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Suicide and bipolar disorder

Zoltán Rihmer

Department of Clinical and Theoretical Mental Health, and Department of Psychiatry and Psychotherapy, Semmelweis Medical University, Kútvölgyi Clinical Centre, Kútvölgyi út 4, 1125 Budapest, Hungary

Abstract

Bipolar disorders are common illnesses with markedly elevated premature mortality, but they remain frequently under-referred, under-diagnosed, and under-treated. Suicide is the cause of death in up to 15% of patients with bipolar disorders, and about half of them make at least one suicide attempt in their lifetime. The suicide rate of (untreated) bipolar patients is 25 times higher than the same rate in the general population. Suicidal behaviour in bipolar patients occurs almost exclusively during severe major depressive episodes, and less frequently in mixed affective episodes or in dysphoric mania. In contrast, suicidal behaviour occurs very rarely during euphoric mania, hypomania, or euthymia, suggesting that suicidal behaviour in bipolar patients is a state- and severity-dependent phenomenon. However, because the majority of bipolar patients never commit (and up to 50% of them never attempt) suicide, risk factors other than bipolar disorder itself also play a significant contributory role. This chapter summarises the clinically most relevant suicide risk and protective factors in bipolar disorders, and touches briefly on the most effective suicide prevention strategies.

Introduction

Bipolar disorders are associated with a substantial burden of illness-related health and economic problems. Given the 1.3–5.0% lifetime prevalence of Bipolar I and Bipolar II disorders [1] they are among the most frequent and also the potentially most life-threatening psychiatric illnesses [2–7]. This elevated risk of premature death is predominantly due to suicide, but increased incidence of accidents, cardiovascular morbidity, and complications due to comorbid substance-use disorders are also contributing causes [2, 4–7]. In spite of the great clinical and public health significance of bipolar disorders, they are still under-referred, under-diagnosed, and under-treated [1, 6]. Because successful acute and long-term treatment with mood stabilisers and other psychotropics markedly reduces the risk of attempted and completed suicide in Bipolar I and Bipolar II disorders [3, 4, 7–9], the early recognition and appropriate acute and long-term treatment of bipolar patients is a key element in suicide prevention for this population. Although suicidal behaviour is very rare in the absence of current major mental disorders [2, 3, 5], suicide is not the linear consequence of psychiatric disorders. It is a very complex and multicausal

human behaviour involving several psychosocial and cultural components. This chapter summarises the clinically most relevant suicide risk and protective factors in bipolar disorders, and also touches briefly on the most effective prevention strategies.

Suicidal behaviour in major mood disorders

In their meta-analysis of studies on suicide risk in all psychiatric disorders, Harris and Barraclough [10] analysed separately the risk of completed suicide in patients with an index diagnosis of unipolar major depression (23 reports, more than 8,000 patients) and in bipolar disorder (14 reports, more than 3,700 patients); some studies had followed these patients for many decades. They found that the risk of completed suicide (i.e., the standardised mortality ratio, SMR) was about 20-fold for patients with an index diagnosis of unipolar major depression, and 15-fold for bipolar disorders. However, this type of analysis cannot provide a precise estimate of separate suicide risk in unipolar and bipolar disorders (i.e., it overestimates the risk for unipolar depression and underestimates the same risk for bipolar disorders). The main source of this imprecision is that the index diagnosis frequently changes over the long-term course of illness from unipolar depression to Bipolar I or Bipolar II disorder [7, 11]; in the studies reviewed by Harris and Barraclough [10] the diagnostic category of Bipolar II depression (major depression with history of hypomania but not with mania), which is the most common form of bipolar disorders [1, 6], was not considered separately. Therefore it is very likely that most Bipolar II patients in these studies were included in the unipolar major depressive subgroup.

Moreover, recent findings showed that up to 50% of patients with unipolar depression were found to have bipolar depression when subthreshold hypomania as well as the bipolar spectrum disorders (i.e., 'unipolar' major depression with bipolar family history, treatment-associated hypomania/mania in major depression, and depressive mixed state/agitated depression) were also considered [1, 6, 12, 13]. Indeed, the most recent meta-analysis of 28 reports, published between 1945 and 2001 (including only patients with an index diagnosis of bipolar disorder without long-term lithium treatment) by Tondo and colleagues [3] found that during an average 10 years of follow-up the SMR for completed suicide in bipolar patients was as high as 22 (15 for males and 21 for females). These authors also calculated that suicide rates in bipolar disorder patients average 0.4%/year, which is more than 25 times higher than the same rate in the general population [3].

