



Review

Suicidal behavior in bipolar disorder: Epidemiology, characteristics and major risk factors



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ABSTRACT

Background: Suicide is one of the leading causes of death and a major public health problem worldwide, and the majority of suicide attempters and completers suffer from some major affective disorder at the time of their death, which, in the majority of cases is unrecognized, under- or misdiagnosed and untreated.

Methods: Based on a systematic literature search, the authors give a detailed and critical overview of established risk factors of suicide in bipolar disorder.

Results: Among affective disorders, bipolar disorder carries the highest risk of suicide, yet not all bipolar patients commit or even attempt suicide during their illness. While the general suicide risk factors also apply for bipolar disorders, there are several disease-specific risk factors as well which should be taken into account when evaluating suicide risk in case of patients.

Conclusion: It is crucial to identify suicide risk factors in bipolar disorder to be able to differentiate those patients within this already increased-risk illness group who are at especially high risk and therefore to allow for better prediction and prevention of suicidal acts.

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Introduction: Epidemiology of suicidal behavior

Suicidal behavior is a worldwide major public health concern and a great challenge for psychiatry, other fields in medicine, and the whole society. Accordingly, suicide prediction and prevention receives increasing attention, however, being a multicausal and complex phenomenon, we are still far away from understanding its etiology and the factors playing a role in the emergence of suicidal behavior. The great majority of suicide victims are patients with major affective disorders, so psychiatric research should pay a major role in determining the key points involved in prediction and prevention of suicidal behavior.

Suicide is one of the ten leading causes of death worldwide and each year about one million suicide-related deaths happen in the general population (Levi et al., 2003; Oquendo et al., 2004b; Rihmer and Akiskal, 2006; Wasserman, 2000). Suicide attempts with varying severity and lethality are 20 to 30 times more common, and an even higher prevalence of suicidal ideation can be predicted (Tondo et al., 2007), since this latter phenomenon is commonly underestimated, in spite of constituting a major suicide risk factor and indicating great suffering in patients (Tondo et al., 2007).

According to the hierarchy of suicidal risk factors established based on their predictive value, psychiatric-medical risk factors are considered primary risk factors, since replicated studies indicate that 90% of suicide attempters and completers suffer from at least one, mostly unrecognized, untreated, or inadequately treated DSM-IV Axis I mental illnesses, most frequently major depressive episode (56–87%), substance use disorder (26–55%) or schizophrenia (6–13%) at the time of their act (Carroll-Ghosh et al., 2003; Rihmer, 2007b; Rihmer et al., 2002; Swann et al., 2005). Several medical conditions and personality disorders are also frequently present (Carroll-Ghosh et al., 2003; Mann et al., 1999; Rihmer, 2007b; Rihmer et al., 2002; Sudak, 2005; Wasserman, 2000). Generally, even when other medical (both psychiatric or somatic) conditions are in the background, depressive episode may be the common final pathway leading to the actual precipitation of suicidal behavior (Akiskal, 2007). However, there is a complex relationship between mental disorders and suicidal behavior and the majority of major mental disorder patients never attempt or commit suicide. Therefore, even in case of major mental and affective disorders the specific risk factors of suicidal behavior should be determined.

From all affective patients presenting with a major depressive episode at one point of their illness, bipolar disorder carries the highest suicide rate, and among bipolar patients with completed suicide more than half are untreated at the time of their death (Cassidy, 2011; Tondo et al., 2003). Considering lifetime prevalence rates, bipolar I disorder affects about 0.6% of the population, while bipolar II disorder affects about 0.4% of the population, but considering its other forms and manifestations, bipolar illness contributes to a prevalence of 2.4% of all bipolar spectrum disorders worldwide according to a study based on more than 60 000 subjects in 11 countries (Merikangas et al., 2011). Furthermore most recent prospective studies of adolescents estimate bipolar II prevalence rates at 3–4% (Merikangas and Lamers, 2012). Although there is increasing recognition of bipolar disorder, it is still underrecognized, underdiagnosed,

underreferred, undertreated and often mistreated (Dunner, 2003; Rihmer and Angst, 2005). Bipolar disorder is still associated with a marked premature mortality, with a mortality rate 2–3 times higher compared to the general population (Muller-Oerlinghausen et al., 2002). This increased and untimely lethality in bipolar disorder patients is in part due to accidents, medical illness and substance abuse, but the greatest part of excess lethality in bipolar patients results from suicide (Sher et al., 2006).

Bipolar disorder patients are at an equally elevated risk for suicidal ideation, attempts and fatal suicides (McIntyre et al., 2008). Although studies and reviews differ about the relative rate of suicide in bipolar patients compared to the general population, it can be estimated that in bipolar disorders the annual risk of attempts is 400–1400/100 000, approximately 0.9%, which means 30 to 60-fold higher than the general population rate (Ahrens et al., 1995; Baldessarini et al., 2006a; Baldessarini et al., 2006b), and without treatment about 1000/100 000 bipolar patients commit suicide every year (Gibbons et al., 2009). Synthesizing the published data, about one third to one half of bipolar patients attempt suicide at least once in their lifetime and approximately 15–20% of bipolar patients die due to suicide (Baldessarini et al., 2006a; Baldessarini et al., 2006b; Chen and Dilsaver, 1996; Engstrom et al., 2004; Goodwin and Jamison, 1990; Grunebaum et al., 2006; Harris and Barraclough, 1997; Rihmer and Angst, 2005; Tondo et al., 2003; Tondo et al., 2007; Valtonen et al., 2005).

