suicide in unipolar major depression and in bipolar disorder (10). They found that the risk of suicide was about 20-fold for patients with index diagnosis of unipolar major depression, and the same figure for bipolar disorder was 15. However, these three studies (6, 9, 10) cannot provide a precise estimate of separate suicide risk in unipolar and bipolar disorder, i.e. they overestimate the risk for unipolar depression and underestimate it for bipolar disorders. The main issues are that the index diagnosis

frequently changes during the long-term course from unipolar depression to bipolar disorder (11, 12, 13, 14) and in the studies (performed several decades ago) reviewed by the mentioned authors the diagnostic category of bipolar II depression (depression with hypomania but not with mania) which is quite a common form of bipolar disorder (12, 15, 16) has not been considered separately; it is very likely that the majority of bipolar II patients in these studies were included in the unipolar major depressive subgroup. Indeed, a recent long-term follow-up study showed that the rate of completed suicide was about double in bipolar disorder (types I and II combined) than in unipolar depression (17). Another recent population-based epidemiological study also found that 28% of bipolar (types I and II combined) and 11% of unipolar major depressive disorder patients reported a lifetime history of suicide attempt (18).

Risk of suicidal behaviour in patients with bipolar disorders

Since specific diagnostic subtypes of major mood disorders (unipolar, bipolar I and bipolar II) show several differences from both clinical and research perspectives (6; 11; 18; 19; 20; 21), it is logical to assume that each subgroup might have its own different suicide risk.

1. Completed suicide

The different risk of suicide in the three main subgroups of major mood disorders was first reported by Dunner et al. (1976) who found that 3% of the 73 unipolar, 6% of the 68 bipolar I and 18% of the 22 bipolar II patients died by suicide during their 1-9 year follow-up study (19).

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. found a five-fold higher rate of completed suicide in bipolar I and II than in unipolar patients (0.25% of patients/year vs. 0.05% of patients/year) (22). They 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. The higher lethality of suicide attempts of bipolar II than bipolar I and unipolar patients has been supported by the study of Sani et al. (17). During the long-term (up to 35 years) follow-up study on 4441 formerly hospitalized psychiatric patients the authors also found that bipolar II patients had the highest risk for suicide; the authors reported that 2.8% of 1163 bipolar I and 4.2% of 602 bipolar II patients completed suicide while the rate for 1142 unipolar major depressive patients was 1.9% (17). Similarly, in the STEP-BD study (4360, mostly pharmacologically-treated bipolar patients, mean follow-up 18 months) the rate of completed suicide was more than two-fold in bipolar II (0.34%) than in bipolar I patients (0.14%, 23).

The results of the two published psychological autopsy studies where the prevalence of bipolar II, bipolar I and unipolar depression have been analysed separately, show that among the 125 consecutive suicide victims with primary major depression at the time of suicide, 44% had bipolar II depression, 2% had bipolar I depression and 54% had first episode or recurrent unipolar depression (24, 25). Because the lifetime prevalence rates of DSM-III/IV bipolar II illness in the population are relatively low compared with unipolar major depression (2-5% and 15-17%, respectively) (26, 27), these results, in agreement with other findings (17, 23), also suggest that among the three different subgroups of major mood disorders bipolar II disorder carries the highest risk of committed suicide.

2. Attempted suicide

In addition to the high mortality rate due to suicide, up to 50% of patients with bipolar disorder attempt suicide at least once during their life (3, 8, 28). Considering only the ten studies, in which unipolar, bipolar I and bipolar II patients were analysed separately, and summarizing the data (3), it can be seen that the rate of previous suicide attempts is lowest in unipolar major depression (13 %) highest in bipolar II patients (33%), and intermediate in bipolar I patients (28%). Re-analysing the ECA database, Judd and Akiskal (29) also reported that the rate of prior suicide attempt(s) was higher in bipolar II (34%) than in bipolar I (24%) patients, while the same figure for unipolar major depression was 16% (30). The long-term prospective study by Tondo et al. also found that the rate of suicide attempts during follow-up was more than double in bipolar (I+II) than in unipolar patients. However,

the annual rate of suicide attempts was highest in bipolar I (1.52%), compared with bipolar II (0.82%) and unipolar (0.48%) depression in this study (22).

The results of a German ten-year prospective longitudinal study showed that 32% of 33 bipolar II, 17% of 65 bipolar I and 6% of 286 pure unipolar major depressive patients attempted suicide during follow-up (31). In the Finnish Jorvi Bipolar Study 16% of the 90 bipolar I and 25% of the 101 bipolar II patients reported at least one prior suicide attempt at the index episode (32). Similar findings were reported from South-Korea; 17% of the 71 bipolar I and 36% of the 34 bipolar II patients reported the history of suicide attempt (33). Analysing the specific diagnostic subtypes of consecutive suicide attempters with current DSM-IV major depressive episode, it has been also found that bipolar, and particularly bipolar II patients were relatively overrepresented both in Budapest (34) and in Rome (35).