However, in a 40–44 years' prospective follow-up study of 406 formerly hospitalised (186 unipolar and 220 bipolar) major mood disorder patients, in which the unipolar–bipolar conversion was carefully considered during the follow-up, Angst and colleagues [7] found that 14.5% of unipolar and 8.2% of bipolar (I+II) patients committed suicide, and the SMR for suicide in unipolar

and bipolar patients were 26 and 12, respectively. In contrast, a very recent long-term prospective follow-up study (average 11 years) of 1983 unipolar major depressives and 843 bipolar (I+II) patients found a much higher rate of completed suicide in Bipolar I and II patients than in unipolar patients (0.25% of patients/year *versus* 0.05% of patients/year) [14].

Suicide risk factors in bipolar disorders

Suicidal behaviour (suicide, suicide attempt) and suicidal ideation in bipolar patients occur mostly during the severe major depressive episodes and less frequently in mixed affective episodes and dysphoric mania. They are very rare during euphoric mania, hypomania, and euthymia [2, 5, 15–17], indicating that suicidal behaviour in bipolar patients is a state- and severity-dependent phenomenon. However, because the majority of bipolar patients never commit (and up to 50% of them never attempt) suicide [2, 3, 4, 18–23], risk factors other than bipolar disorder itself also play a significant contributory role. These include special clinical characteristics as well as some personality, familial, and psychosocial risk and protective factors [2–4, 9, 12]. Most suicide risk factors in bipolar disorders are related to the acute (mostly depressive) major mood episodes but there are several historical and personality factors that can help clinicians identify highly suicidal bipolar patients.

Previous suicide attempt is the most powerful predictor of future completed suicide, particularly in patients with major mood disorders [2, 4, 5, 10, 15]. Considering only the 10 clinical studies (including more than 3,100 patients) in which unipolar and bipolar (I+II) patients were analysed separately, it has been found that the lifetime rate of prior suicide attempt(s) was much higher in bipolar (I+II) patients (mean: 28%, range: 10–61%) than in patients with unipolar depression (mean: 13%, range: 9–30%) [4]. A recent long-term prospective study also found that the rate of suicide attempts during follow-up was more than double in bipolar (I+II) than in unipolar patients [14]. Community-based epidemiological studies from the United States [18, 19] and Hungary [20] also showed that the lifetime rate of prior suicide attempts was 1.5 to 2.5 higher in bipolar (I+II) than in unipolar patients. Similarly, it has been reported that current suicidal ideation, the major precursor of suicidal behaviour [2, 15], was more frequent in Bipolar I and II (36–64%) than in unipolar (32–46%) depressed inpatients and outpatients [21–23].

The clinical conditions that are the most alarming for suicidal behaviour in bipolar disorder are the recent suicide attempt and the severe (mostly melancholic) major depressive episode, particularly when the latter is accompanied by hopelessness, guilt, agitation, insomnia [3, 13, 15, 24], few reasons for living, suicidal ideation [2, 3, 4, 9, 15, 16], and psychotic features [7, 15]. Recent results strongly suggest that mixed depressive episodes (major depression plus three or more co-occurring intra-depressive hypomanic symptoms) substantially increases the risk of both attempted and committed suicide [9, 12, 15,

22–25]. These episodes correspond to the category of 'agitated depression' that is present in up to 60% of bipolar depressives [12, 13, 22, 23].

Moreover, these results offer an explanation for the rarely occurring 'antidepressant-induced' suicidal behaviour; antidepressant monotherapy, unprotected by mood stabilisers or atypical antipsychotics, particularly in bipolar and bipolar spectrum disorder (including 'unipolar' depressive mixed state) can favour not only hypomanic/manic switches and rapid cycling, but also worsen the pre-existing mixed state or generate *de novo* mixed conditions. This makes the clinical picture more serious and ultimately leads to self-destructive behaviour [12, 22, 24, 26]. The role of mood instability in suicidal behaviour was also supported by a recent study showing that a history of rapid mood switching and panic attacks was associated with an increased likelihood of history of self-reported suicidal thoughts or actions in patients with bipolar disorders [27].