Furthermore, suicidal behaviour is much more lethal in bipolar disorder than in the general population. Completed suicide occurs one time for every 30 attempts in the USA in the general population, and one time for every 3–4 attempts in case of bipolar patients (Simon et al., 2007a).

Therefore, completed suicide and suicide attempts are major issues in the management of bipolar disorders. Although it is well known that suicide risk is especially high in bipolar disorders, there is only little available data on the specific epidemiology and risk factors of suicide within bipolar depression, and the majority of even those few studies are retrospective or cross-sectional in nature. Besides better recognition and treatment of bipolar patients, understanding and identifying suicide risk factors within bipolar illness would be a crucial tool of predicting and preventing suicide in bipolar disorder.

To investigate the relevant suicide risk factors in bipolar disorder, we performed a systematic PubMed search for papers published in English between 1990–2011 using the research string “suicidal behaviour OR suicide OR suicidal attempt OR suicidal ideation OR suicidal thoughts AND bipolar disorder OR bipolar depression OR manic-depressive AND risk factors OR prevalence”, in title and/or abstract. The search returned 209 articles. All abstracts were investigated for eligibility for inclusion in the study, quality, and relevance. Of the published papers those not specifically focusing on suicide in bipolar disorder were omitted. Only papers from peer reviewed journals were included.

Risk factors of suicide in bipolar disorder

It was demonstrated that while the general suicide risk factors also apply to bipolar patients (Simon et al., 2007a), there are some

distinct characteristics as well. In the following sections we summarize suicide risk factors replicated in studies concerning bipolar disorder which should be taken into account when evaluating suicide risk in individual patients.

Gender

In the general population, different types of suicidal behavior show a marked association with gender. There is a clear gender difference in suicide mortality, with two thirds of suicide victims being male all around the world except for a few countries such as China or India, which may be related to the fact that males apply violent suicide methods more frequently and seek help for their psychological problems less frequently compared to women. On the other hand, internationally the majority of suicide attempters are female (Harris and Barraclough, 1997). Suicide rate also shows an increase with age in both genders, although the attempted/completed suicide ratio decreases. There are also reports of an increase in suicide mortality in young males in several Western countries (Carroll-Ghosh et al., 2003; Sudak, 2005; Wasserman, 2000).

Risk of bipolar disorder is largely gender-independent and there are no gender differences in the prevalence of bipolar I disorder, but since women report more depressive episodes, they are more likely to be diagnosed bipolar II (Schneck et al., 2004). The gender pattern of suicidal behavior seen in the general population was reproduced in some studies in bipolar disorder as well, however, with many conflicting results.

Some studies found higher rate of attempts in bipolar women compared to men (Tondo et al., 2003). In one bipolar sample suicide attempts were more likely in women and associated with younger age, while completed suicide was not associated with age but with male gender, and the authors concluded that among bipolar patients women younger than 30 years of age are at a highest risk for suicide attempt, but are at a low risk for completed suicide (37/1000 person years and 0.44/1000 person years respectively), while men older than 45 years had a low risk of suicide attempt but a high risk of dying of suicide (9.7/1000 person years and 1.9/1000 person years respectively) (Simon et al., 2007a). Male bipolar patients have a four times higher risk for suicide compared to women, and in bipolar women suicide attempt rates are double compared to men, which indicates a greater lethality of suicidal acts in men (Pompili et al., 2009), however, long-term risk of death by suicide is somewhat greater in bipolar women compared to bipolar men. The results, however are conflicting, other studies found no gender difference in case of suicide attempts (Leverich et al., 2003), in one study the rate of suicide attempts was also similar in males and females (39% vs 36%, respectively) and attempts were found to be as violent in females as in males (Cassidy, 2011), although in another study in spite of no difference between the rate of suicide attempts in the two genders (33% in women and 28% in men), women were found to use less violent while men more violent methods (D'Ambrosio et al., 2012), and other studies also demonstrated that gender is only associated with violence of method but not with differences in suicide attempt rate in bipolar disorder (Raja and Azzone, 2004). Overall, the gender difference seems to be less marked in case of bipolar disorder suicidal patients compared to unipolar patients and to the general population, and concerns rather method than frequency (Angst et al., 2005; Cassidy, 2011; Hawton et al., 2005; Tondo et al., 2003).

It should also be taken into account, however, that gender is also associated with specific risk factors for suicidal behavior in bipolar disorder, for example, one study in bipolar suicide attempters found that women report more sexual and physical abuse in childhood, while men report higher rates of psychoactive

substance utilization parallel to their suicidal behavior (Oquendo et al., 2004a; Stefanello et al., 2008).

Prior suicide attempt

The strongest and most robust predictors of suicide attempts and suicide completion are previous attempts already in the general population, and previous suicide attempt is a particularly important suicide risk factor for bipolar disorder patients (Cassidy, 2011; Goodwin et al., 2003; Harris and Barraclough, 1997; Hawton et al., 2005; Rihmer, 2007a), especially in patients with a major depressive episode (Rihmer, 2007b; Rihmer et al., 2002). In bipolar disorder patients there is a prior suicide attempt in case of 40% of treated bipolar patients (Leverich et al., 2003), while considering those clinical studies where unipolar and bipolar patients were analyzed separately, the lifetime rate of prior suicide attempts was found to be significantly higher in bipolar patients compared to unipolar patients (28% vs 13%) (Rihmer and Angst, 2005). Community-based epidemiological studies 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 (Kessler et al., 1999; Szadoczky et al., 2000), indicating the importance of this risk factor in case of bipolar disorder.

