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Preliminary communication

Is there an association between suicide attempt and delay of initiation of mood stabilizers in bipolar I disorder?

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ABSTRACT

Background: Little is known about the extent to which delay of initiation of mood-stabilizing treatment may influence outcomes in bipolar patients (BP). In this study, our aim was to investigate the association between delay of mood stabilizer treatment in bipolar patients and lifetime history of suicide attempts.
Method: A consecutive sample of 268 bipolar I outpatients from two teaching hospitals in Brazil was recruited. The assessment included a socio-demographic history form, a clinical interview regarding clinical variables and the Structured Clinical Interview for DSM-IV. Participants were divided into three groups: BP that initiated the first mood stabilizer in the same year of the first episode of the disease (FMS ≤ 1), between 1 and 5 years after the first episode of the disease ($1 <$ FMS ≤ 5), and after 5 years after the first episode of BD (FMS > 5).
Results: The mean time from the first episode until the first mood stabilizer medication was 8.6 years (SD 9.8 years). The FMS > 5 group, showed a higher lifetime prevalence of suicide attempts than the other two groups (PR = 1.75, 95% CI: 1.24–2.47), $p = 0.001$. These results remained significant after adjusting for potential confounders, (PR = 1.82, 95% CI: 1.29–2.60), $p = 0.001$.
Limitations: This study evaluated patients retrospectively and does not permit a cause-effect relationship.
Conclusion: The present study supports the importance of early diagnosis and early intervention for BP in order to limit the potentially lethal impact of the disease.

1. Introduction

Bipolar disorder (BD) is a chronic and often life-threatening condition with a lifetime prevalence estimated at 1.0% for BD type I and 1.1% for BD type II in the general population (Merikangas et al., 2007). Numerous studies have documented a strong association between suicidal behavior and BD. Individuals with BD have lifetime suicide attempt rates of 20% to 56%, almost 15 times higher than the rates found in the general population (Valtonen et al., 2005), and a recent meta-analysis reported a similar prevalence of attempted suicide between BD type II and BD type I of 32.4% and 36.3%, respectively. (Novick et al., 2010). The Epidemiologic Catchment Area Study demonstrated that the lifetime rate of suicide attempts was 29.2% for BD compared to 15.9% for major depressive disorder, and 4.2% for all other DSM-III Axis I disorders combined (Chen and Dilsavier, 1996). It is estimated that 15% to 19% of

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bipolar patients die from suicide (Goodwin and Jamison, 2007; Harris and Barraclough, 1997).

Delays of 8 years or longer have been reported from the time of initial symptom onset until the formal diagnosis of BD (Baldessarini et al., 1999). Over 10% of patients remain non-responsive to treatment, more than half of all cases will receive no medical treatment until 5 years after the first episode, and almost 40% remain insufficiently treated or not treated at all (Regier et al., 1988). Consequently, there is often a substantial delay between the onset of BD and the introduction of mood stabilizing medication, with studies reporting a lag time from 8 to 14 years (Agren and Backlund, 2007; Baldessarini et al., 2007; Goldberg and Ernest, 2002). This lag may be due to delay before a first manic or hypomanic episode, or to complicated presentations such as those with mixed episodes or comorbidities.

To our knowledge, only a few studies have addressed the relationship of the time span between symptom onset and initiating mood-stabilizing treatment and its influence on the course, morbidity, and mortality of bipolar patients, specifically related to suicidal behavior. There is a review with 11 studies that did not find a worse outcome with longer maintenance treatment latency, but different from our report, some of the studies included both BD and major depressive disorder, and most of the authors evaluated different morbidity outcomes, such as hospitalization and number of episodes, and not specifically suicide attempts (Baethge et al., 2003a). In this study, our aim was to investigate the association between delay in mood stabilizer treatment in bipolar patients and lifetime history of suicide attempts. We hypothesized that the time lag in mood stabilizer initiation would be associated with elevated rates of suicide attempts regardless of other features related to the severity of the disorder.