However, suicidal behaviour in bipolar patients is not exclusively restricted to depressive episodes. In contrast to classical (euphoric) mania, where suicidal tendencies are extremely rare, suicidal thoughts and attempts are relatively common in patients with mixed affective episode and dysphoric mania [2, 3, 14, 16], supporting the common clinical sense that suicidal behaviour in bipolar patients is linked to depressive symptomatology [7, 14–16].

Although bipolar disorders, in general, carry the highest risk of suicide [3, 4, 9, 14] several studies have shown that Bipolar II patients have an even higher risk than Bipolar I subjects [4, 9, 21, 23, 28–30]. However, other studies have found that suicide risk does not seem to vary according to bipolar subtype [2, 7, 14, 16, 31].

Bipolar disorders show a high frequency of psychiatric and medical co-morbidities [1, 31] and it is well documented that co-morbid anxiety/anxiety disorders [2, 4, 15, 18, 30–32], substance-use disorders [2, 4, 27, 30–32], personality disorders (especially borderline personality disorder) [4, 16, 31], and serious medical illnesses [2, 31], particularly in the case of multiple co-morbidities, also increase the risk of all forms of suicidal behaviour. Although successful acute and long-term treatment of bipolar disorder substantially reduces the risk of both completed and attempted suicide [3, 4, 7–9], lack of medical and family support as well as the first few days of the therapy when antidepressants usually do not work (or rarely can worsen the depression) [24], also should be considered as risk factors for suicide.

As noted previously, prior suicide attempt(s), particularly in the case of violent or more lethal methods, is the single most powerful predictor of future attempts and fatal suicide [2–4, 15, 16, 27]. Bipolar patients in general [33] and Bipolar II patients in particular [14, 34] use more violent and more lethal suicide methods than unipolar depressives and Bipolar I patients respectively, and this is characteristic first of all for males. Therefore, higher rates of suicidal behaviour (mainly completed suicide) in patients with bipolar disorder than in unipolar major depression may be due to a specific effect of bipolar disorder on males, resulting in more dangerous suicidal behaviours [33]. Other

historical variables that have been shown to increase the chance of both attempted and completed suicide include early onset, early stage of bipolar disorder [3, 5, 7, 14, 27, 32], rapid cycling course, predominant depressive polarity, and more prior hospitalisations for depression [2, 3, 7, 16, 31].

Personality characteristics also play a significant role in the development and particularly in the manifestation of suicidal behaviour. The voluminous literature on this subject consistently shows that aggressive/impulsive personality traits [16, 27, 33, 35–37], especially in combination with high level of current hopelessness and pessimism [35, 36], markedly increase the risk of suicidal behaviour in patients with bipolar and other psychiatric disorders. Recently it has been also reported that in Bipolar I and II depressed patients, the level of impulsivity and the rate of prior suicide attempts increased with increasing number of intra-depressive hypomanic symptoms [37], supporting the strong relationship between the bipolar nature of depression and impulsive behaviour [38]. Irritable mood (a core symptom of mania and hypomania) and anger attacks (inappropriate, sudden spells of anger associated with autonomic arousal symptoms and behavioural outbursts) are closely linked to each other, and anger attacks are much more common in bipolar depression than in unipolar depression [13, 38]. Moreover, if anger attacks occur during unipolar major depression, the bipolar nature of these 'unipolar' depressions are supported by their association with most key validating variables (early onset, atypical features of depression, depressive mixed state, bipolar family history) of bipolar disorder [38]. The interaction between personality features and illness characteristics in suicidal behaviour was best formulated by Mann and colleagues [35] in their 'stress-diathesis model', which suggests that suicidal behaviour in psychiatric patients is determined not only by the stressor (acute major psychiatric illness), but also by a diathesis (impulsive, aggressive, pessimistic personality traits).

Cyclothymia/cyclothymic temperament – the attenuated form of bipolar disorder – also seems to be a predisposing factor for suicidal behaviour. Cyclothymic personality appears to be significantly related to lifetime and current suicidal behaviour (ideation and attempts) both in adults and in a pediatric sample [39, 40].

Despite the fact that most suicide victims in the general population are males and the opposite is true for suicide attempters [5, 10, 15, 24], this difference is much smaller among suicidal patients with bipolar disorder [2, 3, 7, 27, 32]. This suggests that gender is not a significant predictor for committed and attempted suicide in this otherwise high-risk population. However, same-sex oriented and bisexual persons, mainly cross-gendered individuals, are at elevated risk for suicidal behaviour, particularly if other suicide risk factors are also present [41].