In contrast to the studies, mentioned above, analysing the NCS-Replication database, Angst et al. found that the history of lifetime suicide attempts was the highest in bipolar I (66%), lower in bipolar II disorder (50%) and lowest in unipolar major depression without subthreshold bipolarity (30%) (28). However, in patients with unipolar major depression with subthreshold hypomanic symptoms, the rate of patients with prior suicide attempt was intermediate between pure unipolar major depression and bipolar II disorder (41%).

3. Clinically explorable suicide risk factors

Bipolar patients with comorbid anxiety, substance-use, and personality disorders as well as with DSM-IV atypical depressive features are also at an increased risk of attempted or completed suicide (3, 4, 8, 21, 30, 34, 36, 37). Beside the highest lethality of suicide attempts (22; 17), the major sources of the highest suicide risk in bipolar II patients may be the very high rate of atypical depression, comorbid anxiety disorders (37, 38; 39), substance-use disorders (38, 40) and depressive mixed states/agitated depression (2, 12, 17, 41; 42). The importance of depressive mixed states in predicting suicidal behaviour is supported by several recent studies (12; 43; 44; 45; 46) and current findings also show that cyclothymic/irritable affective temperaments, that are characteristic also mainly for bipolar II disorder, also increase the risk of suicidal behaviour (47).

Family history of suicide (19; 48; 49), past suicide attempt(s), early onset of the illness, impulsive, aggressive personality features, childhood physical and sexual abuse as well as recent adverse life events, and permanent psychosocial stressors (3, 4, 5, 8, 12, 43, 46; 47, 50, 51), have also been shown to be risk factors for attempted or completed suicide, particularly in the frame of major depressive, mixed depressive or dysphoric manic episodes. In a study on 211 patients suffering from recurrent unipolar major depression or bipolar (I+II) disorder, hospitalized after suicide attempt, it was found that family history of suicide was significantly associated with diagnosis of bipolar disorder and looking for the features associated with serious suicide attempt, bipolar disorder was the only associated diagnosis (52).

It should be noted, however, that in the majority of cases many suicide risk factors are present and they have an additive effect on the self-destructive behaviour; the higher the number of risk factors the higher the suicide risk (2, 3, 4, 8, 43).

Despite of the fact that up to 66% of suicide victims contact different levels of health care (mostly GPs and psychiatrists) 4 weeks before suicide, the rate of adequate pharmacotherapy among depressed suicide victims is disturbingly low (24, 53; 54; 55). While the current prevalence of DSM-III/DSM-IV or ICD-10 major depression in primary care practice is around 8-10%, the majority of depressed patients are not recognised by their GPs. Moreover, the rate of adequate antidepressant pharmacotherapy among diagnosed depressives was less than 20%. However, studies performed 5-10 years later, reported much higher rates of recognition and treatment of depression in primary care practice (62-85%) and 33-50% of them were treated with antidepressants (56, 57).

Since successful acute and long-term pharmacotherapy of mood disorders relieves not only the clinical symptoms, but parallel with this also decreases or eliminates suicidality, appropriate acute

and long-term treatment of mood disorders is a key issue in suicide prevention. GPs and psychiatrists play a crucial role in suicide prevention via early recognition and appropriate management of suicidal patients. (4, 53, 54, 58, 59, 60). Table-1. shows the clinically most important suicide risk factors in bipolar disorders.

Suicide prevention in bipolar disorders

Since suicidal behaviour is a multi-causal phenomenon with many biological, psychological and cultural components, its prevention should also be complex. Bipolar disorder, a major precursor of suicidal behaviour, is quite prevalent, but frequently underdiagnosed. Considering both the bipolar I and II manifestations, the lifetime prevalence is between 3 and 5% (6, 16, 26, 27). Since bipolar disorders usually show a peak onset between 15 and 25 years of age, but there is 8-10 years of delay in correct diagnosis (6, 16, 20, 27), early detection of bipolar, the nature of the mood disorder, including the soft manifestations as well, is the first step in suicide prevention. Misdiagnosis of bipolar depression as unipolar depression results in treatment with antidepressants alone, and this can worsen the course of the illness, because of inducing mixed depressive episodes, hypomanic or manic switches, or rapid cycling, therefore increasing the chance of suicidal behaviour (16, 41, 45, 61, 62, 63).