In bipolar samples previous attempts were identified as an independent risk factor for subsequent suicide attempts and completion (Hawton et al., 2005), and up to 56% of suicide completers have a previous suicide attempt (Nordstrom et al., 1995; Oquendo et al., 2004a; Pompili et al., 2009; Tsai et al., 2002). In a prospective 18-month follow up study of 176 bipolar I and II patients, 20% had attempted suicide and the strongest predictor was previous suicide attempt (OR 3.8), which was present in 90% of attempters (Valtonen et al., 2006). Another prospective study also reported a high hazard ratio of 4.41 for previous suicide attempts in case of suicide attempters (Oquendo et al., 2004a). Prior suicide attempt increases the risk of completed suicide by 37-fold in case of bipolar patients (Harris and Barraclough, 1997).

It was also reported by a small study that history of life suicide attempts in bipolar I disorder is significantly associated with poorer social skills, including conversational skills and social self-confidence, social openness to new people and situations, and self-control of aggressiveness and individual reactions to aversive stimuli requiring the management of anger and aggressiveness, compared to healthy controls and bipolar patients without suicide attempts (Rocca et al., 2011).

Suicidal ideation

Suicidal ideation has been associated with subsequent suicides and suicide attempts. Prevalence of suicidal ideation in bipolar disorder according to different studies varies between 14–59%, and according to cross-sectional studies, risk factors for suicidal ideation include affective disorder, severe depression, psychotic symptoms, past suicide attempt, alcohol abuse or dependence, panic disorder symptoms and earlier age of onset (Bottlender et al., 2000; Goldberg et al., 1999).

Prospective studies reported depression, hopelessness and mixed depression as predictors of suicidal ideation and suicide attempts in bipolar disorder (Johnson et al., 2005). In several studies it was also reported that suicide ideation predicts completed suicide in patients with major affective disorder, although the results are conflicting (Fawcett et al., 1990). In a prospective study 61% of bipolar patients reported suicidal ideation during index episode, and 20% of suicidal ideators reported suicide in the same episode, with all attempters reporting prior suicidal ideation (Valtonen et al., 2005), although in another study the same

authors reported suicidal ideation to predict suicide attempts only in univariate analyses but not in multivariate analyses of bipolar patients (Valtonen et al., 2006). Other studies also indicated that higher levels of suicide ideation are correlated with greater risk of future suicide attempts in bipolar patients (Galfalvy et al., 2006). It was also reported that suicide attempters were more likely to endorse suicidal ideation also during subsequent acute phases or hospitalizations (Fagiolini et al., 2004; Oquendo et al., 2000). Suicide ideation seems to be an important risk factor for suicide attempts, either as a state-like (worsening during depressed or mixed phases) or a trait dependent factor (being associated with a wider pessimism factor including hopelessness and subjective severity of depression (Oquendo et al., 2006; Oquendo et al., 2004a).

Family history of suicide

A further well-established general risk factor for suicide is family history of suicide and family history of mood disorders in first degree relatives (Hawton et al., 2005; Leverich et al., 2003; Mann et al., 1999). Family history of suicide was found to be significantly associated with suicide attempts in a systematic review of 23 studies, with an odds ratio of 1.71 (Hawton et al., 2005). In a study of 648 bipolar patients, significantly more suicide attempters had a positive family history of suicide than nonattempters (44% vs 32%, $p=0.002$) (Leverich et al., 2003).

Family history of completed suicide was found to be a predictor among multiple diagnostic groups, and is also associated with increased risk of suicide attempts in major affective disorder and bipolar patients in most studies (Brent et al., 2002; Cassidy, 2011; Galfalvy et al., 2006). Attempted and completed suicide in the family both increased risk of suicide attempts (Brent et al., 2002; Sanchez-Gistau et al., 2009). Family history seems to be the most relevant risk factor, and transmission of suicidal behavior remains significant even after controlling for the effects of familial aggregation of psychiatric disorders, indicating a possibly independent genetic predisposition for suicide which is different and independent from familial predisposition for bipolar illness (Brent et al., 2002; Oquendo et al., 2004a) or other types of psychopathology (Kim et al., 2005). Bipolar patients are over-represented among patients with a family history of suicide (Guillaume et al., 2010) which may partly be explained by the difference in heritability in affective disorder types, because in the familial transmission of suicidal behavior, transmission of mood disorder is an essential but not sufficient component, so the association between bipolar disorder and family history of suicide may be due to a higher heritability of bipolar disorder compared to unipolar major depression (Brent et al., 2002; Guillaume et al., 2010). Genetic factors have been consistently found to play a role in suicide, as also supported by twin, family and adoption studies (Brent and Melhem, 2008; Ernst et al., 2009).

Suicide in different mood episodes of bipolar disorder

Severe, agitated and/or anxious major depressive state, especially with recurrent insomnia and in the presence of past suicide attempt constitute the highest-risk constellation for suicide (Rihmer, 2007b; Rihmer and Gonda, 2011). Bipolar disorder patients commit or attempt suicide mostly during severe, pure or mixed depressive episodes (78–89%) and less frequently during mixed affective episodes or dysphoric mania (11–20%), but very rarely during states of euphoric mania or euthymia (0–7%) (Baldessarini et al., 2006a; Kessing, 2004; Pompili et al., 2009; Rihmer, 2007b; Sher et al., 2006; Valtonen et al., 2007). Mixed depression shows a strong association with bipolar disorders and particularly bipolar II disorder and mixed depression is an

important suicide risk factor (Rihmer, 2007b). Mixed depressive episodes are three times as frequent in bipolar II disorder compared to unipolar depression, which may in part contribute to the increased suicide risk observable in bipolar II disorder compared to unipolar depression (Balazs et al., 2006; Benazzi, 2003a, b).