2. Methods

2.1. Subjects and clinical assessments

A sample of 314 consecutive bipolar I outpatients seeking treatment at the Bipolar Disorder Program, Hospital de Clínicas, Federal University, Porto Alegre, Brazil and at the Mood and Anxiety Program, Teaching Hospital, Federal University, Bahia, Brazil, from November of 2003 to November of 2009, was invited to participate. Eligible patients were older than 18 years of age and had confirmed BD diagnosis criteria according to the DSM-IV. The samples from the two hospitals had similarities with regard to socio-demographic characteristics, including gender, age, educational level and marital status. Ethical issues were addressed according to the Helsinki Declaration, and the Institutional Review Boards of both sites approved the study protocol. After providing written informed consent, patients were evaluated in person by trained and experienced researchers who had formal training and extensive experience in administering all instruments. The assessment included a socio-demographic history form, a clinical interview regarding clinical variables and the Structured Clinical Interview for DSM-IV (SCID I) (First et al., 1997). Delay of initiation of mood stabilizer was defined as years from age of the first reported mood episode (depressive, manic, hypomaniac or mixed episodes, according to DSM_IV criteria) until the age of reported first mood-stabilizer treatment.

Lifetime suicide attempt histories were identified using the SCID I in conjunction with a semi-structured interview with questions about number, method, and severity of the suicide attempts, and the presence of intention to die associated to the self-injurious act. Patients were classified as having positive history of suicide attempts only if they reported one or more self-injurious acts committed with intent to die.

2.2. Statistical analysis

We divided the participants into three groups: BD patients that initiated the first mood stabilizer (FMS) in the same year as the first episode of the disease (FMS ≤ 1), BD patients that initiated the first mood stabilizer between 1 and 5 years of the first episode of the disease ($1 < \text{FMS} \leq 5$), and BD patients that initiated the first mood stabilizer treatment after 5 years of the first episode of BD (FMS > 5). The three groups were compared with regard to demographic and clinical data.

We conducted a one-way analysis of variance (ANOVA) and Bonferroni corrected post-hoc tests to compare groups on continuous variables. Categorical variables were tested by the Pearson chi-squared test and Fisher's Exact Test (Cordeiro, 1986). In multivariate analyses, the Poisson regression with robust variance estimate (Cordeiro, 1986; Harrell, 2001) was used to obtain the adjusted prevalence ratios (PR) between groups FMS ≤ 1; $1 < \text{FMS} \leq 5$; and FMS > 5 to identify the lifetime history of suicide attempts.

The multivariate model to estimate adjusted PR included gender, age, marital status, lifetime history of psychosis, mood status (mania, depression, mixed state, and hypomania) at the first episode, history of psychiatric comorbidities, type of psychiatric comorbidities, length of illness, age of first mood stabilizer treatment, rapid cycling, lifetime use of antidepressant medications, lifetime use of lithium, electroconvulsotherapy, family history of suicide, and family history of suicide attempts (Harrell, 2001). Variables were considered as possible confounders if they caused a proportional difference between the crude and adjusted association measurements higher than 10% ($\Delta\% \geq 10$). In all analyses, prevalence ratio and 95% confidence intervals (CIs) were reported.

All statistical analyses were performed with the statistical software package STATA (version 9.0), using a significance level of 5% (p-value $\leq .05$).

3. Results

Of the 314 bipolar I outpatients who consented to participate, 46 (14.6%) were excluded because of missing data; thus, 268 patients (85.4%) completed the survey.

Tables 1 and 2 present socio-demographic and clinical characteristics, respectively. Participants had a mean age of 40.5 (SD 11.4 years) and were mostly female (n = 183, 68.3%). Most of them were single (n = 102, 38.1%). Subjects had a mean age at first affective episode of 24.9 (SD 11.1 years), bipolar illness was diagnosed at a mean age of 33 (SD 11.4 years), which occurred 8.1 years (SD 9.7 years) after the first episode. The majority of our sample, 163 subjects (60,8%), had a history of psychiatric comorbidity, of those, 70 (26.1%) only had a

Table 1
Patient socio-demographics characteristics.