The role of health care in the suicide prevention of bipolar patients is summarised in Table 2. As suicide behaviour in bipolar patients occurs 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 behaviour in bipolar patients is a state-dependent and severity-dependent phenomenon) (3; 4, 21;), it is logical to assume that effective acute and long-term treatment has a strong protection against suicidal behaviour and probably against other complications such as secondary substance-use disorders, marital instability, loss of job, cardiovascular morbidity/mortality, violent behaviour, etc.

1. The role of psychopharmacotherapy in suicide prevention of bipolar patients

Successful acute pharmacotherapy of depressive or mixed episodes can only prevent the risk of suicidal behaviour connected with a given episode; therefore it is only the adequate long-term (prophylactic) therapy that can provide ongoing protection in patients with bipolar illness.

a. Lithium and antiepileptic mood stabilizers

The place of lithium and antiepileptic mood stabilizers in the treatment of manic states and in the prevention of recurrences in bipolar patients is well documented (6, 64, 65, 66). Recent data also indicate that the combination of lithium (and other mood-stabilizers) with antidepressants reduces the risk of hypomanic or manic switching when bipolar depression is treated with antidepressant monotherapy (62, 67).

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. reported about 80 percent risk reduction for attempted and completed suicides in either unipolar or in bipolar patients with long-term lithium treatment (58). The risk reduction was similar for suicide attempts and for completed suicides. The incidence-ratio of attempts to suicides increased 2.5 times with lithium treatment, indicating reduced lethality of suicidal acts. This marked anti-suicidal 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 the moderate responders (78%) and poor responders (70%) (68). The clinical consequence of this finding is that, in the case of lithium non-response, 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.

In a 34-38 year long naturalistic follow-up study including 220 formerly hospitalized bipolar I and bipolar II patients, Angst et al. found that patients who received long-term pharmacotherapy (lithium, neuroleptics, antidepressants) tended to live longer and to have significantly (2.5-fold) lower suicide rate (13.1% vs. 5.2%) than untreated bipolar patients (69). The authors also found significantly lower rates from all natural deaths among treated vs. untreated patients.

In a randomized, open-label, prospective 2.5-year-follow-up study Thies-Flechtner et al. investigated the number of suicide events in 175 bipolar, 110 schizoaffective and 93 recurrent depressive patients (70). 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 findings also support the strong anti-suicidal effect of lithium that may be related to its well-known anti-aggressive and serotonin-agonistic activity (6, 68).

The anti-suicidal effect of lithium in bipolar and unipolar major mood disorder patients has been also supported from an epidemiological perspective. Investigating the lithium levels in drinking 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 (71). Very similar results were published recently from Austria (72).

In a retrospective chart review study of 140 outpatients with bipolar disorders treated continuously for a minimum of 6 months during a 23-year-period of private practice, Yerevanian et al. found a more than two-fold reduction in non-lethal suicidal behaviour during, compared with after, discontinuation of mood stabilizers (lithium, valproate or carbamazepine) (73). The frequency of non-lethal suicidal behaviour was not different during treatment with lithium, compared with valproate or carbamazepine.

In a naturalistic, retrospective chart review study of 405 bipolar patients seen in a large US Veterans Administration health-care system, Yerevanian et al. analysed the risk of suicidal behaviour of the patients followed for a mean of 3 years (74). 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. The findings showed that mood stabilizer monotherapy (lithium, divalproex, carbamazepine) reduced the risk of suicidal behaviour by more than 90 percent. Lithium and antiepileptic mood stabilizers showed similar benefits in this respect.

In a population-based retrospective "real world" cohort study on more than 20,000 patients with bipolar I or bipolar II disorder Goodwin et al. compared the risk of suicide and suicide attempts during lithium treatment with that during divalproex or carbamazepine treatment (75). 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 non-suicidal cases were probably over-represented among patients who had never been treated with any mood stabilizer, a 42% reduction in suicide death among patients taking lithium was found, when 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 was about twice as high during treatment with divalproex and with carbamazepine than during treatment with lithium. These results are in good agreement with the findings of Thies-Flechtner et al. who reported that among patients treated for bipolar disorders the risk of suicidal behaviour was lower during lithium treatment than during treatment with carbamazepine (70).

Using linkage of national registers, Sondergard et al. investigated the association between continued mood-stabilizing treatment and suicide among all patients discharged nationwide from hospital psychiatry as inpatients or outpatients during 1995 and 2000 in Denmark with an ICD-10 diagnosis of bipolar disorder (n=5926) (59). The results showed that 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. Although long-term treatment with lithium and antiepileptic mood stabilizers was associated with similar reduction in the suicide mortality, these results suggest that lithium may have some superiority in preventing suicide.