The majority of suicides in bipolar patients attempted and committed during depressive episodes supports the common clinical observation that suicidal behavior in bipolar patients is linked to depressive symptomatology, however, suicide in bipolar patients may occur outside of depressive episodes, and suicidal ideation is relatively common in dysphoric mania and mixed affective episodes (Angst et al., 2005; Valtonen et al., 2005; Valtonen et al., 2008b). Mixed depressive episode significantly contributes to an increased risk of attempted and completed suicide (Akiskal et al., 2005; Balazs et al., 2006; Benazzi, 2005; Rihmer and Akiskal, 2006; Sato et al., 2005; Valtonen et al., 2008a), which also might explain the rare phenomenon of “antidepressant-induced suicidal behavior” (Benazzi, 2003c; Rihmer, 2007b; Rihmer and Akiskal, 2006).

Specifically focusing on mania and distinguishing pure and mixed forms of it, 26–55% of patients in mixed (dysphoric) mania have current suicidal ideation while in case of pure mania patients the frequency is only 2–7% (Baldessarini et al., 2006a).

Suicidal ideation occurs in 79% of depressed phases of bipolar disorder, and is also strongly associated with mixed phases, and in both of these states it is more common than during mania (Dilsaver et al., 1994; Isometsa et al., 1994; Sher et al., 2006; Valtonen et al., 2007). Patients with bipolar depression are more likely to be suicidal compared to patients with depressive mania and these latter are more likely suicidal compared to patients with pure mania (Dilsaver et al., 1997). Since suicide ideation, attempt and completed suicide occurs most likely in given phases of bipolar disorder, suicidal behavior in bipolar patients seems to be a state- and severity-dependent phenomenon (Rihmer, 2007b; Rihmer and Kiss, 2002).

Rapid cycling course

Prevalence of current rapid cycling in bipolar disorder is 13–56% (Gao et al., 2009). There are several differences between rapid cycling and non-rapid cycling bipolar patients concerning clinical course, comorbid conditions and response to treatment (Coryell et al., 2003) and rapid cycling was identified as a risk factor for suicide attempts across most (Leverich et al., 2003; MacKinnon et al., 2005; Maj et al., 1994; McIntyre et al., 2008), but not all studies (Kupka et al., 2005; Valtonen et al., 2006). In one study on 387 patients with rapid cycling bipolar disorder more than 41% of patients had at least one suicide attempt (Gao et al., 2009). Risk of suicide attempt in rapid cycling bipolar disorder is 36–57% (Gao et al., 2009). Suicidal risk was found to be higher in rapid cyclist bipolar patients and those characterized by mixed states, and patients with rapid cycling carry a 54% higher risk to attempt suicide (Hawton et al., 2005). Besides a higher risk of suicide attempts, rapid cycling course of bipolar disorder is also associated with attempts characterized by a higher intent and lethality compared to non-rapid cyclers (Coryell et al., 2003).

Illness characteristics

Suicide is associated with particular characteristics of bipolar illness course. Suicide attempts are common at the onset of bipolar illness during the first depressive episode, and early in the illness course (Baldessarini et al., 2006a; Engstrom et al., 2004). Among bipolar patients, those with a longer duration of untreated illness show a higher frequency of suicide attempts,

and among patients with a longer duration of untreated illness there is a higher frequency of depressive first episode, which is also associated with increased suicide risk. Therefore the length of untreated bipolar disorder seems to be associated with a worse outcome of the illness and particularly suicide as an outcome (Altamura et al., 2011). In patients with more than two years of untreated illness, the frequency of suicide attempts and suicide attempters was significantly higher compared to those with 2 years or less of untreated bipolar disorder (number of suicide attempts: 0.40 ± 0.86 vs 0.15 ± 0.44 , respectively; and frequency of suicide attempters: 23.9% vs 12.5% respectively in patients with more than 2 years and 2 years or less than two years of untreated bipolar illness) (Altamura et al., 2011). There is often a 5–10 year delay of proper diagnosis and thus establishment of sustained long-term therapy, and this delay is even longer in women and in bipolar II depression (Baldessarini et al., 2006a). Number of previous episodes was also associated with suicide attempts, and attempters were found to have twice as many previous depressive episodes as non-attempters (Oquendo and Mann, 2001).

High risk of suicide in bipolar patients most likely reflects high levels of unresolved depressive morbidity (Tondo et al., 2007). Suicidal acts were associated with a bipolar diagnosis and indicators of greater illness severity or illness burden, and suicidal ideation was independently associated with bipolar I diagnosis, presence of affective temperaments and being ill for less time (Tondo et al., 2007).

Suicide attempters also have had more prior hospitalizations due to depression (Leverich et al., 2003), and patients with more severe depressive episodes were at a higher risk of attempting suicide during follow up and subjective and clinical severity of depressive phases was also associated with suicide attempts (Marangell et al., 2006; Oquendo et al., 2000). Although severity of depression is associated with suicide attempt risk, it seems that it is associated not with clinician-rated objective severity, but with patients' subjective severity both in depressed and mixed states (Galfalvy et al., 2006; Valtonen et al., 2007). Bipolar patients with a history of suicide attempts are also characterized by a pattern of increasing severity of mania, increased number of prior psychiatric admissions, greater incidence of suicidal thoughts when manic or depressed, and more medical illnesses (Leverich et al., 2003).