Characteristics	Bipolar I patients (n = 268)
Age in years (mean ± SD)	40.5 ± 11.4
Educational level in years (mean ± SD)	10.7 ± 4.0
Gender	
Female (n/%)	183 (68.3)
Male (n/%)	85 (31.7)
Marital status	
Single (n/%)	102 (38.1)
Married (n/%)	90 (33.6)
Separated/Widowed (n/%)	76 (28.3)

SD = standard deviation.

Table 2
Patient clinical characteristics.

Characteristics	Bipolar I patients (N = 268)
Age in the first affective episode (mean ± SD)	24.9 ± 11.1
Age of the first psychiatric medication (mean ± SD)	27.6 ± 11.2
Age of the bipolar disorder diagnose (mean ± SD)	33.0 ± 11.4
Delay of the bipolar diagnose (mean ± SD)	8.1 ± 9.7
Age of the first mood stabilizer medication (mean ± SD)	33.5 ± 11.5
Delay of initiation of mood stabilizer (mean ± SD)	8.6 ± 9.8
Length of illness (mean ± SD)	15.5 ± 10.9
Type of first epsiode	
Mania (n/%)	109 (40.7)
Depression (n/%)	124 (46.3)
Mixed state (n/%)	23 (8.6)
Hypomania (n/%)	5 (1.9)
Unknown (n/%)	7 (2.6)
Lifetime using of lithium	
Yes (n/%)	239 (89.2)
No (n/%)	29 (10.8)
Lifetime using of antidepressants	
Yes (n/%)	172 (64.2)
No (n/%)	96 (35.8)
Electroconvulsetherapy	
Yes (n/%)	32 (11.9)
No (n/%)	236 (88.1)
Hospitalization	
Yes (n/%)	220 (82.1)
No (n/%)	48 (17.9)
Rapid cycling	
Yes (n/%)	56 (20.9)
No (n/%)	212 (79.1)
Lifetime psychosis	
Yes (n/%)	218 (81.3)
No (n/%)	50 (18.7)
Lifetime suicide attempt	
Yes (n/%)	110 (41.0)
No (n/%)	158 (59.0)
Family history of suicide	
Yes (n/%)	48 (17.9)
No (n/%)	210 (78.4)
Unkown (n/%)	10 (3.7)
Family history of suicide attempt	
Yes (n/%)	58 (21.6)
No (n/%)	199 (74.3)
Unkown (n/%)	11 (4.1)
Lifetime psychiatric comorbidity	
Yes (n/%)	163 (60.8)
No (n/%)	105 (39.2)

SD = standard deviation.

history of anxiety disorders, 39 (14.6%) only had lifetime substance abuse or dependence, and 53 subjects (19.8%) had history of both these comorbidities; there was only 1 patient (0.4%) with another type of psychiatric comorbidity. The mean time from the first episode until the first mood stabilizer medication was 8.6 years (SD 9.8 years).

A history of suicide attempts occurred in 110 (41%) patients. The mean time for the diagnosis of bipolar disorder was significantly longer for subjects who attempted suicide, 9.9 years (SD 9.8, 95% CI: 8.14–11.67) than for those who did not, 6.7 years (SD 9.4, 95% CI: 5.20–8.29), with $p = 0.0079$, and the mean delay until the first use of a mood stabilizer was also significantly longer in the group with history of suicide attempts, 10.4 years (SD 10.0, 95% CI: 8.66–12.27), than in the group with no such history, 7.0 years (SD 9.7, 95% CI: 5.45–8.62), with $p = 0.005$.

In our sample, 30.2% (n = 81) of the subjects were prescribed the first mood stabilizer in the year after the first affective episode (FMS ≤ 1); 22% (n = 59) after the first year and before the 5th year (1 < FMS ≤ 5), and 47.8% (n = 128) 5 years after the first affective episode (FMS > 5). Mood stabilizer distribution is presented in Table 3.