Analysing the 12,662 Oregon Medicaid patients diagnosed with bipolar disorders and treated with mood stabilizers between 1998 and 2003 Collins and McFarland found that the adjusted hazard ratios (versus lithium) for suicide attempts was significantly higher for divalproex users ($p=0.001$), and for completed suicide for gabapentin users ($p=0.001$) (76). However, a recent, small-scale, double-blind, 2.5 year long trial on bipolar I and II patients showed no significant difference in the frequency of suicide attempts in patients treated with lithium or valproate (77).

b. Antidepressants and antipsychotics

The role of typical and atypical antipsychotics in the acute treatment of mania, mixed states and psychotic depression is well considered (6, 65, 66). Recent results suggest that some atypical antipsychotics (olanzapine, quetiapine and aripiprazole) have long-term mood-stabilizing effects in patients with bipolar disorders (78, 79, 80, 81), but their putative specific anti-suicidal effects need further studies.

Antidepressants have limited value in the long-term treatment of bipolar disorders because of their mood-destabilizing effects (45, 61, 65, 66). However, mood stabilizers reduce the risk of the mood switch (62, 66, 67). The study by Yerevanian et al. also showed that during the long-term pharmacotherapy of bipolar patients the risk of suicidal behaviour is highest in patients with antidepressant and antipsychotic monotherapy (82, 83), lowest in patients with mood stabilizer monotherapy (74) and the risk of patients with combination therapy (mood stabilizers + antidepressants or antipsychotics) showed an intermediate position with similar risk of suicidal behaviour to bipolar patients during the period "off" any psychotropics (74, 82, 83). The clinical implications of these findings is that 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 behaviour; 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.

2. Psychosocial interventions in suicide prevention of bipolar patients

Recently, more and more effective psychosocial interventions in the field of bipolar disorders were developed, primarily for patients who showed insufficient response to acute and long-term pharmacotherapy, who could not tolerate drugs or who were noncompliant with the treatment (84, 85). The main targets of these interventions are: preventing medication non-compliance with psychoeducation or with cognitive-behavioural therapy, lifestyle modification, teaching patients and relatives to identify early symptoms of relapse and obtain treatment as early as possible, and modification of family and other interpersonal conflicts (84, 86, 87, 88). These psychosocial techniques specifically designed for relapse/recurrence prevention in bipolar patients are effective either alone, or mostly in combination with mood stabilizers (see for review: 84, 85, 86). The interaction between pharmacotherapy and psychosocial interventions is quite complex as successful episode-preventive medication with mood stabilizers in bipolar patients counteracts dysfunctional cognitions (including lowered self-esteem), and adjunctive cognitive therapy helps to optimize the long-term course of bipolar illness (89).

Mental health professionals and physicians are, of course, unable to prevent all suicides and it is not only healthcare workers who are responsible for suicide prevention. However, our present pharmacological and psychosocial interventions are effective enough to minimize the chance of suicide in patients with bipolar disorder that represent the highest risk of self-inflicted death.

GP Comment

What have I learned from this paper?

Bipolar disorder carries one of the highest rates of suicide of any psychiatric disorder. The risk is especially raised in those with unrecognised illness or in those who are undertreated, especially with mixed states, which are common but difficult to diagnose. All patients who make a suicide attempt should have a careful assessment for bipolar disorder and it is noteworthy that bipolar II has a higher suicide risk than bipolar I, due to the relentless depressive symptoms in bipolar II. However, the challenge is to identify when 'depression' is actually bipolar depression.

Lithium appears to be protective against suicide and even if patients appear well, lithium should not be stopped unless there has been a very careful assessment by the patient's psychiatrist. GPs and other healthcare professionals should endeavour to provide high levels of support, holistic care and compassion for these patients. Outcomes are good and there is hope where there is psychosocial support and expert management.

Dr Daniel Dietch, Lonsdale Medical Centre.