In studies on both unipolar and bipolar II depressed patients, higher odds for suicidal behavior were found for those with atypical depression, which shows a higher prevalence in bipolar II depression compared to unipolar depressives (Matza et al., 2003); (Sanchez-Gistau et al., 2009). In bipolar II patients frequency of atypical depression may range from 12–60% (Sanchez-Gistau et al., 2009). Increased number of suicide attempts was also associated with history of psychosis during depression (Gao et al., 2009).

Multiple factors that affect the severity, course and outcome of bipolar disorder may also be related to suicide in bipolar disorder, such as medical comorbidity, being overweight/obese, presence of metabolic syndrome and these results suggest that suicidal behavior in bipolar disorder emerges on the ground of an interaction between sociodemographic, clinical, anamnestic, environmental and iatrogenic factors, with the burden of depressive symptoms as a common risk factor for both attempted and completed suicide, and medical comorbidity already showing a higher frequency in bipolar illness is also associated with this suicide risk (McIntyre et al., 2008).

Age of onset

Age of onset of bipolar disorder also seems to be a risk factor for suicide attempt in bipolar disorder, as it was confirmed by systematic reviews (Hawton et al., 2005). Although median age of

onset in BD is 25 years, in a quarter of patients the onset of disease is before the age of 17 (Pompili et al., 2009). In the STEP-BD study there was a significant difference in the prevalence of lifetime suicide attempts with respect to age at illness onset (48.8%, 37.0% and 24.6% in case of onset before 13 years, onset between 13–18 years, onset after 18 years respectively) and very early onset of the illness (before 13 years of age versus 18 years) was found to increase the risk of suicide attempts 2.8-fold (Perlis et al., 2004). Very early disease onset was also associated with increased risk of such comorbid conditions, including anxiety disorders, alcohol dependence and abuse disorder, which in turn also increase risk of suicidal behavior (Perlis et al., 2004). Several individual studies reported an association between early age of onset and suicide attempts in bipolar disorder (Galfalvy et al., 2006; Grunebaum et al., 2006; Leverich et al., 2003; Tondo et al., 2007), however, it remains to be elucidated whether age of onset is an independent risk factor, or is related to increased risk due to its association with other factors increasing suicide risk, including severity of illness, rapid cycling, more Axis I and II comorbidities or increased childhood physical and sexual abuse (Abreu et al., 2009).

Episode polarity and polarity of first affective episode

Episode polarity has also been associated with suicide attempts in bipolar disorder. Suicidal behavior is mainly associated with depressed and mixed phases (Oquendo et al., 2000), and dominance of depressive and mixed phases of bipolar disorder is also associated with higher risk of suicide attempts (Hawton et al., 2005).

According to some studies, bipolar disorder course is associated with polarity of the initial affective episode (Chaudhury et al., 2007; Perlis et al., 2005). In one study it was reported that patients with a first mood episode of depressive polarity show an eightfold greater odds for suicide attempts (Chaudhury et al., 2007).

Life events related to suicide in BD

There are also suicide risk factors related to personal history, which include early negative life events (Leverich et al., 2003; Rihmer, 2007b), as well as permanent chronic adverse life situations and acute psychosocial stressors (Hawton et al., 2005; Leverich et al., 2003; Rihmer, 2007b). Negative life events without available social support are also related to suicidality in bipolar disorder (Leverich et al., 2003). However, especially in case of bipolar I disorder, acute psychosocial stressors are not independent of the patient's own behavior, and manic and hypomanic episodes are indeed associated with several behaviors including aggressive-impulsive acts, episodic promiscuity, financial extravagance which may generate multiple interpersonal conflicts and lead to negative life events constituting acutely and permanently pressing psychosocial stressors (Isometsa et al., 1995).

Bipolar patients with a history of suicide attempts are also characterized by early traumatic experiences, prior interpersonal losses, a greater mean number of negative life events prior to the most recent affective episode, increased number of prior psychiatric admissions, and problems with access to health care in the year before their last affective episode. Lack of confidant prior to illness onset was also important, but familial relationships were not (Leverich et al., 2003).

Childhood abuse

Such distal life stressors as childhood adversity and abuse including physical and sexual abuse and other types of stress experienced in early life is increasingly associated with suicide

risk in bipolar disorder (McIntyre et al., 2008). Early physical and sexual abuse was found to increase suicide attempt risk across several studies (Grunebaum et al., 2006; Leverich et al., 2003; Oquendo et al., 2004a). There appears to be a dose effect in the frequency of abuse (Leverich et al., 2003). Early stressful life events may be vulnerability factors, and contribute to the development of an underlying neural substrate for provocation by stress events in adulthood (Leverich et al., 2003).

Although early abuse and life stress seems to be a general risk for suicide in bipolar disorder, there is also increasing evidence that different types of early stress contribute to different nature of increased suicide risk. Leverich et al. reported an association between childhood and adolescent physical or sexual abuse and suicide attempts in bipolar disorder (Leverich et al., 2003), with the physically abused group reporting increased suicidal ideation in manic phase and the sexually abused group reporting increased suicidal ideation in depressed phase (Leverich et al., 2003). Although sexual abuse in childhood shows a significant association with suicide attempts, in one study no association was found between suicidal behavior and physical or emotional abuse or emotional neglect (Goldberg and Garno, 2005).