When we categorized the delay of the first mood stabilizer use in these three groups, a lifetime prevalence of suicide attempts was 33.3% in the FMS ≤ 1 group, 32.2% in the 1 < FMS ≤ 5 group, and 58.6% in the FMS > 5 group. In a crude analysis, a lifetime prevalence of suicide attempts between the FMS ≤ 1 group, the reference group, and the 1 < FMS ≤ 5 group was similar (PR = 0.96, 95% CI: 0.59–1.56), $p = 0.889$. However, when we compared the FMS ≤ 1 reference group with the FMS > 5 group, the latter group showed a significantly higher prevalence of suicide attempts (PR = 1.75, 95% CI: 1.24–2.47), $p = 0.001$.

After adjusting for potential socio-demographic and clinical confounders (gender, age, marital status, lifetime history of psychosis, type of first episode, history and type of psychiatric

Table 3
Patient medication distribution.

Medication type	Bipolar I patients (n = 268)
Type of first psychiatric medication	
Mood stabilizers (n/%)	58 (21.6)
Antipsychotics (n/%)	76 (28.4)
Antidepressants (n/%)	49 (18.3)
Benzodiazepines (n/%)	25 (9.3)
Mood stabilizers + antipsychotcs (n/%)	27 (10.1)
Mood stabilizers + antidepressants (n/%)	9 (3.4)
Antipsychotics + antidepressants (n/%)	5 (1.9)
Other medications (n/%)	9 (3.3)
Unknown (n/%)	10 (3.7)
First mood stabilizer	
Lithium (n/%)	190 (70.9)
Divalproex (n/%)	24 (9.0)
Carbamazepine (n/%)	29 (10.8)
Mood stabilizers association (n/%)	21 (7.8)
Unknown (n/%)	4 (1.4)
Time for iniciated the first mood stabilizer treatment	
≤ 1 year	81 (30.2)
1 < and ≥ 5 years	59 (22)
> 5 years	128 (47.8)

SD = standard deviation.

comorbidities, length of illness, psychiatric hospitalization, age of first mood-stabilizer treatment, rapid cycling, lifetime use of antidepressant medication, lifetime use of lithium, electroconvulsotherapy, family history of suicide, and family history of suicide attempts) in the two groups of patients with less than a 5-year delay for FMS (FMS≤1 and 1<FMS≤5), the lower prevalence of suicide attempts remained significant when compared with the FMS>5 group. Moreover, there continued to be no significant difference between these two groups (PR=0.97, 95% CI: 0.59–1.59), p=0.924. When the FMS≤1 reference group was compared with the FMS>5 group, adjusting for the same socio-demographic and clinical confounders, the higher prevalence of suicide attempts remained significant in the latter group, with a statistically significant difference between these groups (PR=1.82, 95% CI: 1.29–2.60), p=0.001 (Table 4).

4. Discussion

The present study adds to the literature by showing a higher prevalence of lifetime suicide attempts in patients who initiated the mood stabilizer after 5 years from the first affective episode (58.6%), compared with the patients who began the mood stabilizer before one year or between 1 to 5 years from the first affective episode. Thus, a delay in prescribing mood stabilizers seems to adversely affect the outcome of risk of suicidal behavior, regardless of clinical and socio-demographic characteristics strongly associated with suicide and suicide attempts, such as gender (Oquendo et al., 2000; Valtonen et al., 2006), presence or type of psychiatric comorbidities (Oquendo et al., 2010), marital status, rapid cycling, family history of suicide or suicide attempt (Hawton et al., 2005; Nery-Fernandes et al., 2009; Quarantini et al., 2010; Slama et al., 2004), lifetime history of psychosis (Oquendo et al., 2000), type of first episode, length of illness (Valtonen et al., 2006), psychiatric hospitalization (Grunebaum et al., 2006; Leverich et al., 2003; Oquendo et al., 2000), lifetime use of antidepressant medication (Marangell et al., 2008; Slama et al., 2004) and lifetime use of lithium (Tondo and Baldessarini, 2009).

