

Suicidal behavior in bipolar affective disorder and socio-demographic, clinical and neuroanatomical characteristics associated

Comportamento suicida no transtorno afetivo bipolar e características sociodemográficas, clínicas e neuroanatômicas associadas

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Received: 7/29/2012 – Accepted: 6/4/2013

Abstract

Background: Bipolar patients have a higher risk of suicide when compared with the general population and other psychiatric disorders. The aim of this article is to review the social-demographic, clinical and neuroanatomical aspects of suicidal behavior in bipolar patients. **Methods:** A non-systematic review of literature through PsycInfo, Lilacs, Medline and PubMed electronic databases was conducted, using the keywords: “suicide attempt”, “suicidal behavior”, “suicide”, “bipolar disorder”, “suicide risk factor”, “neuroimaging”, and “suicide neurobiology”. **Results:** Several clinical and sociodemographics characteristics have been associated with suicide attempts in bipolar patients, but results are conflicting. Regarding to neuroimaging, the data are rare, and the results are inconsistent, with reports of white matter hyperintensities and changes in structure and function of the prefrontal cortex. **Discussion:** Given that suicide is a potentially preventable cause of death, the understanding of neurobiological and clinical correlates of suicidal behavior can be useful in reducing rates of attempt suicide in bipolar patients.

Nery-Fernandes F, Miranda-Scippa A / *Rev Psiq Clín.* 2013;40(6):220-4

Keywords: Attempt suicide, suicidal behavior, bipolar disorder, suicide risk factor, neuroimaging.

Resumo

Contexto: Pacientes com transtorno bipolar possuem risco maior de suicídio, quando comparados com a população geral e com outros transtornos psiquiátricos. Este artigo tem como objetivo revisar os aspectos sociodemográficos, clínicos e neuroanatômicos associados ao comportamento suicida em pacientes com transtorno bipolar com história de tentativa de suicídio. **Métodos:** Revisão não sistemática da literatura, por meio dos indexadores eletrônicos: *PsycoInfo*, *Lilacs*, *Medline* e *PubMed*, utilizando-se as palavras-chave: “attempt suicide”, “suicidal behavior”, “suicide”, “bipolar disorder”, “suicide risk factor”, “neuroimaging” e “suicide neurobiology”. **Resultados:** Diversas características sociodemográficas e clínicas têm sido associadas às tentativas de suicídio em pacientes bipolares, porém os resultados são ainda conflitantes. Em relação aos achados de neuroimagem, os dados também são escassos e inconsistentes. Destes, a hiperintensidade periventricular em substância branca e as alterações na estrutura e função do córtex pré-frontal são os mais descritos. **Conclusões:** Considerando que o suicídio é uma causa potencialmente evitável de morte, a compreensão dos correlatos clínicos e neurobiológicos do comportamento suicida pode ser útil na prevenção desse comportamento. Sendo assim, estudos que avaliem melhor os fatores de risco para o comportamento suicida nessa população são necessários.

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Palavras-chave: Tentativa de suicídio, comportamento suicida, transtorno bipolar, fator de risco, neuroimagem.

Introduction

Bipolar disorder (BD) is a chronic and severe illness and has an estimated prevalence of between 1% and 1.6% in the general population¹⁻³, and may reach 8.3% if we consider the prevalence of bipolar spectrum, which includes, beyond the classic presentations of the disorder, subsyndromal forms which also generate functional impairment, such as substance-induced mania and mild episodes of short duration or incomplete diagnostic criteria⁴. The etiology of BD is still not fully known, and the study of genetic polymorphism associated with this disorder raises the hypothesis that associating BD with common genetic variants is outdated. It is currently believed that the search for genetic information associated with the onset of BD fundamentally entails research on environmental and structural factors⁵. Although it is not yet possible to draw cause and effect relations, recent literature portrays acute episodes of mood as being toxic. This systemic toxicity combines with progressive and disabling features related to the disorder, especially cognitive dysfunction, chronic medical comorbidities and premature mortality⁶.