References

1. Hawton K, van Heeringen K. Suicide. *Lancet* 2009; 373:1372-81.
2. Akiskal HS. Targeting suicide prevention to modifiable risk factors: Has bipolar II been overlooked? (Editorial). *Acta Psychiatrica Scandinavica* 2007; 116: 395-402.
3. Rihmer Z. Prediction and prevention of suicide in bipolar disorders. *Clin Neuropsychiatry* 2005; 2: 48-54.
4. Rihmer Z. Suicide risk in mood disorders. *Current Opinion in Psychiatry* 2007; 20: 17-22.
5. Cheng ATA, Chen THH, Chen CC, Jenkies R. Psychological and psychiatric risk factors for suicide. Case-control psychological autopsy study. *British Journal of Psychiatry* 2000; 177: 360-365.
6. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. Oxford University Press, New York; 1990.
7. Rihmer Z, Belső N, Kiss K. Strategies for suicide prevention. *Current Opinion in Psychiatry* 2002; 15: 83-87.
8. Pompili M, Rihmer Z, Innamorati M, Lester D, Girardi P, Tatarelli R. Assessment and treatment of suicide risk in bipolar disorders. *Expert Rev Neurother* 2009;9: 109-136.
9. Guze SB, Robins E. Suicide and primary affective disorders. *British Journal of Psychiatry* 1970;117: 437-438.
10. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. *British Journal of Psychiatry* 1997;170: 205-228.
11. Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M. Switching from "unipolar" to bipolar II: a 11-year prospective study of clinical and temperamental predictors in 559 patients. *Archives of General Psychiatry* 1995;52: 114-123.
12. Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. *Journal of Affective Disorders* 2005;85: 245-258.
13. Goldberg JF, Harrow M., Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *American Journal of Psychiatry* 2001;158: 1265-1270.
14. Akiskal HS, Hantouche F-G, Allilare J-F, Sechter D, Bourgeois ML, Azorin J-M, Chatenet-Duchene L, Lancrenon S. Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). *Journal of Affective Disorders* 2003;50: 143-151.
15. Benazzi F, Akiskal HS. Refining the evaluation of bipolar II: Beyond the SCID-IV guidelines for hypomania. *Journal of Affective Disorders* 2003a;73: 33-38.
16. Ghaemi SN, Boima EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. *Journal of Clinical Psychiatry* 2000;61: 804-808.
17. Sani G, Tondo L, Koukopoulos A, Reginaldi D, Kotzalidis GD, Koukopoulos AE, et al. Suicide in a large population of former psychiatric inpatients. *Psychiatry Clin Neurosci*. 2011; 65:286-95.

18. Schaffer A, Cairney J, Veldhuizen S, Kurdyak P, Cheung A, Levitt A. A population-based analysis of distinguishers of bipolar disorder from major depressive disorder. *J Affect Disord* 2011;125: 103-110.
19. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. *Biological Psychiatry* 1976;11: 31-42.
20. Akiskal HS. Classification, diagnosis and boundaries of bipolar disorders: A review. In *Bipolar disorder*. Maj M, Akiskal HS, Lopez-Ibor JJ, Sartorius N (eds), John Wiley and Sons, Chichester, pp. 1-52; 2002
21. Tondo L, Baldessarini RJ, Hennen J, Minnai GP, Salis P, Scamonatti L, Masisa M, Ghiani C, Mannu P. Suicide attempts in major affective disorder patients with comorbid substance use disorders. *Journal of Clinical Psychiatry* 1999;60 (Suppl. 2): 63-69.
22. Tondo L, Lepri B, Baldessarini R. Suicidal risk among 2826 Sardinian major affective disorder patients. *Acta Psychiatr Scand*, 2007;116: 419-28.
23. Dennehey EB, Marangell LB, Allen MH, Chessick C, Wisniewski SR, Thase ME. Suicide and suicide attempts in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BP). *J Affect Disord* 2011;133: 423-427.
24. Rihmer Z, Barsi J, Arató M, Demeter E. Suicide in subtypes of primary major depression. *Journal of Affective Disorders* 1990;18: 221-225.
25. Rihmer Z, Rutz W, Pihlgren H. Depression and suicide on Gotland. An intensive study of all suicides before and after a depression-training programme for general practitioners. *Journal of Affective Disorders* 1995;35: 147-152.
26. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *Journal of Affective Disorders* 1998;50: 143-151.
27. Szádóczy E, Papp Zs, Vitrai J, Rihmer Z, Füredi J. The prevalence of major depressive and bipolar disorders in Hungary. *Journal of Affective Disorders* 1998;50: 153-162.
28. Angst J, Cui L, Swendsen J, Rothen S, Cravchik A, Kessler RC, Merikangas KR. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. *Amer J Psychiatry* 2010;167: 1194-1201.
29. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *Journal of Affective Disorders* 2003; 73: 123-131.
30. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. *Biological Psychiatry* 1996;3: 896-899.
31. Zimmermann P, Bruckl T, Nocon A, Pfister H, Lieb R, Wittchen HU, et al. Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. *Archives of general psychiatry*. 2009; 66:1341-52.
32. Valtonen H, Suominen K, Mantere O, Leppamäki S, Arvilommi P, Isometsä ET. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry*. 2005; 66:1456-62.
33. Baek JH, Park DY, Kim JS, Choi JS, Ha K, Kwon JS, Lee D, Hong KS. (2011) Differences between bipolar I and bipolar II disorders in clinical features, comorbidity and family history. *J Affect Disord*, 131: 59-67.
34. Balázs J, Lecrubier Y, Csiszér N, Koszták J, Bitter I (2003) Prevalence and comorbidity of affective disorders in persons making suicide attempts in Hungary: importance of the first depressive episodes and of bipolar II diagnoses. *Journal of Affective Disorders*, 76, 113-119.
35. Raja M, Azzoni A (2004) Suicide attempts: Differences between unipolar and bipolar patients and among groups with different lethality risk. *J Affect Disord*, 82: 437-442.
36. Isometsä ET, Henriksson MM, Aro HM, Lönnqvist JK (1994) Suicide in bipolar disorder in Finland. *American Journal of Psychiatry*, 151, 1020-1024.
37. Sánchez-Gistau V, Colom F, Mané A, Romero S, Sugranyes G, Vieta E (2009) Atypical depression is associated with suicide attempt in bipolar disorder. *Acta Psychiatrica Scandinavica*, 120, 30-36.
38. Akiskal HS (1981) Subaffective disorders. Dysthymic, cyclothymic and bipolar II disorders in the "borderline" realm. *Psychiatric Clinics of North America*, 4, 25-46.
39. Rihmer Z, Szádóczy E, Füredi J, Kiss K, Papp Zs (2001) Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: Results from a population-based study in Hungary. *Journal of Affective Disorders*, 67, 175-179.
40. Brieger P (2000) Comorbidity in bipolar affective disorder. In *Bipolar disorders. 100 years after*