Comorbid Axis I and II disorders

One possible reason for the increased risk of suicide in bipolar disorder is that bipolar illness shows an unusually high ratio of axis I and II comorbidities (Leverich et al., 2003). 65% of bipolar patients have at least one psychiatric comorbidity, 42% two or more, and 24% three or more comorbid conditions besides their bipolar illness (McElroy et al., 2001). Axis I and II disorder comorbidity in bipolar disorder was found to be associated with suicide attempts. Although results are conflicting, the strongest association with suicide attempts was found in case of anxiety disorders, eating disorder, and alcohol and drug abuse disorders (Hawton et al., 2005). Presence of comorbid anxiety disorder or extreme agitation and panic during a depressive phase, dysphoric mania, and history of alcohol and drug abuse has been associated with suicide (Leverich et al., 2003). However, the role of these comorbid conditions is controversial, since in some studies Axis I comorbid disorders were significant predictors of suicide attempts only in univariate analyses (Leverich et al., 2003).

Comorbid anxiety symptoms and disorders

Although comorbid anxiety appears to be a risk factor for suicide both in general samples (Stordal et al., 2008) and in bipolar disorder (Simon et al., 2007a), in studies investigating the role of comorbid anxiety in suicide risk elevation in bipolar disorder results are conflicting: some studies find an association between anxiety or anxiety disorders and suicide ideation or attempt history in bipolar patients (Engstrom et al., 2004), others do not (Leverich et al., 2003; Neves et al., 2009; Slama et al., 2004) especially after applying multivariate and logistic regression analyses. In one study with bipolar patients a comorbid anxiety disorder diagnosis was associated with an increased risk for completed and attempted suicide (Simon et al., 2007a). A cross sectional study of 120 bipolar outpatients indicated that comorbid anxiety disorders, and especially generalized social anxiety disorder (GSAD) are associated with current suicidal ideation, lifetime suicidal ideation and lifetime suicidal behaviors in bipolar disorder, also after controlling for age, gender and substance abuse (Simon et al., 2007b). One large metaanalysis also indicate increased suicide risk with anxiety disorder comorbidity (Tondo et al., 2003).

Anxiety disorders constitute a risk for suicide in bipolar disorder both cross-sectionally and on the long term as well. In

one study with patients suffering from major affective disorder it was concluded that severe psychic anxiety, panic attacks and severe insomnia may be imminent or acute risk factors for suicide (Fawcett et al., 1990). In a study of association of current and lifetime comorbid anxiety disorders with suicidality it was found that current comorbid anxiety is associated with more than double odds for current suicidal ideation. In those patients with current anxiety, more suicidal ideation, greater belief that suicide would yield relief, and higher expectancy of future suicide behaviors was found (Simon et al., 2007b). In other studies the long-term role of anxiety as a suicide risk factor was also reported, indicating that there may be several mechanisms by which anxiety mediates suicide in bipolar patients. It was described in one study that in a span of 20 years, baseline anxiety predicts and increases time spent depressed over a period of 20 years' follow up (Coryell et al., 2009). Lifetime anxiety disorders more than doubled the odds of past suicide attempts, and current comorbid anxiety more than doubled the odds of current active and passive suicidal ideation (Simon et al., 2007b).

One reason for the possible importance of the role of anxiety comorbidity as a suicide risk factor is that anxiety and anxiety disorders may be modifiable risk factors. Furthermore, there have been studies describing an association between bipolar disorder severity and panic, bipolar course and generalized social anxiety disorder, and suicide attempts and panic attacks and disorder, and generalized social anxiety disorder, which indicate an increased risk for anxiety disorder comorbidity for bipolar disorder patients (Otto et al., 2006; Simon et al., 2004; Statham et al., 1998). Some studies argue that the association between suicide attempts and ideation and anxiety disorders is explained by the comorbidity between panic and affective disorders, while according to others, anxiety disorders seem to be independent risk factors for subsequent suicide ideations and attempts (Sareen et al., 2005). Indeed, anxiety disorders like generalized social anxiety disorder and panic have been associated with such disease characteristics of bipolar disorders which themselves are associated with increased risk of suicide, such as earlier onset of bipolar disorders, greater disability and poorer illness course (Otto et al., 2006) so maybe the association between comorbid anxiety disorders and suicidal behavior in bipolar illness may be mediated by the greater illness severity and earlier onset in case of the lifetime analyses and lack of recovery in current analyses, which is in turn associated with greater risk of suicide (Simon et al., 2007b). Comorbid anxiety disorders may be involved in certain other characteristics of bipolar illness which elevate the risk for suicide ideation and attempts, such as resulting in early stress, affective instability, social and role function impairment leading to early onset of initial mood episodes and the exact role of these factors and their relationship in the causative pathway is yet to be elucidated (Perlis et al., 2004). Anxiety disorders may increase suicide risk in other, possibly independent pathways, for example avoidance strategies used in face of stress have been linked to greater suicide risk (Simon et al., 2007b). Anxiety may also be involved in increased risk of suicidal behaviours through leading to increased distress, intolerability of negative affect and illness symptoms, increased rumination and increased intrusive and distressing suicidal ideation (Schmidt et al., 2001). As in bipolar patients with anxiety disorder comorbidity more associated depressive symptoms are observed, the role of anxiety in the background of increased risk of suicide in bipolar disorder may be mediated by depression (Azorin et al., 2009). Furthermore, social support and social problem solving is also impaired in social anxiety disorder and thus psychotherapy targeted at these aspects may be effective in reducing suicide attempts (Simon et al., 2007b). Anxiety disorder comorbidity may also be a phenotypic expression of a more severe form of bipolar disorder

contributing to a bipolar-anxiety subtype, with distinct genetic and biological background, which leads to earlier onset and increased risk of suicide attempts, and it is also possible that biological factors contribute to increased risk of suicide attempts and ideation in bipolar disorder comorbid with anxiety disorders (Simon et al., 2007b).