With regard to clinical and socio-demographic factors associated with BD, there continues to be a shortage of studies indicating variables that lead bipolar patients to present social maladjustment, however the results are unanimous as regards the influence of disease severity, in work performance and in interpersonal relationships^{7,8}. According to the World Health Organization (WHO), BD occupies 9th place in the list of leading causes of global dysfunction in individuals between 15 and 44⁹.

Patients with bipolar disorder also have an increased risk of suicide compared to the general population. In patients with BD, an estimated risk of suicide was observed at 0.4% per year, about 23 times higher than the rates observed in the general population, which is estimated at 0.017%¹⁰. Although suicide is more frequent in patients with BD, many patients have never attempted suicide; thus it is believed there may be different subgroups among these individuals.

The causes of suicidal behavior are manifold and complex. Although the presence of BD is an important predisposing factor, the occurrence of this condition alone is not sufficient to fully explain

suicidal behavior without interaction from other factors such as the presence of hopelessness, impulsiveness, and aggression, among others. The clinical predictors of suicidal behavior are not generally robust, meaning that they are not reproducible for different patient samples or for a particular patient individually, in part because suicide and suicidal behavior are the result of a combination of individual risk factors, other than the influence of stressors and disease characteristics occurring at that particular moment in the life of the individual¹¹.

Methods

We conducted a classic review of the literature through the *PsychoInfo*, *Lilacs*, *Medline* and *PubMed* electronic databases, using the keywords: "suicide attempt", "suicidal behavior", "bipolar disorder", "suicide", "suicide risk factor", "neuroimaging", and "suicide neurobiology". When indicated, other bibliographies were consulted from the reference lists of these articles. The search was restricted to articles published in English and Portuguese, targeting the adult population over 18 years of age, in the period between January 2000 and December 2011. The database queries were performed in February 2012. After this step, the titles and abstracts of all articles found were read in order to identify studies that addressed the theme and purpose of this review.

Results and discussion

A total of 72 potentially relevant articles were found, taking into consideration the defined parameters of databases and descriptors. After reading the titles and abstracts of the articles, seven studies were excluded based on the criteria presented. Of these, five were excluded because they assessed populations with different diagnoses and two for approaching the subject in a superficial way.

Suicidal behavior

A suicide attempt (SA) was defined in 1995 by Ayd as any non-fatal, self-inflicted, potentially injurious behavior with any intent to die. This type of behavior encompasses a variety of attitudes, from the simplest acts of self-harm that do not need medical attention, to even more serious actions in which the patient's hospitalization is required¹². According to the WHO, in 2002, suicide attempts (SAs) worldwide accounted for 1.4% of overall damage caused by all diseases and this rate is estimated to reach 2.4% in 2020¹³.

In most countries, men display higher rates of completed suicide, but in females a greater number of attempts are observed, probably due to the fact that men generally use more lethal methods and plan the SA with greater determination¹⁴. Brazilian studies confirm this trend with a 3:1 ratio of suicide in men compared to women. This ratio is reversed for SAs, with rates three times higher for women than men¹⁵.

It is estimated that SAs are eight to fifteen times more frequent than suicides^{14,16}. In Brazil, Botega *et al.*, in a study that evaluated, via household survey, 515 randomly selected individuals in the city of Campinas, São Paulo, found prevalence rates of 17.1% for suicidal ideation, 4.8% for suicidal plan and 2.8% for SA¹⁷.

Suicidal behavior and bipolar disorder

Suicide is most often a complication of psychiatric illness. More than 90% of suicide victims have a diagnosable psychiatric illness, as well as the vast majority of people who attempt suicide. The pathology most commonly associated with suicide and SAs is severe mood disorder^{18,19}. Goodwin and Jamison reported a prevalence of SA in patients with BD between 20% and 56%¹¹. The suicide mortality in these patients reaches rates of between 7% and 19%²⁰, which comes to fifteen times more than rates found in the general population²¹.

