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Original article

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Risk factors for suicide in bipolar disorder

Summary

Objectives
Aim of this review is to analyse, update and categorize data coming from literature about risk factors for suicide in Bipolar Disorder (BD). Suicide represents the most fearsome complication of BD. The epidemiological rates of suicide attempts and deaths in BD are extremely high compared to the general population and other psychiatric conditions, underlining the need for a specific assessment of risk factors for suicide in BD patients.

Methods
The authors performed a systematic literature search in order to give a detailed overview of risk factors for suicide in bipolar disorder.

Results
Suicide risk factors have been classified into three categories: sociodemographic, biological and clinical factors. In each group, there are several disease-specific risk factors which should be considered in the evaluation of suicide risk of a patient.

Conclusions
Considering the high rate of suicide attempts and deaths in bipolar subjects and the social impact of this behaviour, it is important to early recognise such patients, thus allowing for better prediction and prevention of suicidal behaviours.

Key words
Bipolar disorder • Suicide • Risk factors • Suicide attempt • Suicide death.

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According to the World Health Organization, the global burden of suicide accounts for around one million deaths per year. More than 90% of people who die from suicide are affected by a psychiatric disorder and, among those, Bipolar Disorder (BD) is one of the most common diseases: about half the people with BD have suicidal thoughts, 21% a plan, and 16% report a suicide attempt within the past year [1 2]. Furthermore, lethality of suicide attempts is higher in bipolar population than in the general population [3]. Concerning suicide attempts method, some studies evaluated the frequency of violent *vs* non-violent methods: non-violent methods, in particular self-poisoning, are the most frequently used [3]. Considering the high rate of suicide attempts and deaths in bipolar subjects and the social impact of this behaviour, it is important to early recognise such patients and identify specific suicidal risk factors, in order to timely implement therapeutic interventions. There is an extensive literature about risk factors for suicide in BD, pointing out the importance of this issue. Aim of this review is to analyse, update and categorize data coming from literature and regarding risk factors for suicide attempts and deaths in BD.

Methods
We performed a systematic review of articles regarding risk factors for suicide in Bipolar Disorder. A PubMed research of studies published from 1980 to 2018 has been conducted, using search terms as "bipolar disorder", "sui-

cide", "risk factors". In addition, we evaluated data from recently published reviews and international guidelines. All papers were analysed. In the event that a study was mentioned in a subsequent review or guideline, we decided to reference the latest published paper.

Risk factors for suicide attempt and suicide death

Suicide risk factors mentioned by literature data may be systematically analysed and divided in three categories: sociodemographic, genetic-biological and clinical factors (Table I).

Sociodemographic factors

Gender

Most of the studies available in literature highlight an association between female gender and suicide attempts: women appear to have an increased risk of suicide attempts compared to men and this association seems to be stronger in BD than in other psychiatric conditions [4]. However, lethality of suicide attempts seems to be higher in men [5].

Race

There is a paucity of data regarding the relationship between suicidality and ethnicity. Only one study showed that bipolar non-Hispanic whites had a higher risk of suicide behaviours, compared to other races. No such difference was found by other authors [4].

Age

Among subjects who committed suicide, those who were affected by BD appear to be significantly younger than others[4]. Regarding the relationship between age and suicide in BD, there are findings which showed that attempters are significantly younger compared to non-attempters: the age group 20-29 reported the highest lifetime suicide attempt rate (42.9%), followed by the 30-39 age group (25%) [4 6]. Moreover, young people with BD are more vulnerable to develop suicidal ideation [7]. That is associated with some clinical conditions: in particular, onset of the disorder after the age of 12, mixed and psychotic symptoms, greater severity of depressive symptoms, psychiatric comorbidities, such as attention deficit hyperactivity disorder (ADHD), panic disorder and substance use, history of physical and/or sexual abuse and family history of suicide and mood disorder are related to an increased likelihood of suicide attempt [4 7]. Some authors suggest that children with decreased familial support, increased conflict, greater family rigidity and lower self-esteem may run a higher suicidal risk [5 8]. No age difference has been found when analysing the methods of suicide attempt (violent *vs* non-violent) [4 9].

Family status

Data from literature show that suicide attempts are strongly associated with a condition of psychosocial isolation [4 5]. Indeed, patients with BD who are single or divorced and without children present an increased risk of suicide [4 5]. This is evident for both mothers and fathers [4].

Religious affiliation

The correlation between religious affiliation and suicide is controversial. Suicidal behaviour seems to be correlated to the moral and religious objection to this conduct. However, in a mixed sample of patients affected by mood disorders (unipolar and bipolar disorder), high religious belief was associated with greater likelihood of suicide attempts [4].