- manic depressive insanity, Marneros A, Angst J (eds), Kluwer Academic Publishers, Dordrecht, pp. 215-229.
41. Benazzi F, Akiskal HS (2003b) Clinical and factor-analytic validation of depressive mixed states: A report from the Ravenna-San Diego collaboration. *Current Opinion in Psychiatry*, 16 (Suppl. 2), 70-78.
 42. Koukopoulos A, Koukopoulos A (1999) Agitated depressions as a mixed state and the problem of melancholia. *Psychiatric Clinics of North America*, 22, 547-563.
 43. Maser JD, Akiskal HS, Schettler P, Scheftner W, Mueller T, Andicott J, Solomon D, Clayton P (2002) Can temperament identify affectively ill patients who engage in lethal or non-lethal suicidal behavior? A 14-year prospective study. *Suicide and Life-Threatening Behavior*, 32, 10-32.
 44. Balázs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS (2006) The close link between suicide attempts and mixed (bipolar) depression: Implications for suicide prevention. *Journal of Affective Disorders*, 91, 133-138.
 45. Rihmer Z, Akiskal HS (2006) Do antidepressants treat (h)reat (en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. *Journal of Affective Disorders*, 94, 3-13.
 46. Valtonen, HM., Suominen, K., Haukka, J., Mantere, O., Leppamäki, S., Arvilomni, P., Isometsä ET. (2008) Differences in incidence of suicide attempts during phases of bipolar I and bipolar II disorders. *Bipolar Disorders*, 10, 588-96.
 47. Rihmer Z, Akiskal KK, Rihmer A, Akiskal HS (2010) Current research on affective temperaments. *Current Opinion in Psychiatry*, 23, 12-18.
 48. Roy A (1983) Family history of suicide. *Archives of General Psychiatry*, 40, 971-974.
 49. Tondo L, Baldessarini RJ, Hennen J, Floris G (1998) Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. *American Journal of Psychiatry*, 155, 638-645.
 50. Caraballo JJ, Harkavy-Friedman J, Burke AK, Sher L, Baca-Garcia E, Sullivan GM, Grunebaum MF, Parsey RV, Mann JJ, Oquendo MA (2008) Family history of suicidal behaviour and early traumatic experiences: Additive effect on suicidality and course of bipolar illness? *J Affect Disord*, 109: 57-63.
 51. Sarchiapone M, Jaussent I, Roy A, Carli V, Guillaume S, Jollant F, Malafosse A, Courtet P. (2009) Childhood trauma as a correlative factor of suicidal behavior – via aggression traits. Similar results in an Italian and French sample. *Eur Psychiatry*, 24: 57-62.
 52. Guillaume S, Jaussent I, Jollant F, Rihmer Z, Malafosse A, Courtet P. (2010) Suicide attempt characteristics may orientate toward a bipolar disorder in attempters with recurrent depression. *J Affect Disord*, 122: 53-59.
 53. Isacson G (2000) Suicide prevention — a medical breakthrough? *Acta Psychiatrica Scandinavica*, 102, 113-117.
 54. Rihmer Z, Kiss K (2002) Bipolar disorders and suicide risk. *Clinical Approaches in Bipolar Disorders*, 1, 15-21.
 55. Luoma JB, Martin CE, Pearson JL (2002). Contact with mental health and primary care providers before suicide: A review of the evidence. *Amer J Psychiatry*, 159, 909-916.
 56. Berardi D, Menchetti M, Cevenini N, Scaini S, Versari M, De Ronchi D (2005). Increased recognition of depression in primary care. *Psychotherapy and Psychosomatics*, 74, 225-230.
 57. Rihmer Z. and Rutz W. Treatment of attempted suicide and suicidal patients in primary care. In: *Oxford Textbook of Suicidology and Suicide Prevention*, (Eds: Wasserman, D, Wasserman C.), Oxford University Press, New York, 2009, pp: 463-470.
 58. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J (2006) Decreased risk of suicides and attempts during long-term lithium treatment: A meta-analytic review. *Bipolar Disorders*, 8, 625-639.
 59. Sondergard L, Lopez AG, Andersen PK, Kessing LV (2008) Mood stabilizing pharmacological treatment in bipolar disorders and risk of suicide. *Bipolar Disorders*, 10: 87-94.
 60. Tondo L., Baldessarini RJ., (2000) Reduced suicide risk during lithium maintenance treatment. *Journal of Clinical Psychiatry*, 61 (Suppl. 9) 97-104.
 61. Benazzi F (2003) How could antidepressants worsen unipolar depression? (*l*tr) *Psychotherapy and Psychosomatics*, 72, 107-108.
 62. Henry C, Sorbara F, Lacoste J, Gindre C, Leboyer M (2001) Antidepressant-induced mania in bipolar patients: Identification of risk factors. *Journal of Clinical Psychiatry*, 62, 249-255.
 63. Koukopoulos A, Caliairi B, Tundo A, Floris G, Reginaldi D, Tondo L (1983) Rapid cyclers, temperament