A study conducted in American cities that evaluated the database of an Epidemiologic Catchment Area (ECA) with more than 18,000

patients, reported a prevalence of one or more lifetime SAs of 29.2% in patients with BD, 15.9% in patients with unipolar depression, and 4.2% in patients with other axis I psychiatric disorders according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III). According to the same study, patients with BD have a relative risk of SA twice that of patients with unipolar depression and six times higher than patients with other psychiatric disorders²².

In Brazil, a population-based epidemiological study, which assessed 1,464 individuals in the city of São Paulo, showed a prevalence of lifetime SA of 20.8% in patients with BD type I and 32% in patients with BD type II. Among patients with other psychiatric disorders, the rate was 1.1%⁴.

In Porto Alegre, Gazalle *et al.* assessed 169 patients with bipolar disorder, types I and II, and showed that 48.5% of them had a lifetime history of SA. In this study, the number of SAs was associated with polypharmacy, suggesting that the use of several medications in bipolar patients may be an indicator of disease severity, and therefore associated with an increased number of SAs²³.

Risk factors

Although suicide commonly presents itself as a complication of mental illness, most individuals with psychiatric disorders have never attempted suicide. Thus, we can infer that patients who present the same pathology with and without a history of SA may have different clinical, socio-demographic and neurobiological characteristics. To understand these differences, it is essential to evaluate and compare the characteristics of patients with and without a history of SA.

A variety of factors, including socio-demographic and clinical characteristics have been associated with SAs in patients with BD, however the results are not consistent. Most research suggests that impulsiveness²⁴⁻²⁶, a greater number of depressive episodes over the course of the disease²⁷⁻³⁰, a greater number of psychiatric hospitalizations^{28,31,32}, early age of onset of the disorder^{27,32-34}, a previous history of SAs^{29,30,35,36}, the presence of aggression and impulsiveness throughout life^{28,30,32} and suicidal ideation in the past^{28,29,31,33}, are risk factors for suicidal behavior (Table 1).

Table 1. Main clinical characteristics associated with suicide attempts in patients with BD

Clinical features
Impulsiveness
Incidence of depressive episodes
Early age of onset
History of suicide attempt
Suicidal ideation in the past
Greater number of psychiatric hospitalizations
Presence of aggression

A few other studies point to such factors as: physical and sexual abuse^{31,33}, comorbidity with narcissistic, antisocial, or borderline personality disorders^{31,35}, the presence of hopelessness^{29,35}, male gender^{28,29}, the slightest presence of psychosis, few reasons to live²⁸, lower scores for quality of life³⁷, marital status of single, a family history of suicide and SA, the predominance of depressive symptoms, the severity of episodes, mixed states, rapid cycling, the abuse of alcohol/drugs^{27,33}, mania induced by antidepressants (ADs)²⁷, lack of confidence³¹, anxiety, fewer episodes of the illness, shorter duration of illness, early age of admission, severity, and the first episode of depression²⁹. However, not all studies confirm these findings²⁷⁻³¹. These diverse results may be due to the differences in methodologies employed, as well as the conjunction of multiple types of bipolar disorder in the tested samples.

Among the various clinical characteristics associated with suicidal behavior, impulsiveness has become one of the main aspects

studied in bipolar patients. Indeed, impulsiveness is a prominent and measurable feature of BD, and may contribute to the risk of suicidal behavior³⁸. Individuals with a history of SAs display higher rates of impulsiveness as assessed by the Barratt Impulsiveness Scale (BIS-11), which is a scale that measures impulsiveness as a stable characteristic, but studies also report an influence from the clinical status of the patient in this type of evaluation³⁹.

Recent evidence supports the hypothesis of the presence of greater impulsiveness in bipolar patients compared to healthy controls, independent of other clinical variables, in that higher scores of Barratt are associated with a history of SA, even when factors such as gender, age and education level are controlled for^{40,41}.