Biological factors

Genetic factors

The assumption according to which certain genes may play a role in suicide in bipolar patients is supported by twin, family and adoption studies [10]. There is an extensive literature about the association between suicidal behaviour in BD and family history of suicide or mood disorders in first-degree relatives [10 11]. That appears to be the most important risk factor for suicide in BD and it is still significant even after controlling for the effect of familial aggregation of psychiatric disorders, suggesting an independent genetic predisposition for suicide, which is different from the familial predisposition for bipolar disorder. Many genes have been studied and appear to be possible predictors of completed suicide and suicide attempt. Among those, some findings show a possible association between the brain-derived neuro-trophic factor (BDNF) gene and suicidal behaviours; this correlation seems also to apply to the modality of suicide (violent *vs* non-violent). Other candidate genes under study are the polymorphisms of the tryptophan hydroxylase 1 and 2, who seem to be correlated with a higher lethality of suicide attempts and with completed suicides. Moreover, some authors showed that the serotonin transporter polymorphism 5-HTTLPR is significantly associated with violent suicidal behaviour in BD individuals [5 12]. Nonetheless, other researches are needed to discuss this issue in more detail [4].

Biomarkers

Some biological elements could be considered as possible predictors of suicide in patients affected by BD. Nevertheless, there were no significant findings among studies about non-genetic central and peripheral markers. Neuroimaging researches have focused on white matter, cerebral cortex (dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate, superior temporal cortex, parieto-occipital cortex) and basal ganglia, but results require replications [3]. Living at higher altitude seems to be correlated to a major risk of death by suicide in bipolar samples, compared to other psychiatric illnesses [4 5]. A possible explanation is that higher altitude, which has a reduced oxygen partial pressure, may result in a different concentration of cerebral neurotransmitters: due to hypox-

TABLE I. *Risk factors for suicide in bipolar disorder.*

Risk factors for suicide	Strong evidence	Weak evidence
Sociodemographic factors	• Female gender • Young age • Psycho-social isolation	• Race • Religious affiliation
Biological factors		
Genes		• BDNF • TPHL 1 and TPHL 2 • 5-HTTLPR • Other genes
Biomarkers		• Living at higher altitude • HPA axis alterations • Neurobiological alterations
Clinical factors		
Disorder features	• Early age of onset • Family history of suicide • Family history of mood disorder • Prior suicide attempt • Rapid-cycling course • Depressive polarity of the first affective episode • Depressive predominant polarity • Longer DUI • N. of previous depressive episodes • Psychiatric comorbidities (substance use, anxiety and cluster B personality disorder)	• Bipolar disorder subtype • Medical comorbidities (metabolic syndrome) • Psychiatric comorbidities (eating disorders)
Current episode features	• Depressive episode polarity • Mixed features • Suicidal ideation	• Psychotic features • Atypical features
Treatment features	• AD as monotherapy • Treatment discontinuation	

BDNF: Brain-Derived Neurotrophic Factor; TPHL 1: Tryptophan Hydroxylase 1; TPHL 2: Tryptophan Hydroxylase 2; 5-HTTLPR: 5-Hydroxy Tryptamine Transporter Gene-Linked Polymorphic Region; HPA: Hypothalamic-Pituitary-Adrenal; DUI: Duration of Untreated Illness; AD: Anti-Depressant.

ia, lower levels of serotonin and higher levels of dopamine and norepinephrine could increase irritability, depression, instability of mood and suicide rates [5]. The hypothalamic-pituitary-adrenal axis may be related to suicidal attempts in BD as well: more elevated bedtime salivary cortisol has been found in subjects who have a lifetime history of suicidal behaviour, compared to those who have not [3 13].

Clinical factors

There is an extensive literature concerning clinical risk factors for suicide in BD. By using a systematic approach, they could be divided into three categories: factors related to disorder features, those related to current episode characteristics and those associated with pharmacological treatment.

Disorder features

Age of onset. Data from literature underline that earlier age of onset of BD is related to a higher rate of suicidal behaviours [4]. Nevertheless, it is unclear if this is an independent risk factor or it is associated to other variables linked to a greater risk of suicide (for example, psychiatric comorbidities, rapid cycling, severity of illness and increased childhood physical abuse) [10].

Family history of suicide and mood disorder. This topic has been discussed within the genetic risk factors of suicide.

Prior suicide attempts. A lifetime history of suicidal behaviours is thought to be one of the most important predictors of suicide attempt and death in the general population. This appears to be particularly significant in BD: up to 56% of suicide deaths have a history of suicide attempts [3 10]. Preliminary data suggest that the presence of previous suicide attempts can be associated with lower social skills (conversational skills, social self-confidence, social openness to new people and situations, self-control of ag-

gressiveness and individual reactions to aversive stimuli), which may be related to the risk of suicidal behaviours [14].