With regards to suicide risk factors related to personal history, early negative life-events (e.g., parental loss, isolation, or emotional, physical, and sexual abuse) [2, 4, 15, 31, 35], permanent adverse life situations (e.g., unemployment, isolation) [2, 4, 15], and acute psychosocial stressors (e.g., loss events,

financial disasters) [4, 15, 31, 42] are the most important and clinically useful indicators of possible suicidality, primarily if other risk factors are also present. However, acute psychosocial stressors commonly depend on the victim's own behaviour, particularly in the case of Bipolar I disorder [42]. For example, hypomanic and manic periods can easily lead to aggressive-impulsive behaviour, financial extravagance, or episodic promiscuity, thus generating several interpersonal conflicts, marital breakdown, and new negative life events, all of which have a negative impact on the further course of the illness.

Family history of suicidal behaviour and/or major mood disorders in first- and second- degree relatives is also a strong risk factor for both attempted and completed suicide in psychiatric patients in general, and in bipolar patients in particular [2, 4, 15, 27, 31, 35]. However, the familial component of suicidal behaviour seems to be independent of psychiatric disorders. Suicidal persons are over 10 times more likely than relatives of comparison subjects to attempt or complete suicide after controlling for psychopathology [43].

Table 1 Clinically detectable suicide risk factors in bipolar disorders

1. Risk factors related to acute mood episodes
   A. Severe major depressive episode
      - Current suicide attempt, plan, ideation
      - Hopelessness, guilt, few reasons for living
      - Agitation, depressive mixed state, insomnia
      - Psychotic features
      - Bipolar II diagnosis
      - Co-morbid Axis I, Axis II, and serious Axis III disorders
      - Lack of medical treatment and family/social support
      - First few days of the treatment (particularly if appropriate care and co-medication is lacking)
   B. Mixed affective episode (simultaneously occurring manic and major depressive episodes)
   C. Dysphoric mania (mania and three or more intra-manic depressive symptoms)
2. Risk factors related to prior course of the illness
   - Previous suicide attempt/ideation (particularly the violent/highly lethal methods)
   - Early onset/early stage of the illness
   - Rapid cycling course
3. Risk factors related to personality features
   - Aggressive/impulsive personality traits
   - Cyclothymic temperament
   - Same-sex orientation, bisexuality
4. Risk factors related to personal history
   - Early negative life events (separation, emotional, physical, and sexual abuse)
   - Permanent adverse life situations (unemployment, isolation)
   - Acute psychosocial stressors (loss events, financial catastrophe)
5. Risk factors related to family history
   - Family history of mood disorders (first and second degree relatives)
   - Family history of suicide and/or suicide attempt (first and second degree relatives)

The clinically explorable suicide risk factors in bipolar disorders are listed in Table 1. Because suicidal behaviour in bipolar patients is very rare in the absence of major mood episodes, suicide risk factors related to these conditions are the most powerful predictors of suicide, particularly if other risk factors (and high lethality suicide methods) are also present. The higher the number of risk factors, the higher the chance of suicidal behaviour.

Suicide protective factors in bipolar disorders

In contrast to what is known about risk factors for suicide, few circumstances are known to protect against suicidal behaviour. Good family and social support, pregnancy and postpartum period (but also see Chapter by Roy and Payne, this volume), having a great number of children, holding strong religious beliefs, and restricting lethal suicide methods whenever possible (e.g., reducing domestic and car exhaust gas toxicity, and introducing stricter laws on gun control), seem to have some protective effect [4, 5, 44–47]. However, the most extensively studied suicide protective factor in major mood disorders is acute and long-term pharmacological treatment, particularly with lithium (see below) [3, 4, 7–9, 15, 24].

Although suicide is a rare event in the community, it is very frequent among patients with bipolar disorder, and most of them come into contact with varying levels of healthcare some weeks or months before their death [3, 4, 8, 15, 29]. The high rate of bipolar disorders and recent medical contact before suicidal behaviour underlines the priority role of healthcare workers in suicide prevention. Unfortunately, less than one-third of bipolar suicide victims and suicide attempters were receiving appropriate pharmacotherapy at the time of their suicide event [29, 30, 48]. Because about two-thirds of suicide victims die in their first attempt [5, 15, 49], the risk of suicide in bipolar patients is very high even if a patient has never attempted suicide before. The careful estimation of all suicide risk factors (see Tab. 1) is helpful in assessing suicide risk as early as possible and intervening prior to the patient making the first suicidal act.