Although bipolar disorder remains highly prevalent in the general population, a lag time of 8 years or longer has been described, from the time of initial affective symptoms until the formal diagnosis (Baethge et al., 2003b; Baldessarini et al., 2007; Goldberg and Ernest, 2002). Consistent with these previous reports, in our clinical sample of bipolar I outpatients, we found a mean delay of 8.1 years from the time of the first affective episode until the correct diagnosis of bipolar disorder, and the mean time from the first episode until the first mood-stabilizer medication was 8.6 years. Therefore, these data also demonstrated the strong association between correct diagnosis and appropriate treatment. Our results could be explained by the fact that most of the bipolar patients begin the illness with a depressive episode, and this might contribute to the longer period of time until the diagnosis of bipolar disorder, as also described in other studies. Furthermore, many patients could have been treated only with antidepressants, and this could lead to their mood symptoms not being stabilized, which promotes poorer outcomes (Baldessarini et al., 2010). So, now it is quite important to understand the role of the appropriate and early pharmacotherapy and its influence on the course of illness, including rates of suicide attempts and suicide (Goldberg and Ernest, 2002; Post et al., 2010).

We also show that the mean time for the bipolar diagnosis was significantly longer for subjects who attempted suicide (9.9 years), compared with those with no suicide attempt history (6.7 years), and the mean lag time until initiation of the first mood stabilizer treatment was also significantly longer in the suicidal group, (10.4 years), compared with no suicidal group (7.0 years), suggesting a more severe illness in the first group, which probably did not receive the correct treatment. Thus, since suicide risk for bipolar patients may be highest in the first few years of illness, a delay in diagnosis and consequently mood stabilization could increase the suicide risk (Goodwin and Jamison, 2007). Furthermore, it's also important to highlight that lithium has become established as a valuable pharmacology strategy for suicide prevention in bipolar disorder. Previous reviews have shown a dramatic reduction in suicide risk with lithium use in bipolar patients (Cipriani et al., 2005), with a meta-analysis of 31 studies demonstrating that lithium reduces completed and attempted suicide risk by a factor of about 5 compared with no lithium treatment (Baldessarini et al., 2006). Data on the efficacy of anticonvulsant mood stabilizers in reducing suicide risk are not so numerous, however studies have shown an overall 16-fold increase in non-lethal suicidal behavior after discontinuation of mood stabilizers and no differences in rates of suicide attempts treated with lithium, compared with divalproex or carbamazepine (Yerevanian et al., 2003; Yerevanian et al., 2007). This finding supports the possibility

Table 4
Delay in initiation of the first mood stabilizer treatment and lifetime prevalence of suicide attempts.

	No suicidal (n=158)	Suicidal (n=110)	Crude difference		Adjusted* difference	
			Prevalence ratio (95% CI)	Value-p	Prevalence ratio (95% CI)	Value-p
FMS≤1 (n=81) n (%)	54 (66.6)	27 (33.3)				
1<FMS≤5 (n=59) n (%)	40 (67.8)	19 (32.2)	0.96 (0.59–1.56)	0.889	0.97 (0.59–1.59)	0.923
FMS>5 (n=128) n (%)	53 (41.4)	75 (58.6)	1.75 (1.24–2.47)	0.001	1.83 (1.2–2.60)	0.001

(FMS≤1) = patients that initiated the first mood stabilizer treatment in the same year of the first episode of the disease.
(1<FMS ≤5) = patients that initiated the first mood stabilizer treatment between 1 and 5 years of first episode of the disease.
(FMS>5) = patients that initiated the first mood stabilizer treatment after 5 years of first episode of the disease.
SD = standard deviation.
* Adjusted for gender, age, marital status, lifetime history of psychoses, type of the first episode, history of psychiatric comorbidities, type of psychiatric comorbidities, length of illness, age of first mood stabilizer treatment, rapid cycling, lifetime using of antidepressants medication, lifetime using of lithium, electroconvulsotherapy, family history of suicide, and family history of suicide attempt.

that anticonvulsant mood stabilizers offer similar protective benefits against non-lethal suicide behavior as lithium.