Another aspect related to suicidal behavior in bipolar patients has been demonstrated in studies which reveal that the suicide risk in this population may be higher during the early years of the disease, and thus a delay in diagnosis and, consequently, in stabilizing mood could increase the risk of suicide^{42,43}.

The importance of treatment in preventing suicide attempts

With regard to treatment, it is important to note that lithium has been established as a valuable pharmacological strategy for suicide prevention with BD. Previous surveys have demonstrated a dramatic reduction in the risk of suicide with the use of lithium in patients with bipolar disorder⁴⁴. In fact, a meta-analysis of 31 studies showed that lithium reduced fivefold the risk of completed suicide and SAs in those who were treated with lithium, compared to those who did not use lithium⁴⁵. Data on the efficacy of anticonvulsants as a mood stabilizer in reducing the risk of suicide are not as numerous as the studies that evaluated lithium, but studies show a sixteen-times increase in the prevalence or incidence of SAs after discontinuation of anticonvulsants. Additionally, some studies suggest that there is no difference in the rate of SAs in patients treated with lithium, compared with those who used carbamazepine or valproic acid^{46,47}. These results support the theory that anticonvulsants offer similar protective benefits against SA when compared to lithium.

Whereas lithium, and possibly other mood stabilizers, have the potential to provide neuroprotection against neuronal loss, any delay in the initiation of treatment with these medications may result in disease progression or clinical deterioration⁴⁸. The function of mood stabilizers as neuroprotective agents has been demonstrated, and this accumulation of evidence reinforces the idea of neuroprotection as an important therapeutic target in early intervention, in order to positively affect the course of the disease and consequently reduce the risk of suicide.

Neuroanatomy and suicidal behavior in bipolar disorder

The neurobiology of suicide in mental disorders, particularly BD, is little known, and the limited literature on the subject suggests possible genetic, neurochemical and neurostructural influences as etiological factors for this outcome⁴⁹.

Neuroimaging studies that seek structural changes in specific brain regions of bipolar patients showed volumetric changes in various structures such as the amygdala, hippocampus, hypothalamus, basal ganglia, cerebellum and corpus callosum (CC)⁵⁰. However, a meta-analysis of 38 studies that measured volumes of brain structures found no significant structural differences between adult bipolar patients and healthy controls, except for enlargement of the right lateral ventricle – the most common neuroanatomical change reported in this population⁵¹.

The discrepancy in the results of neuroimaging studies can be explained by several factors, such as the limited quantity of studies that evaluated each brain region separately, thus providing small samples for measurement; the existence of clinical samples consisting of patients in different phases of bipolar disorder and with different diagnoses (Type I, II, or unspecified); the use of varied apparatuses and types of image acquisition. Thus, the assessment of bipolar pa-

tients in euthymia, and their grouping according to classification, becomes crucial, unlike in previous studies, to avoid encountering any changes related to phases and subtypes of the disease, bearing in mind that structural changes in euthymic bipolar patients may be a sign of markers of biological characteristics of BD, independent of mood, which could play a future role in the diagnosis, course and treatment of the disease.

Neuroanatomical assessments of a bipolar group who have attempted suicide are scantier still. However, studies show periventricular hyperintensities of white matter in patients with affective disorders who have attempted suicide, independent of the type of diagnosis^{52,53}. There is also evidence of changes in the structure and function of the prefrontal cortex in bipolar patients with a history of SA, characterized by decreased gray matter volume and reduced perfusion in the frontal lobes, but these abnormalities were also found in suicidal patients with other psychiatric diagnoses⁵⁰. Hence, research has shown a neuroanatomy that is ostensibly related to suicidal behavior *per se*, independent of psychiatric diagnosis.

In relation to neuroanatomical changes specifically reported in patients with a mood disorder, studies are rare and mostly performed on patients with major depressive disorder. A study which evaluated changes to the serotonergic system in the amygdala of depressed suicidal patients showed a reduction in the relative density of presynaptic and postsynaptic 5-HT₂ receptors, reinforcing the importance of the study of the amygdala for suicidal behavior in patients with a mood disorder⁵⁴.