As several forms of anxiety symptoms and disorders have been found to be associated with suicidality in bipolar illness, including different manifestations of the anxiety spectrum from anxiety-related traits such as harm avoidance to social anxiety, panic attacks, agoraphobia, apprehension and anticipatory worry, it is not yet understood which aspect of anxiety is related to the observed association with increased risk of suicidal behaviours in bipolar disorder (Frank et al., 2002; Marangell et al., 2006; Young et al., 1993), but research results suggest that more than one features would be involved (Engstrom et al., 2004). The exact association between anxiety comorbidity and increased suicide risk in bipolar disorder is therefore not understood yet. However, whichever mechanism lies behind, anxiety disorder comorbidity is useful in identifying high risk suicidal patients in bipolar disorder (Simon et al., 2007b) and also offers a potential target of intervention.

Drug and alcohol abuse disorders, nicotine abuse

In the general population nicotine use and alcohol and drug abuse are well established risk factors of suicide, but in bipolar disorder samples this association is not as clear, with contradictory results from studies (Cassidy, 2011). In several studies in bipolar samples suicide attempts were not associated with alcohol abuse or general drug abuse (Cassidy, 2011; Galfalvy et al., 2006); cocaine abuse/dependence, however appeared to predict suicide attempts (Cassidy, 2011), possibly due to the dysphoria experienced upon withdrawal. In one study in bipolar disorder comorbid substance abuse was only found to be related to increased risk of suicide attempt but not completed suicide (Simon et al., 2007a).

In an exclusively bipolar population including only Caucasian patients, family history of suicide and history of cocaine abuse were found to be predictors of suicide attempts, while nicotine use, and alcohol and other drug abuse was not (Cassidy, 2011). Benzodiazepine abuse may be possibly related to suicide attempts in bipolar samples (Cassidy, 2011). The association between nicotine use and suicide attempts was not significant in some studies (Cassidy, 2011; Galfalvy et al., 2006; Marangell et al., 2006; Oquendo et al., 2000) and significant in others (Ostacher et al., 2006).

Axis II comorbidities

Suicidality is also increased in bipolar patients with axis II comorbidity, and it is particularly true for bipolar patients with cluster B personality disorders including histrionic, narcissistic, borderline and antisocial personality disorder (Leverich et al., 2003; Neves et al., 2009), and the effect of these personality disorders on suicide in bipolar illness seems to go beyond simply that of disease burden, loss of social support, lack of health care effects, and increased negative life events (Leverich et al., 2003; Sanchez-Gistau et al., 2009). Since about 30% of bipolar patients have comorbid cluster B personality disorders, with 17% comorbidity for borderline, 8% for narcissistic, 65% for antisocial and 5% for histrionic personality disorder (Garno et al., 2005), these comorbid conditions should be carefully investigated to evaluate suicide risk in patients.

In one study in 239 bipolar patients comorbid borderline personality disorder was observed in 20.5% of patients, and just as other comorbid conditions it was significantly more frequent in suicide attempters (79.5%) than nonattempters (20.5%).

Furthermore, borderline personality disorder was the only comorbid condition which maintained statistical significance after logistic regression analysis of the association between comorbidity and suicide attempt (Neves et al., 2009). Borderline personality disorder was also significantly more frequent in violent suicide attempts and was, besides alcoholism, the only significantly associated condition with violent suicide attempts after logistic regression (Neves et al., 2009).

There are several conditions associated with borderline personality disorder comorbidity in bipolar disorder which also increase suicide risk and therefore may mediate the role of borderline personality disorder comorbidity in increasing suicide attempt risk in bipolar disorder, including younger age, other comorbidities, earlier onset and higher lifetime number of both manic and depressive episodes and higher incidence of previous suicide attempts, higher incidence of early abuse (Garno et al., 2005; Neves et al., 2009), indicating unfavourable aspects of the disease in borderline bipolar patients with an approximately 4 times increased suicide risk compared to non-borderline bipolars (Neves et al., 2009).

One possible proposed mechanism for increased suicide risk in the bipolar-cluster B personality disorder group may be the sum of severe affective episodes resulting from bipolar disorder and high environmental reactivity resulting from borderline and other personality disorders, or the sum of increased impulsivity and aggressiveness present in both conditions (Garno et al., 2005; Leverich et al., 2003; Neves et al., 2009).