Specifically in bipolar disorder, current theories about episode recurrence and long-term morbidity suggest that poorer treatment outcome may be in part from behavior sensitization or kindling-like mechanisms due to frequent uncontrolled episodes (Ghaemi et al., 1999). A recent study shows that individuals at the earliest stages of illness consistently had a more favorable response to treatment (Berk et al., 2011). Even in the early phases of the illness, there is evidence suggesting the presence of disease-related neuroanatomical and neurochemical abnormalities in key brain regions that regulate cognition and mood. These changes may be progressive and related to both illness course and treatment outcome (Farrow et al., 2005; Frazier et al., 2005). A study comparing euthymic bipolar patients assessed after recurrent bipolar episodes, euthymic bipolar patients assessed after a single manic episode and healthy controls, showed higher impairment in cognitive functions in the first group in comparison to the second group, and in the single manic episode group compared to healthy control subjects (Elshahawi et al., 2011).

Recent evidence indicates that some medications may provide neuroprotection from this neuroanatomical change. A growing body of molecular, preclinical and preliminary clinical studies suggests that the therapeutic effects of mood stabilizers may be mediated by modulating the expression of neurotrophic and neuroprotective factors, having the potential to reverse impairments of cellular resilience in brain volume, and cell death or atrophy (Chuang et al., 2002; Manji et al., 1999). This line of research is based on recent evidence that has been speculating about the effects of excitotoxicity of bipolar disorders, particularly in manic phases (Kapczinski et al., 2011).

In fact, a recent study showed a pharmacologically induced increase in human gray matter volume after four weeks of treatment with lithium in bipolar depressed patients who clinically responded to treatment (Moore et al., 2009). Another piece of evidence regarding the influence of pharmacotherapy in bipolar disorder outcomes is the strong and bidirectional relationship between poor treatment adherence and cognitive impairment. Poor treatment adherence may worsen the course of bipolar disorder, increasing the episodes of the illness, for example, and so indirectly worsen cognitive performance; on the other hand, cognitive impairment may also contribute to poor treatment adherence, promoting more severe illness (Martinez-Aran et al., 2009).

It is possible that because lithium and potentially other mood stabilizers may give some degree of neuroprotection against neuronal loss; lag time until their introduction could result in disease progression or clinical deterioration (Manji et al., 2000). In summary, the role of mood stabilizers as neuroprotective agents is being strongly established. This accumulation of evidence is increasingly supporting neuroprotection as a key therapeutic target in early intervention.

Some limitations of our study related to the cross-sectional design warrant consideration. First, this design precluded examination of chronological relationships among BD patients before and after initiation of mood stabilizer treatment and suicide attempt. Consequently, we could not compare the distribution of suicide attempts in treated and untreated BD patients. Second, we did not evaluate patients' pre-stabilizer treatment morbidity severity, leading to an impossibility to control the analyses for this variable. And third, due to the lack of accurate information we did not evaluate the time spent in stabilizer treatment. Nevertheless, this study design evaluated patients retrospectively and did not permit a cause-effect relationship. Future prospective studies are necessary to understand the importance of the use of mood stabilizers and other psychotropic drugs in the course and treatment of bipolar patients, with the objective of decreasing the risk of suicidal behavior.

In conclusion, the present study suggests that the latency in initiating mood stabilizers in BD patients may hold implications for outcome aspects, and particularly in this case, a higher risk for suicide attempts. Nonetheless, it is important to highlight that in order to limit the often devastating and potentially lethal impact of these highly prevalent and treatment-responsive disorders, early diagnosis and early intervention for BD should be preferred and continuously pursued.

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Conflict of interest

The authors do not have any actual or potential conflict of interest, including any financial, personal, or other relationships with other people or organizations, within three years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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References

Agren, H., Backlund, L., 2007. Bipolar disorder: balancing mood states early in course of illness effects long-term prognosis. Physiology and Behavior 92 (1–2), 199–202.