In a study which measured the cerebella of patients with BD, no differences were observed in relation to the cerebellar volume of bipolar patients with or without a history of SA, just as there was no correlation between cerebellar volume and number of SAs⁵⁵.

Recently, a report by Matsuo *et al.* showed that bipolar patients with a history of SA were more impulsive than bipolar patients with no history of SA. In this study, bipolar patients with SA displayed an inverse correlation between the scores of the Barratt Impulsiveness Scale and the volume and total area of the genu of the CC. This evidence supports the hypothesis that reductions in areas anterior to the CC are related to greater impulsiveness in bipolar patients with a history of SA⁵⁶. In another recent study, which evaluated patients more than 65 years of age with major depressive disorder (MDD), there was a reduction in the posterior third of the CC in patients with a history of SA, compared to those without a history of SA and healthy controls⁵⁷.

Conclusion

BD is a severe psychiatric illness associated with suicidal behavior. Hence, understanding the neurobiological and clinical correlates of suicidal behavior can contribute to a reduction of suicide rates in this population. Evidence of the importance of early diagnosis and intervention in bipolar patients suggests that these factors may have significant implications in the evolution and prognosis of such patients, especially in relation to risk of SAs. However, neuroimaging findings in bipolar patients with a history of SA are meager and inconsistent.

Prospective studies are essential to understanding suicidal behavior in patients with BD so that evaluation strategies can be improved, especially detection and prevention of suicidal behavior in this population.

References

1. Almeida-Filho N, Mari J, Coutinho E, Franca J, Fernandes J, Andreoli S, et al. Brazilian multicentric study of psychiatric morbidity. Methodological features and prevalence estimates. *Br J Psychiatry*. 1997;171(12):524-9.
2. American Psychiatric Association. Diretrizes para o tratamento de pacientes com transtorno bipolar. In: American Psychiatric Association. Diretrizes para o tratamento de transtornos psiquiátricos. Porto Alegre: Artmed; 2004. p. 341-96.