Prevention of suicidal behaviour in bipolar patients

Several open clinical studies and randomised controlled trials have consistently found that acute and long-term treatment with lithium and other mood stabilisers (sometimes in combination with antidepressants and antipsychotics) markedly reduces the risk of attempted and completed suicide in Bipolar I and Bipolar II patients [3, 4, 7, 24]. It has been also reported that the overall suicide rate of bipolar patients decreased progressively with increasing number of prescriptions for mood stabilisers [50]. Bipolar patients with long-term pharmacotherapy frequently need (and more frequently receive) antidepressants and/or antipsychotics in addition to their mood stabilisers for shorter or longer

period of time. However, there is a growing body of evidence suggesting that antidepressant monotherapy can worsen the course and outcome of bipolar disorder [6, 8, 9, 22, 24]. For instance, the most recent naturalistic, prospective chart review analysis of 405 Bipolar I and II patients also showed that mood stabiliser monotherapy markedly reduced the risk of suicidal behaviour; however, the frequency of suicidal behaviour was highest in patients with antidepressant and antipsychotic monotherapy, lowest in patients with mood stabiliser monotherapy, and the risk to patients with combination therapy (mood stabilisers + antidepressants or antipsychotics) was intermediate, suggesting that a combination of antidepressants or antipsychotics with mood stabilisers markedly reduces (but does not fully eliminate) this increased suicide risk [51–53]. However, it is possible that those patients receiving a combination of medications may have a more severe form of the illness, thus making it appear that that monotherapy is better.

These results support and extend prior findings [8, 9, 24] and suggest that not only antidepressants but also antipsychotics can worsen the cross-sectional and longitudinal course of bipolar disorders, and this worsening is most clearly reflected in the elevated rate of suicidality. Doctors should keep their bipolar patients on these supplementary medications as short a time as possible and the main component of the long-term treatment should be mood stabiliser pharmacotherapy. However, because the risk reduction for suicidal behaviour among bipolar patients treated with mood stabilisers, although clinically significant, is still incomplete, development of alternative or supplementary treatment strategies is also required.

Recently, several effective psychosocial interventions in the field of bipolar disorders were developed (psychoeducation, cognitive-behavioural therapy, interpersonal and social rhythm therapy, etc.), initially to help noncompliant, drug-intolerant, and drug-nonresponsive patients [4, 54, 55]. Because they are designed for relapse/recurrence prevention, they might be effective in suicide prevention as well, and a combination of these methods with long-term pharmacotherapy may substantially decrease suicide risk.

References

1 Rihmer Z, Angst J (2005) Epidemiology of bipolar disorder. In: S Kasper, RMA Hirschfeld (eds): *Handbook of bipolar disorder*. Taylor and Francis, New York, 21–35
2 Hawton K, Sutton L, Haw C, Sinclair J, Harris L (2005) Suicide and attempted suicide in bipolar disorder: A systematic review of risk factors. *J Clin Psychiatry* 66: 693–704
3 Tondo L, Isacsson G, Baldessarini RJ (2003) Suicidal behavior in bipolar disorder. *CNS Drugs* 17: 491–511
4 Rihmer Z (2005) Prediction and prevention of suicide in bipolar disorder. *Clin Neuropsychiatry* 2: 48–54
5 Goodwin FK, Jamison KR (2007) *Manic-Depressive Illness: Bipolar disorders and recurrent depression*. Oxford University Press, New York
6 Dunner DL (2003) Clinical consequences of under-recognized bipolar spectrum disorder. *Bipolar Disord* 5: 456–463