Rapid-cycling course. There is a consistent evidence underlining that rapid-cycling patients show a higher risk of suicide attempt. Furthermore, rapid-cycling course is associated to a higher intent and lethality [10].

Polarity of the first affective episode. Individuals with a first mood episode of depressive polarity present an increased suicide risk [10]. Moreover, despite depressive polarity of the onset of the disorder is associated with a lifetime history of suicidal behaviours, a first episode of mania has been correlated with a greater likelihood of suicide by a violent method [4].

Predominant polarity. Data from literature suggest that depressive predominant polarity is strongly associated to lifetime suicide attempts, compared to manic predominant polarity [4].

Bipolar disorder subtype. Several studies analysed the correlation between the subtype of the disorder (BD I *vs* BD II) and suicidal behaviours. Costa and colleagues underlined that BD II patients have a greater risk of suicide than BD I [5]; however other authors did not find clear differences [4].

Duration of untreated illness (DUI). A longer DUI has been associated to a higher risk of suicide [4]. In individuals with more than two years of DUI, suicide attempt rates were significantly higher compared to patients with a DUI ≤ 2 years [10].

Number of previous episodes. Data from literature show that subjects with a lifetime history of suicidal behaviours were found to have twice as many previous depressive episodes, compared to non-attempters [10].

Comorbidities. Medical comorbidities: patients affected by BD present high rates of metabolic syndrome, which has been associated to a more severe course: lower response to treatment, increased illness burden and suicide [15]. Individuals who had a lifetime history of suicidal behaviour showed higher mean Body-Mass-Index values, compared to those who have not (30.2 *vs* 27.9) [16]. To date, only one study specifically analysed the correlation between metabolic syndrome, lipid profile and methods of suicide, without finding a significant association [17]. However, considering the paucity of data, more researches are needed.
Psychiatric comorbidities: substance use disorder, anxiety disorder and personality disorder have been constantly associated to an increased risk of suicide. International guidelines underline that substance use disorder in BD patients is related to a poorer course of illness and to an increased risk of suicide [11,15]. Even analysing alcohol and other substances separately, authors found out that both categories were associated with suicide [4]. Furthermore, cigarette smoking (currently or lifetime) has been strongly correlated with suicidal behaviours [4]. Comorbidity with anxiety disorder is one of the most studied risk factors for suicide in BD patients. Considering different subtypes of anxiety disorders, generalized anxiety disorder, panic disorder and post-traumatic stress disorder turn out to be more common among suicide attempters. There are no such clear findings about agoraphobia and social phobia [4]. It is well known that a cluster B comorbid personality disorder is correlated with higher risk of suicide attempts, but there is a paucity of data concerning the relationship between other personality disorders and suicide [4]. Focusing on personality traits, levels of aggression and hostility were found to be significantly correlated with suicidal behaviours; findings about the effect of impulsivity are less clear and conducted to contradictory results. Other personality features associated with a history of suicide attempts in BD were: extreme attributional style, lower social skills or self-directedness, hopelessness and affect lability [2,4,5]. Hopelessness appears to be a multi-faceted construct, in which lack of positive future thinking would seem more relevant than the presence of negative future thinking. However, hopelessness could be also a consequence of a more severe BD and could predispose to suicide from that perspective [5]. Subjects with high affect lability present a greater risk of suicidal ideation. This may be linked to suicide by the perception of a lack of control on the mood and a greater fear of relapse [2]. Available data as regards temperaments show that cyclothymic, irritable, depressive and anxious affective temperaments are more frequent in attempters than in non-attempters, in contrast to hyperthymic temperament [4,10]. Moreover, some findings suggest a correlation between eating disorders and suicidal behaviours [4].

Current episode features

Episode polarity. Suicidal behaviours seem to be strongly correlated to major depressive episodes and mixed episodes (as classified in DSM-IV), compared to pure mania and euthymia. Less than 3% of all suicide attempts in individuals with BD occur during manic episodes [4].

Mixed features. The presence of mixed features during major depressive episode is another important suicide risk factor. Considering that mixed features are more likely to happen in BD than in unipolar depression, this may contribute to increase suicide rates in bipolar patients compared to unipolar [1,8]. Moreover, mixed depressive episodes are associated not only to a greater amount of suicide attempts, but also to an increase of suicide deaths [1,11,19] which could be explained by the phenomenon of antidepressant-induced suicidal behaviour [10].

Psychotic features. Data regarding a possible association between psychotic symptoms and suicidal behaviour are not clear. Some authors found that suicide attempters showed fewer psychotic symptoms, compared to non-attempters [18]. A possible explanation is that psychotic features might hinder the capacity to plan and perform suicide. Other studies found an association between history of psychosis during depression and an increased number of suicidal behaviours [10]; instead, others reported no differences [20]. Moreover, psychotic features seem not to be correlated to the lethality of suicide [4].