Personality features and affective temperaments

Suicide has well-established personality correlates, however, these traits and characteristics may show a differential or more pronounced association with suicidal behaviors in bipolar and affective patients. Suicidality is also associated with certain personality characteristics, such as aggressive/impulsive traits, hopelessness and pessimism, and an increased risk is present if these traits are present in combination (MacKinnon et al., 2005; Mann et al., 1999; Oquendo et al., 2004a). Impulsivity was associated with nonlethal suicide attempts in general samples, and in case of affective patients it is also associated with severe suicide attempts and completed suicide (Swann et al., 2005). This is a very important finding, since impulsivity is a characteristic trait in bipolar patients (Tondo and Baldessarini, 2005). Impulsivity distinguishes suicidal and non-suicidal affective inpatients and control subjects, and in bipolar patients suicidal intent correlated with impulsivity even when controlling for aggression (Swann et al., 2005). Synthesizing results from studies it seems that impulsivity increases suicide risk when combined with depression (Swann et al., 2005). In a factoranalytic study past suicidal behavior was associated with aggressive traits in bipolar patients (Grunebaum et al., 2006). Suicidal ideation, an important precursor and risk factor of suicide, was associated with having an affective temperamental type (Tondo et al., 2007). It is increasingly reported that cyclothymia and cyclothymic temperament is also a predisposing factor for suicidal behavior in the general population, and affective temperaments are also known to be subclinical manifestations and precursors of affective, including bipolar, disorders (Akiskal et al., 2003; Kochman et al., 2005; Pompili et al., 2008). Current studies show that in contrast to hyperthymic temperament, cyclothymic, irritable, depressive and anxious affective temperaments were overrepresented in suicide attempters (Pompili et al., 2008; Rihmer et al., 2009). In another study on bipolar patients Harm Avoidance and Persistence as measured by Cloninger's TCI seemed to have an effect on suicide attempts (Engstrom et al., 2004). Hostility was also found to be a suicide attempt risk factor, while many reasons for living an

Table 1
Clinically relevant and explorable risk factors of suicidal behavior in bipolar disorder patients.

Longitudinal risk factors	
Personality features	<ul style="list-style-type: none"> ● Aggressive/impulsive personality traits ● Cyclothymic temperament
Personal and/or family history	<ul style="list-style-type: none"> ● Early negative life events (separation, emotional, physical and sexual abuse) ● Acute psychosocial stressors ● Permanent adverse life situations ● Family history of mood disorders in first and second degree relatives ● Family history of suicide and/or suicide attempt in first and second degree relatives
Illness course	<ul style="list-style-type: none"> ● Bipolar II diagnosis ● Early onset ● Early stage of the illness ● Longer duration of untreated illness (delayed diagnosis or proper diagnosis) ● Polarity of first episode ● Predominantly depressive course ● Number of previous episodes ● Prior suicide attempt/ideation (especially violent/highly lethal methods) ● Rapid cycling course
Cross-sectional risk factors	
Characteristics of current mood episode:	<ul style="list-style-type: none"> ● Severe major depressive episode ● Agitated or mixed depressive mixed state ● Dysphoric mania ● Severe anxiety and insomnia ● Current suicide attempt, plan, ideation ● Hopelessness, guilt, few reasons for living ● Psychotic features ● Atypical features ● Bipolar II diagnosis ● Comorbid Axis I (anxiety disorder, substance-use disorders) and Axis II disorders ● Serious medical illness ● Lack of medical treatment ● Lack of social or family support ● Initiation and first few days of the treatment ● First few weeks and months after hospital discharge

important protective factor in bipolar disorder (Chaudhury et al., 2007).

Bipolar disorder patients show higher emotional intensity and lability during intercrisis periods and it is possible that during depressive states this increased emotional intensity may lead to emotional hyperreactivity, and consequently to a depressive mixed state, and both bipolar depression and depressive mixed states are associated with suicidality (Brent et al., 2002).

Conclusion

As seen above not only do bipolar disorders carry a much higher risk of suicide compared to the general population and also to other psychiatric disorders, there are multiple risk factors of suicidal behavior in bipolar illness, and many of these risk factors are specific to bipolar disorder. Multiple features and characteristics of each patients, their illness and also their past history and present circumstances should be taken into account when trying to weigh the risk of suicidal behavior in case of each patient. Furthermore, prediction of suicide in bipolar disorder is made even more difficult by the fact that a great majority of suicidal patients are unrecognized affective patients or misdiagnosed unipolar patients, so even if we had adequate tools to predict approaching suicidality in bipolar patients, we still miss a great portion of undiagnosed or misdiagnosed people at high risk due to their illness. Therefore the understanding and identification of suicide risk factors in bipolar disorders should proceed hand in hand with better recognition and diagnosis of this illness in order to make suicide prediction and prevention in bipolar illness an achievable goal. However, careful exploration and investigation of the above risk factors concerning the clinical characteristics and illness course, along with monitoring cross sectional features of

the illness provide important possible tools. Understanding of the exact role and pathway of the influence of the above factors in the emergence of suicidality is still lacking and demands future research, and the ultimate goal could be developing suicide prediction algorithms based on the identification of risk factors and their action mechanism. Taking into consideration clinically explorable and identifiable risk factors (Table 1) and weighing them carefully for each patient suicide may become to a large extent foreseeable and predictable, and then it is the turn of finding adequate intervention strategies to prevent those suicides which are preventable in bipolar patients.

We must mention certain limitations of our paper. We tried to summarize the available literature for suicide in bipolar disorder and give a balanced overview of often conflicting results, but inclusion and exclusion of papers to be reviewed depends on the selection of the authors based on their expertise and consultation with experts.

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Contributors

Xenia Gonda has designed the study, collected the papers, reviewed and analysed them and wrote the paper.

Maurizio Pompili participated in selecting and reviewing the included studies and in writing the paper. Gianluca Serafini

contributed to designing the work, reviewing and analyzing the papers and writing the paper.

Franco Montebovi, Sandra Campi, Peter Dome, and Timea Duleba participated in the literature search, study selection and writing the paper.

Paolo Girardi contributed to conceiving the study, developing the idea, designing the literature search, evaluating the selected articles and writing the paper.

Author Zoltan Rihmer conceived the study and participated in studies and writing the paper.

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