7 Angst J, Angst F, Gerber-Werder R, Gamma A (2005) Suicide in 406 mood-disorder patients with and without long-term medication: A 40 to 44 years' follow-up. *Arch Suic Res* 9: 279–300
8 Rihmer Z (2007) Pharmacological prevention of suicide in bipolar patients – A realizable target. (Editorial). *J Affect Disord* 103: 1–3
9 Akiskal HS (2007) Targeting suicide prevention to modifiable risk factors: Has bipolar II been overlooked? (Editorial). *Acta Psychiat Scand* 116: 395–402
10 Harris EC, Barraclough B (1997) Suicide as an outcome for mental disorders: A meta-analysis. *Br J Psychiatry* 170: 205–228
11 Goldberg JF, Harrow M, Whiteside JE (2001) Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry* 158: 1265–1270
12 Akiskal HS, Benazzi F, Perugi G, Rihmer Z (2005) Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. *J Affect Disord* 85: 245–258
13 Benazzi F (2006) Mood patterns and classification in bipolar disorder. *Curr Opin Psychiatry* 19: 1–8
14 Tondo L, Lepri B, Baldessarini R (2007) Suicidal risk among 2826 Sardinian major affective disorder patients. *Acta Psychiat Scand* 116: 419–428
15 Rihmer Z (2007) Suicide risk in mood disorders. *Curr Opin Psychiatry* 20: 17–22
16 Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P, Isometsa E (2005) Suicidal ideation and attempts in bipolar I and bipolar II disorders. *J Clin Psychiatry* 66: 1456–1462
17 Sokero P, Eerola M, Rytsala H, Melartin T, Leskela U, Lestela-Mielonen P, Isometsa E (2006) Decline in suicidal ideation among patients with MDD is preceded by decline in depression and hopelessness *J Affect Disord* 95: 95–102
18 Chen YW, Dilsaver SC (1996) Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. *Biol Psychiatry* 39: 896–899
19 Kessler RC, Borges G, Walters EE (1999) Prevalence and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 56: 617–626
20 Szádóczky E, Vitrai J, Rihmer Z, Füredi J (2000) Suicide attempts in the Hungarian adult population. Their relation with DIS/DSM-III-R affective and anxiety disorders. *Eur Psychiatry* 15: 610–617
21 Hantouche EG, Akiskal HS, Lancreon S, Allilare J-F, Sechter D, Azorin J-M, Burgeois M, Fraud J-P, Chatenet-Duchénne L (1998) Systematic clinical methodology for validating bipolar II disorder: Data in mid-stream from a French national multi-site study. *J Affect Disord* 50: 163–173
22 Benazzi F (2005) Suicidal ideation and depressive mixed states. *Psychother Psychosom* 74: 107–108
23 Sato T, Bottlender R, Kleindienst N, Möller H-J (2005) Irritable psychomotor elation in depressed inpatients: A factor validation of mixed depression. *J Affect Disord* 84: 187–196
24 Rihmer Z, Akiskal HS (2006) Do antidepressants t(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. *J Affect Disord* 94: 3–13
25 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. *J Affect Disord* 91: 133–138
26 Rihmer Z, Benazzi F, Gonda X (2007) Suicidal behavior in unipolar depression: Focus on mixed states. In: R Tatarelli, M Pompili, P Girardi (eds): *Suicide in psychiatric disorders*. Nova Science Publishers Inc, New York, 223–235
27 MacKinnon DF, Potash JB, McMahon FJ, Simpson SG, dePaulo Jr, JR, the National Institutes of Mental Health Bipolar Disorder Genetics Initiative, Zandi PP (2005) Rapid mood switching and suicidality in familial bipolar disorder. *Bipolar Disord* 7: 441–448
28 Bulik CM, Carpenter L, Kupfer DJ, Frank E (1990) Features associated with suicide attempts in recurrent depression. *J Affect Disord* 18: 29–37
29 Rihmer Z, Barsi J, Arató M, Demeter E (1990) Suicide in subtypes of primary major depression. *J Affect Disord* 18: 221–225
30 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 episode and of bipolar II diagnosis. *J Affect Disord* 76: 113–119
31 Leverich GS, Altshuler Frye MA, Suppes T, Keck PE, McElroy SL, Denicoff KD, Obrocea G, Nolen WA, Kupka R, Walden J et al (2003) Factors associated with suicide attempts in 684

patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry* 64: 506–515
32 Simon GE, Hunkeler E, Fireman B, Lee JY, Savarino J (2007) Risk of suicide attempt and suicide death in patients treated for bipolar disorder. *Bipolar Disord* 9: 526–530
33 Zalsman G, Braun M, Arendt M, Grunebaum MF, Sher L, Burke AK, Brent D, Chaudhury SR, Mann JJ, Oquendo MA (2006) A comparison of the medical lethality of suicide attempts in bipolar and major depressive disorder. *Bipolar Disord* 8: 558–565
34 Vieta E, Benabarre A, Colom F, Gastó C, Nieto C, Otero A (1997) Suicidal behavior in bipolar I and bipolar II disorder. *J Nerv Ment Dis* 185: 407–409
35 Mann JJ, Waternaux C, Haas GL, Malone KM (1999) Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 156: 181–189
36 Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ (2004) Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder and bipolar disorder. *Am J Psychiatry* 161: 1433–1441
37 Swann AC, Moeller FG, Steinberg JL, Schneider L, Barratt ES, Dougherty DM (2007) Manic symptoms and impulsivity during bipolar depressive episode. *Bipolar Disord* 9: 206–212
38 Benazzi F (2003) Major depressive disorder with anger: A bipolar spectrum disorder? *Psychother Psychosom* 72: 300–306
39 Akiskal HS, Hantouche EG, Allilare JF (2003) Bipolar II with and without cyclothymic temperament: dark and sunny expressions of soft bipolarity. *J Affect Disord* 73: 49–57
40 Kochman FJ, Hantouche EG, Ferrari P, Lancrenon S, Bayart D, Akiskal HS (2005) Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. *J Affect Disord* 85: 181–189
41 Fritzpatrick KK, Euton SJ, Jones JN, Schmidt NB (2005) Gender role, sexual orientation and suicide risk. *J Affect Disord* 87: 35–42
42 Isometsa E, Heikkinen M, Henriksson M, Aro H, Lönnqvist J (1995) Recent life events and completed suicide in bipolar affective disorder: A comparison with major depressive disorder in Finland. *J Affect Disord* 33: 99–106
43 Kim CD, Seguin M, Therrien N, Riopel G, Chawkay N, Lesege AD, Turecki G (2005) Familial aggregation of suicidal behavior: A family study of male suicide completers from the general population. *Am J Psychiatry* 162: 1017–1019
44 Marzuk PM, Tardiff K, Leon AC, Hirsch CS, Portera L, Hartwell N, Iqbal MI (1997) Lower risk of suicide during pregnancy. *Am J Psychiatry* 154: 122–123
45 Dervic K, Oquendo MA, Grunebaum MF, Ellis S, Burke AK, Mann JJ (2004) Religious affiliation and suicide attempt. *Am J Psychiatry* 161: 2303–2308
46 Driver K, Abed R (2004) Does having offspring reduce the risk of suicide in women? *Int J Psychiat Clin Pract* 8: 25–29
47 Rihmer Z (2004) Suicide prevention strategies – A brief review. *Neuropsychopharmacol Hung* 6: 195–199
48 Isometsa ET, Henriksson MM, Aro HM, Lönnqvist JK (1994) Suicide in bipolar disorder in Finland. *Am J Psychiatry* 151: 1020–1024
49 Isometsa ET, Lönnqvist JK (1998) Suicide attempts preceding completed suicide. *Br J Psychiatry* 173: 531–533
50 Sondergard L, Lopez AG, Andersen PK, Kessing LV (2008) Mood stabilizing pharmacological treatment in bipolar disorders and the risk of suicide. *Bipolar Disord* 10: 87–94
51 Yerevanian BI, Koek RJ, Mintz J (2007) Bipolar pharmacotherapy and suicidal behavior. Part I: Lithium, divalproex and carbamazepine. *J Affect Disord* 103: 5–11
52 Yerevanian BI, Koek RJ, Mintz J, Akiskal HS (2007) Bipolar pharmacotherapy and suicidal behavior. Part 2: The impact of antidepressants. *J Affect Disord* 103: 13–21
53 Yerevanian BI, Koek RJ, Mintz J (2007) Bipolar pharmacotherapy and suicidal behavior. Part 3: Impact of antipsychotics. *J Affect Disord* 103: 23–28
54 Michalak EE, Yatham LN, Lam RW (2004) The role of psychoeducation in the treatment of bipolar disorder: A clinical perspective. *Clin Appr Bipol Disord* 3: 5–11
55 Rucci P, Frank E, Kostelnik B, Fagiolini A, Malinger AG, Swartz HA, Thase ME, Siegel L, Wilson D, Kupfer DJ (2002) Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. *Am J Psychiatry* 159: 1160–1164