Baethge, C., Tondo, L., Bratti, I.M., Bschor, T., Bauer, M., Viguera, A.C., Baldessarini, R.J., 2003a. Prophylaxis latency and outcome in bipolar disorders. Canadian Journal of Psychiatry 48 (7), 449–457.

Baethge, C., Smolka, M.N., Gruschka, P., et al., 2003b. Does prophylaxis-delay in bipolar disorder influence outcome? Results from a long-term study of 147 patients. Acta Psychiatrica Scandinavica 107, 260–267.

Baldessarini, R.J., Tondo, L., Hennen, J., et al., 1999. Latency and episodes before treatment: response to lithium maintenance in bipolar I and II disorders. Bipolar Disorders 1 (2), 91–97.

Baldessarini, R.J., Tondo, L., Davis, P., et al., 2006. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disorders 8 (5 Pt 2), 625–639.

Baldessarini, R.J., Tondo, L., Baetjge, C.J., et al., 2007. Effects of treatment latency on response to maintenance treatment in manic-depressive disorders. Bipolar Disorders 9 (4), 386–393.

Baldessarini, R.J., Vieta, E., Calabrese, J.R., et al., 2010. Bipolar depression: overview and commentary. Harvard Review of Psychiatry 18 (3), 143–157.

Berk, M., Brnabic, A., Dodd, S., et al., 2011. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disorders 13 (1), 87–98.

Chen, Y., Dilsavier, S., 1996. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biological Psychiatry 39, 896–899.