- and antidepressants. *Comprehensive psychiatry*, 24, 249-258.
64. Goodwin FK (1999) Anticonvulsant therapy and suicide risk in affective disorders. *Journal of Clinical Psychiatry*, 60 (Suppl. 2), 89-93.
 65. Maj M, Tortorella A, Bartoli L (2000) Mood stabilizers in bipolar disorder. In *Bipolar disorders. 100 years after manic depressive insanity*, Marneros A, Angst J (eds), Kluwer Academic Publishers, Dordrecht, pp. 351-372.
 66. Bowden CL (2002) Pharmacological treatment of bipolar disorder: A review. In *Bipolar disorder*, Maj M, Akiskal HS, Lopez-Ibor JJ, Sartorius N (eds), John Wiley and Sons, Chichester, pp. 191-221.
 67. Mundo E, Cattaneo E, Russo M, Altamura AC (2006) Clinical variables related to antidepressant-induced mania in bipolar disorder. *J Affect Disord*, 92: 227-230.
 68. Ahrens B, Müller-Oerlinghausen B (2001) Does lithium exert an independent antisuicidal effect? *Pharmacopsychiatry*, 34, 132-136.
 69. Angst F, Stassen HH, Clayton PJ, Angst J (2002) Mortality of patients with mood disorders: follow-up over 34-38 years. *Journal of Affective Disorders*, 68, 167-181.
 70. Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W (1996) Effect of prophylactic treatment on suicide risk in patients with major affective disorders. *Pharmacopsychiatry*, 29, 103-107.
 71. Ohgami H, Tearao T, Shiotsuki I, Ishii N, Iwata N. (2009) Lithium in drinking water and risk of suicide. *British Journal of Psychiatry*, 194, 464-465.
 72. Kapusta, N.A., Mossaheb, N., Etzersdorfer E., Hlavin, G., Thau, K., Willeit, M., Praschack-Rieder, N., Sonjneck, G., Leithner-Dziubas, K., 2011. Lithium in drinking water and suicide mortality. *Brit J Psychiatry*. 198: 346-350.
 73. Yerevanian BI, Koek RJ, Mintz J (2003) Lithium, anticonvulsants and suicidal behavior in bipolar disorder. *Journal of Affective Disorders*, 73, 223-228.
 74. Yerevanian BI, Koek RJ, Mintz J (2007a) Bipolar pharmacotherapy and suicidal behaviour. Part 1: Lithium, divalproex and carbamazepine. *Journal of Affective Disord*, 103, 5-11.
 75. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee Y, Revicki D (2003) Suicide risk in bipolar disorder during treatment with lithium and divalproex. *Journal of American Medical Association*, 290, 1467-1473.
 76. Collins JC, McFarland BH. (2008) Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. *Journal of Affective Disorders*, 107, 23-28.
 77. Oquendo MA, Galfalvy HC, Currier D, Grunebaum MF, her L, Sullivan GM, Burke AK, Harkavy-Friedman J, Sublette ME, Parsey RV, Mann JJ. (2011) Treatment of suicide attempters with bipolar disorder: A randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. *Amer J Psychiatry*, 168: 1050-1056.
 78. Keck PE, Jr, McElroy S (2003) Redefining mood stabilization. *Journal of Affective Disorders*, 73, 163-169.
 79. Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Müller-Oerlinghausen BM, Koukopoulos A, Cassano GB, Grunze H, Licht RW, Dell'Osso L, Evans AR, Risser R, Baker RW, Crane H, Dossenbach MR, Bowden CL. (2005) Olanzapine versus lithium in the maintenance treatment of bipolar disorder: A 12-month, randomized, double-blind, controlled clinical trial. *American Journal of Psychiatry*, 162: 1281-1290.
 80. Young A, McElroy S, Olausson B, et al. (2008): Quetiapine monotherapy up to 52 weeks in patients with bipolar depression: Continuation phase data from EMBOLDEN I and EMBOLDEN II. (Abstract). 21th ECNP Conference, 2008, Barcelona, Spain.
 81. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran V, Young LT, Young AH, Alda M, Milev R, Vieta E, Calabrese JR, Berk M, Ha K, Kapczinski F (2009): Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2009. *Bipol Disord*, 11: 225-255.
 82. Yerevanian BI, Koeck RJ, Mintz J, Akiskal HS (2007b) Bipolar pharmacotherapy and suicidal behaviour. Part 2: The impact of antidepressants. *Journal of Affective Disorders*, 103, 13-21.
 83. Yerevanian BI, Koek RJ, Mintz J (2007c) Bipolar pharmacotherapy and suicidal behaviour. Part 3: Impact of antipsychotics. *Journal of Affective Disorders*, 103, 23-28.
 84. Bauer MS (2002) Psychosocial interventions for bipolar disorder: A review In *Bipolar disorder*, Maj M, Akiskal HS, Lopez-Ibor JJ, Sartorius N (eds), John Wiley and Sons, Chichester, pp. 281-313.