Atypical features. Atypical symptoms are more common in bipolar-II depression, compared to unipolar depression, ranging from 12% up to 60%. In some studies, individuals with atypical depression, both bipolar and unipolar, showed higher risk of suicidal behaviours [4 10].

Peripartum episodes. Even if women affected by BD present high rates of affective recurrences in the peripartum and particularly in post-partum period [21], there is no evidence that such period exposes BD patients to an increased risk of suicide.

Suicidal ideation. It has been highly correlated with suicide attempts and deaths [5 10]. Suicidal ideation presents a high prevalence in subjects with BD (up to 79% of major depressive episodes) and is itself a risk factor associated with suicide [10].

Treatment features

Some aspects related to the pharmacological treatment of BD should be considered when risk factors for suicide are analysed. Several studies underline that the risk of suicidal behaviour is higher in individuals treated with antidepressants (AD) as monotherapy and lower in those treated with mood-stabilizers as monotherapy [18]. It is well known that AD may induce manic switch; thus, McElroy and colleagues suggested that AD could be correlated with suicide by manic conversion in a subset of depressive presentations [5 22]. International guidelines indicate that treatment discontinuation exposes to high risk of relapse, recurrence and suicide [15].

Protective factors of suicide

There is a paucity of data regarding factors that could protect patients from suicidal behaviours in BD. International guidelines indicate that the use of lithium or anticonvulsants reduces the risk of suicide in BD [1 11 15 19]. Nonetheless data regarding the anti-suicidal effect of lithium mostly come from retrospective researches, thus more prospective studies are needed [4]. Despite the large use of others treatment in BD (atypical antipsychotics, psychotherapeutic approaches and electroconvulsive therapy), there is a lack of research about the relationship between these therapies and suicide [4]. The European Association guidance on suicide treatment and prevention underlines that some elements could be recognized as protective factors in the general population, such as cognitive flexibility, active coping strategies and healthy lifestyles (diet, sleeping schedule and physical exercise) [23]. Focusing on BD, only one study with a small sample found that having a good social network could be protective against suicide [24]. More research is needed to study this issue.

Conclusions

Aim of this review was to analyse, update and categorize data coming from literature and regarding risk factors for suicide in Bipolar Disorder. BD is a mood disorder characterised by periods of low mood (depressive episodes) and periods of elevated mood (ipo/manic episodes), with a prevalence of 2.4% in the general population[1]. Suicide represents the most fearsome complication of BD. The epidemiological rates of suicide attempts and deaths in BD are extremely high compared to the general population and other psychiatric conditions, underlining the need for a specific assessment of risk factors for suicide in BD patients. Many studies evaluate risk factors for suicide attempt and death in BD [3 4]; by using a systematic approach, we classified them into three categories: sociodemographic, biological and clinical factors.

Regarding sociodemographic elements, there is a strong evidence that female gender, younger age and psychosocial isolation (single, divorced and widowed individuals) are associated with a higher risk of suicide behaviours. However, despite women have a higher rate of suicide attempts, man frequently commit suicide by violent methods, resulting in a greater lethality of suicidal acts. There is a paucity of data about the role of religious affiliation and ethnicity in the contest of suicidal behaviours: more research is needed to explore these issues.

Data concerning biological factors are preliminary. At this time, it is not possible to highlight a specific correlation between genes or biomarkers and suicide attempts/deaths. Few genetic polymorphisms, neurobiological alterations and peripheral biomarkers abnormalities have been found to be correlated to suicide in preliminary studies; however, results require replications. In order to timely implement therapeutic interventions, the use of specific biological markers could help clinicians to promptly recognize individuals with a higher risk of suicide, even in the early stages of BD.

A lot of studies underline the importance of clinical factors in the assessment of suicide risk in BD. Among those, disorder features strongly related to suicidal behaviours are: early age of onset, family history of suicide/mood disorder, previous suicide attempts, rapid-cycling course, depressive polarity of the first affective episode and depressive predominant polarity, longer DUI, number of previous

episodes and some psychiatric comorbidities (substance use, anxiety and cluster B personality disorder). Further analysis is needed to clarify if specific bipolar disorder subtype, metabolic syndrome and comorbid eating disorder are associated to suicide. Current episode characteristics consistently linked to suicidal behaviours are: depressive episode polarity, mixed features and suicidal ideation, as well as can be expected. Even if the presence of psychotic and atypical features seems to be a possible risk factors for suicide, more research is necessary. Finally, using AD as monotherapy and interrupting the assumption of mood stabilizers are established risk factors for suicide in BD. To date, the only verified protective factor for suicide that is consistently mentioned by literature is lithium therapy, due to the anti-suicidal effect that this treatment has proved to have.

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