Chuang, D.M., Chen, R.W., Chalecka-Franaszek, E., et al., 2002. Neuroprotective effects of lithium in cultured cells and animal models of diseases. Bipolar Disorders 4 (2), 129–136.
Cipriani, A., Pretty, H., Hawton, K., Geddes, J.R., 2005. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. The American Journal of Psychiatry 162 (10), 1805–1819.
Cordeiro, G.M., 1986. Modelos Lineares Generalizados. Abstract of VII Simpósio Nacional de Probabilidade e Estatística. Campinas, SP, pp. 1–23.
Elshahawi, H.H., Essawi, H., Rabie, M.A., Mansour, M., Beshry, Z.A., Mansour, A.N., 2011. Cognitive functions among euthymic bipolar I patients after a single manic episode versus recurrent espisodes. Journal of Affective Disorders 130 (1–2), 180–191.
Farrow, T.F.D., Whitford, T.J., Williams, L.M., et al., 2005. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. Biological Psychiatry 58, 713–723.
First, M.B., Spitzer, R.L., Gibbon, M., et al., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders: Clinical Version (SCID-CV). American Psychiatric Press, Washington, DC.
Frazier, J.A., Breeze, J.L., Makris, N., et al., 2005. Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. Bipolar Disorders 7, 555–569.
Ghaemi, S.N., Boiman, E.E., Goodwin, F.K., 1999. Kindling and second messengers an approach to the neurobiology of recurrence in bipolar disorder. Biological Psychiatry 45, 137–144.
Goldberg, J.F., Ernest, C.L., 2002. Features associated with the delayed initiation of mood stabilizers at illness onset in bipolar disorder. The Journal of Clinical Psychiatry 63 (11), 985–991.
Goodwin, F., Jamison, K., 2007. Suicide, In: Goodwin, F., Jamison, K. (Eds.), Manic-Depressive Illness, 2nd ed. Oxford University Press, NY, pp. 247–269.
Grunebaum, M., Ramsay, S., Galfalvy, H., et al., 2006. Correlates of suicide attempt history in bipolar disorder: a stress-disthesis perspective. Bipolar Disorders 8, 551–557.
Harrell Jr., F.E., 2001. Regression Modeling Strategies: with applications to linear models, logistic regression, and survival analysis. Springer, NY.
Harris, E.C., Barraclough, B., 1997. Suicide as an outcome for mental disorders: a meta analysis. The British Journal of Psychiatry 170, 205–228.
Hawton, K., Sutton, L., Haw, C., et al., 2005. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. The Journal of Clinical Psychiatry 66, 693–704.
Kapczinski, F., Dal-Pizzol, F., Teixeira, A.L., et al., 2011. Peripheral biomarkers and illness activity in bipolar disorder. Journal of Psychiatric Research 45 (2), 156–161.
Leverich, G., Altshuler, L., Frye, M., et al., 2003. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. The Journal of Clinical Psychiatry 64, 506–515.
Manji, H.K., Moore, G.J., Chen, G., 1999. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? Biol. Psychiatry 46 (7), 929–940.
Manji, H.K., Moore, G.J., Chen, G., 2000. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers implications for the pathophysiology and treatment of manic depressive illness. Biological Psychiatry 48, 740–754.
Marangell, L.B., Dennehy, E.B., Wisniewski, S.R., et al., 2008. Case–control analyses of impact of pharmacotherapy on prospectively observed suicide attempts and completed suicides in bipolar disorder: findings from STEP-BD. The Journal of Clinical Psychiatry 69, 916–922.
Martinez-Aran, A., Scott, J., Colom, F., et al., 2009. Treatment nonadherence and neurocognitive impairment in bipolar disorder. The Journal of Clinical Psychiatry 70 (7), 1017–1023.
Merikangas, K.R., Akiskal, H.S., Angst, J., et al., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of General Psychiatry 64 (5), 543–552.
Moore, G.J., Cortese, B.M., Glitz, D.A., et al., 2009. A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. The Journal of Clinical Psychiatry 70 (5), 699–705.
Nery-Fernandes, F., Quarantini, L.C., Galvão-de-Almeida, A., et al., 2009. Lower rates of comorbidities in euthymic bipolar patients. The World Journal of Biological Psychiatry 10 (4 Pt 2), 474–479.
Novick, D.M., Swartz, H.A., Frank, E., 2010. Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. Bipolar Disorders 12 (1), 1–9.
Oquendo, M., Waternaux, C., Brodsky, B., et al., 2000. Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. Journal of Affective Disorders 59, 107–117.
Oquendo, M.A., Currier, D., Liu, S.M., et al., 2010. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The Journal of Clinical Psychiatry 71 (7), 902–909.
Post, R.M., Leverich, G.S., Kupka, R.W., et al., 2010. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. The Journal of Clinical Psychiatry 71 (7), 864–872.
Quarantini, L.C., Miranda-Scippa, A., Nery-Fernandes, F., et al., 2010. The impact of comorbid posttraumatic stress disorder on bipolar disorder patients. Journal of Affective Disorders 123 (1–3), 71–76.
Regier, D.A., Boyd, J.H., Burke Jr., J.D., et al., 1988. One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Archives of General Psychiatry 45 (11), 977–986.
Slama, F., Bellivier, F., Henry, C., et al., 2004. Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. The Journal of Clinical Psychiatry 65 (8), 1035–1039.
Tondo, L., Baldessarini, R.J., 2009. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. Epidemiologia e Psichiatria Sociale 18 (3), 179–183.
Valtonen, H., Suominen, K., Mantere, O., et al., 2005. Suicidal ideation and attempts in bipolar I and II disorders. The Journal of Clinical Psychiatry 66, 1456–1462.
Valtonen, H., Suominen, K., Mantere, O., et al., 2006. Prospective study of risk factors for attempted suicide among patients with bipolar disorder. Bipolar Disorders 8, 576–585.
Yerevanian, B.I., Koek, R.J., Mintz, J., et al., 2003. Lithium, anticonvulsants and suicidal behavior in bipolar disorder. Journal of Affective Disorders 73 (3), 223–228.
Yerevanian, B.I., Koek, R.J., Mintz, J., 2007. Bipolar pharmacotherapy and suicidal behavior. Part I: lithium, divalproex and carbamazepine. Journal of Affective Disorders 103 (1–3), 5–11.