85. Fountoulakis KN, Gonda X, Siamouli M, Rihmer Z (2009) Psychotherapeutic intervention and suicide risk reduction in bipolar disorder: A review of the evidence. *Journal of Affective Disorders*, 113, 21-29.

86. Colom F, Vieta E (2002) Treatment adherence in bipolar patients. *Clinical Approaches in Bipolar Disorders*, 1, 49-56.

87. Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P (2003) A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder. *Archives of General Psychiatry*, 60, 145-152.

88. Fava GA, Bartolucci G, Rafanelli C, Mangelli L (2001) Cognitive-behavioral management of patients with bipolar disorder who relapsed while on lithium prophylaxis. *Journal of Clinical Psychiatry*, 62, 556-559.

89. Wolf T, Müller-Oerlinghausen B (2002) The influence of successful prophylactic drug treatment on cognitive dysfunction in bipolar disorders. *Bipolar Disorders*, 4, 263-270.

Table 1

Clinically significant suicide risk factors in bipolar disorders

- Diagnostic subtype
 - Bipolar II > bipolar I
- Early onset of the illness (< 25 years)
- Previous/current suicidal ideation
- Previous suicide attempt
 - Violent > nonviolent
 - High lethality > low lethality
- Current clinical features
 - Severe depression, hopelessness, insomnia, guilt
- DSM-IV atypical features (hypersomnia, hyperphagia, mood-reactivity, rejection sensitivity, leaden paralysis, etc.)
 - Mixed depressive episode/agitation
 - Dysphoric (mixed) mania or hypomania
 - Mixed affective episode
 - Rapid cycling course,
 - First episode depression, predominantly depressive polarity
 - Comorbid anxiety/anxiety disorders, substance-use and personality disorders
 - Cyclothymic/irritable affective temperament
 - Impulsive/aggressive personality features
- 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 adequate acute and long-term treatment/care
- Noncompliance or reduced compliance with the acute and long-term treatment

Table 2

Suicide prevention strategies in bipolar disorders

The role of health care

- I. Elimination of acute suicide danger
 - (emergency hospitalization, sedation, anxiolysis, crisis-intervention)
- II. Improving the diagnosis and treatment of bipolar disorders with particular regard to the soft clinical manifestations
 - 1. Education of health care workers, patients, relatives and gate-keepers
 - 2. Adequate acute and long-term treatment/aftercare
 - (pharmacotherapy, non-pharmacological interventions such as psychoeducation,

psychotherapy, cognitive therapy, family counselling/family therapy etc.)

III. Improving the patients' compliance

(psychoeducation, psychotherapy, cognitive therapy, regular contact, etc.)

IV. Reducing the stigma against bipolar disorders and suicide via media