3. Jonas B, Brody D, Roper M, Narrow W. Prevalence of mood disorders in national sample of young American adults. *Soc Psychiatr Epidemiol*. 2003;38:618-24.
4. Moreno D, Andrade L. The lifetime prevalence, health service utilization and risk of suicide of bipolar spectrum subjects, including subthreshold categories in the São Paulo ECA study. *J Affect Disord*. 2005;87:231-41.
5. Alves V, Silva A, Neto V, Andrade T, Nardi A. Associação entre polimorfismos genéticos e transtorno bipolar. *Rev Psiquiatr Clin*. 2012;39(1):34-9.
6. Magalhães P, Fries G, Kapczinski F. Marcadores periféricos e a fisiopatologia do transtorno bipolar. *Rev Psiquiatr Clin*. 2012;39(2):60-7.
7. Judd L, Akiskal H. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord*. 2003;73(1-2):123-31.
8. Tucci A, Kerr-Corrêa F, Dalben I. Ajuste social em pacientes com transtorno afetivo bipolar, unipolar, distímia e depressão dupla. *Rev Bras Psiquiatr*. 2001; 23(2):79-87.
9. World Health Organization. The World Health Report, 2001: Mental Health – new understanding, new hope. 2001.
10. Baldessarini R, Tondo L. Suicide risk and treatment for patients with bipolar disorder. *JAMA*. 2003;290(11):1517-8.
11. Goodwin F, Jamison K. *Manic-Depressive Illness*. 2nd ed. New York: Oxford University Press; 2007. p. 223-69.
12. Meleiros A, Bahls S. O comportamento suicida. In: Meleiros A, Teng CT, Wang YP. *Suicídio: Estudos Fundamentais*. São Paulo: Segmento Farma; 2004. p. 21-2.
13. World Health Organization. *Shaping the future. The World Health Report 2003*. Geneva: WHO; 2003.
14. Mann JJ. A current perspective of suicide and attempted suicide. *Ann Intern Med*. 2002;136:302-11.
15. Wang YP, Mello-Santos C, Bertolote JM. Epidemiologia do suicídio. In: Meleiros A, Teng CT, Wang YP. *Suicídio: Estudos Fundamentais*. São Paulo: Segmento Farma; 2004. p. 104.
16. Grinspoon L. Suicide - part I. The Harvard Medical School. *Mental Health Newsletter*. 1986;2:8-16.
17. Botega N, Barros M, Oliveira H, Dalgalarondo P, Marin-León L. Suicidal behavior in the community: prevalence and factors associated with suicidal ideation. *Rev Bras Psiquiatr*. 2005;27(1):45-53.
18. Isometsä E, Henriksson M, Marttunen M, Heikkinen M, Aro H, Kuoppasalmi K, et al. Mental disorders in young and middle aged men who commit suicide. *BMJ*. 1995;310:1366-7.
19. Beautrais AL, Joyce PR, Mulder RT, Fergusson DM, Deavoll BJ, Nightingale SK. Prevalence and comorbidity of mental disorders in persons making serious suicide attempts: a case-control study. *Am J Psychiatry*. 1996;153:1009-14.
20. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord*. 2002;68:167-81.
21. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta analysis. *Br J Psychiatry*. 1997;170:205-28.
22. Chen Y, Dilsaver S. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. *Biol Psychiatry*. 1996;39:896-9.
23. Gazalle F, Hallal P, Tramontina J, Rosa A, Andreazza A, Zanato V, et al. Polypharmacy and suicide attempts in bipolar disorder. *Rev Bras Psiquiatr*. 2007;29(1):35-8.
24. Nery-Fernandes F, Rocha MV, Jackowski A, Ladeia G, Guimarães JL, Quarantini LC, et al. Reduced posterior corpus callosum area in suicidal and non-suicidal patients with bipolar disorder. *J Affect Disord*. 2012;142(1-3):150-5.
25. Swann A. Mechanisms of impulsivity in bipolar disorder and related illness. *Epidemiol Psychiatr Soc*. 2010;19(2):120-30.
26. Perroud N, Baud P, Mouthon D, Courtet P, Malafosse A. Impulsivity, aggression and suicidal behavior in unipolar and bipolar disorders. *J Affect Disord*. 2011;134(1-3):112-8.
27. Slama F, Bellivier F, Henry C, Rousseva A, Etain B, Rouillon F, et al. Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. *J Clin Psychiatry* 2004;65(8):1035-9.
28. Oquendo M, Watkinson C, Brodsky B, Parsons B, Haas G, Malone K, et al. Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. *J Affect Disord*. 2000;59:107-17.
29. Valtonen H, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä E. Prospective study of risk factors for attempted suicide among patients with bipolar disorder. *Bipolar Disord*. 2006;8:576-85.
30. Oquendo M, Currier D, Mann J. Prospective studies of suicidal behavior in major depressive and bipolar disorders: what is the evidence for predictive risk factors? *Acta Psychiatr Scand*. 2006;114:151-8.
31. Leverich G, Altshuler L, Frye M, Suppes T, Keck P, McElroy S, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry*. 2003;64:506-15.
32. Grunebaum M, Ramsay S, Galfalvy H, Ellis S, Burke A, Sher L, et al. Correlates of suicide attempt history in bipolar disorder: a stress-disthesis perspective. *Bipolar Disord*. 2006;8:551-7.
33. Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry* 2005;66:693-704.
34. Tsai S, Lee J, Chen C. Characteristics and psychosocial problems of patients with bipolar disorder at high risk for suicide attempt. *J Affect Disord*. 1999;52:145-52.
35. Valtonen H, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä E. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry*. 2005;66(11):1456-62.
36. Marangell L, Bauer M, Dennehy E, Wisniewski S, Allen M, Miklowitz D, et al. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. *Bipolar Disord*. 2006;8:566-75.
37. De Abreu L, Nery F, Harkavy-Friedman J, De Almeida K, Gomes B, Oquendo M, et al. Suicide attempts are associated with worse quality of life in patients with bipolar disorder type I. *Compr Psychiatry*. 2012;53(2):125-9.
38. Swann A, Dougherty D, Pazzaglia P, Pham M, Steinberg J, Moeller F. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *Am J Psychiatry*. 2005;162:1680-7.
39. Swann A, Steinberg J, Lijffijt M, Moeller F. Impulsivity: differential relationship to depression and mania in bipolar disorder. *J Affect Disord*. 2007;106:241-8.
40. Swann A, Lijffijt M, Lane S, Steinberg J, Moeller F. Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disord*. 2009;11(3):280-8.
41. Ekinci O, Albayrak Y, Ekinci A, Caykoğlu A. Relationship of trait impulsivity with clinical presentation in euthymic bipolar disorder patients. *Psychiatry Res*. 2011;190(2-3):259-64.
42. Goodwin F, Jamison K. *Suicide*. In: Goodwin F, Jamison K. *Manic-Depressive Illness*, 2nd ed. New York, NY: Oxford University Press, 2007. p. 247-69.
43. Nery-Fernandes F, Quarantini LC, Guimarães JL, de Oliveira IR, Koenen KC, Kapczinski F, et al. Is there an association between suicide attempt and delay of initiation of mood stabilizers in bipolar I disorder? *J Affect Disord*. 2012;136(3):1082-7.
44. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry*. 2005;162(10):1805-19.
45. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord*. 2006;8(5 Pt 2):625-39.
46. Yerevanian BI, Koek RJ, Mintz J. Lithium, anticonvulsants and suicidal behavior in bipolar disorder. *J Affect Disord*. 2003;73(3):223-8.
47. Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior. Part I: lithium, divalproex and carbamazepine. *J Affect Disord*. 2007;103(1-3):5-11.
48. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers implications for the pathophysiology and treatment of manic depressive illness. *Biol Psychiatry*. 2000;48:740-54.
49. Mann J. The neurobiology of suicide. *Nat Med*. 1998;4:25-30.
50. Sublette M, Oquendo M, Mann J. Rational approaches to the neurobiological study of youth at risk for bipolar disorder and suicide. *Bipolar Disord*. 2006;8:526-42.

51. McDonald C, Zanelli J, Rabe-Hesketh S, Ellison-Wright I, Sham P, Kalidindi S, et al. Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. *Biol Psychiatry.* 2004;56:411-7.
52. Grangeon M, Seixas C, Quarantini LC, Miranda-Scippa A, Pompili M, Steffens D. White matter hyperintensities and their association with suicidality in major affective disorders: a meta-analysis of magnetic resonance imaging studies. *CNS Spectr.* 2010;15:375-81.
53. Pompili M, Innamorati M, Mann J, Oquendo M, Lester D, Del Casale A. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:1501-7.
54. Hrdina PD, Demeter E, Vu TB, Sotonyi P, Palkovits M. 5-HT uptake sites and 5-HT 2 receptors in brain of antidepressant-free suicide victims: increase in 5-HT 2 sites in cortex and amygdala. *Brain Res.* 1993; 614(1-2):37-44.
55. Baldaçara L, Nery-Fernandes F, Rocha M, Quarantini LC, Rocha GG, Guimarães JL, et al. Is cerebellar volume related to bipolar disorder? *J Affect Disord.* 2011;135(1-3):305-9.
56. Matsuo K, Nielsen N, Nicoletti MA, Hatch JP, Monkul ES, Watanabe Y, et al. Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. *Neurosci Lett.* 2010;18;469(1):75-80.
57. Cyprien F, Courtet P, Malafosse A, Maller J, Meslin J, Meslin C, et al. Suicidal behavior is associated with reduced corpus callosum area. *Biol Psychiatry.* 2011;70(4):320-6.