Socio-demographic and clinical characterization of patients with Bipolar Disorder I vs II: a Nationwide Italian Study

A. Carlo Altamura, Massimiliano Buoli, Bruno Cesana, Bernardo Dell'Osso, Gianluigi Tacchini, Umberto Albert, Andrea Fagiolini, Andrea de Bartolomeis, Giuseppe Maina, Emilio Sacchetti

Socio-demographic and clinical characterization of patients with Bipolar Disorder I vs II: a Nationwide Italian Study

EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE 2017 Apr 1.

Socio-demographic and clinical characterization of patients with Bipolar Disorder I vs II: a Nationwide Italian Study

A. Carlo Altamura, Massimiliano Buoli, Bruno Cesana, Bernardo Dell'Osso, Gianluigi Tacchini, Umberto Albert, Andrea Fagiolini, Andrea de Bartolomeis, Giuseppe Maina, Emilio Sacchetti

Abstract

Bipolar disorders (BDs) are prevalent, comorbid and disabling conditions, associated with the highest suicide risk among psychiatric illnesses. In the last few years, new efforts to better characterize the socio-demographic and clinical profiles of BD type I vs II have been documented by several reports, with novel and insightful findings in the field. The present multicenter study aimed to provide a comprehensive and reliable representation of the Italian reality, through the analysis of the largest national sample of bipolar patients collected so far. A total of 1500 patients (BD I n = 963 and BD II *n* = 537) from different psychiatric departments, participating in the Italian Chapter of the "International Society of Bipolar Disorders" (ISBD), were assessed and divided into two groups on the basis of their diagnostic subtype, and different socio-demographic and clinical variables were compared between the two subgroups. Chi-squared tests for categorical variables and *t* tests for continuous variables were performed for group comparison. Furthermore, a multivariable logistic regression was performed, considering diagnostic bipolar subtype (type I or II) as dependent variable, and socio-demographic/clinical characteristics as independent variables. BD I vs II patients showed an overall less favorable socio-demographic and clinical profile. In addition, the multivariable logistic regression showed that BD II vs BD I was predicted by the absence of lifetime suicide attempts (OR = 1.58, $p = 0.01$), a later age of diagnosis (OR = 1.03, $p < 0.01$), less hypomanic episodes in the last year (OR = 2.29, $p < 0.0001$) and absence of psycho-educational interventions in the last year (OR = 0.51, $p < 0.01$). BD I and II patients were found to significantly differ in relation to specific clinical variables, which should be considered within updated diagnostic–therapeutic algorithms.

Keywords

Bipolar disorder (BD) BD type I BD type II Socio-demographic features Clinical variables

Introduction

Bipolar disorders type I (BD I) and II (BD II) represent the main defined conditions within the chapter of bipolar disorders by the DSM-5 [1] and are characterized by variable prevalence, socio-demographic and clinical features [2, 3]. In alternative to the DSM classification, BD can be seen as a diagnostic entity included within the Mood Spectrum Disorders, which are characterized by alternation of mood episodes of different severity [4]. In addition a number of authors claim the revision of manic/hypomania criteria to have more reliable figures of prevalence of BD in the general population [5]. A shortening of duration of hypomania and mania as a criterion for a diagnosis of BD has demonstrated its validity to discriminate bipolar patients from unipolar subjects [6]. In addition, similar social dysfunction (increased in health service utilization, need for welfare and suicidal behavior) was found between subsyndromal manic patients and manic/hypomania subjects with respect to healthy individuals [7]. Recent investigation showed that the two bipolar

subtypes may not be better conceived as a more and less severe variant of the same illness but, more likely, as subgroups of disorders with peculiar longitudinal expressions of illness severity, including, for instance, lifetime number of mood episodes, suicide risk, and treatment response. In this perspective, in fact, BD II compared to BD I patients can in multiple ways be more severe, as evidenced by more common associations with unfavorable illness characteristics [8], including more depressive [9, 10, 11] and overall episodes [12], and higher rates of anxiety disorder comorbidity [13, 14], rapid cycling course [15, 16], and family history of mood disorders [9, 17]. In addition, patients suffering from BD II vs I have shown greater risk of suicide attempt in some [18, 19, 20] but not all studies [21, 22, 23]. On the other hand, most studies in the field have found that BD I vs II patients show more severe characteristics of illness, as evidenced by more common associations with prior psychosis [24], psychiatric hospitalization [24, 25] and overall less favorable socio-demographic status and global functioning [26].

Ultimately, the presence of specific clinical features, including childhood onset [27], lifetime presence of psychotic symptoms [28] and the presence of certain comorbidity patterns [29], associated with the different subtypes of BD, may confer a higher severity of illness to BD I and II patients.

Factors that can contribute to a higher severity of illness, within specific subgroups of BD I and II patients, may be, moreover, represented by the setting, with more severe cases—particularly amongst BD II subjects [8]—potentially attending tertiary clinics and not necessary reflecting the characteristics of patients followed elsewhere.

Overall, the available data about the clinical severity of the two main BD subtypes are partly contradictory and for this reason the purpose of the present paper is to compare socio-demographic and clinical features between BD subtypes in a large Italian multicenter sample. This can clarify the terms in which one of the two forms of BD may be more severe than the other. For example, a greater association of one of the two forms with suicide attempts could drive the clinicians towards targeted treatments [30]. Conversely an earlier age at onset of BD I vs BD II could orient preventive measures to certain age groups in the general population [31].

Methods

An overall sample of 1609 patients was intially enrolled from different Italian psychiatric clinics. The sample was intended to be representative of the entire national territory. The protocol was approved by the local Ethical Committees. Patients had a diagnosis of BD (type I or type II) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria [32]. Mood episodes, including hypomania, were also defined according to DSM criteria. Diagnoses were made by expert psychiatrists, who had regularly followed up the selected patients and confirmed by the MINI International Neuropsychiatric Interview [33]. Patients consecutively presenting to outpatient or inpatient services were included in the study. Clinical information was gathered through a review of the clinical charts and clinical interviews with patients and available relatives. Data were entered into an electronic central database (electronic Case Report Form: e-CRF). Collected data included the following socio-demographic and clinical variables divided into three clusters:

- cluster 1 (socio-demographic variables): age, gender, education (years), employment, marital status (at least 1 marriage or partnership), living alone;
- cluster 2 (lifetime clinical variables): age at onset of BD, age at first pharmacological prescription (including benzodiazepines), age at first contact with psychiatric services, first psychiatric diagnosis, age at first diagnosis of BD, age at first mood stabilizer/atypical

antipsychotic, polarity of first episode, number of manic/hypomanic episodes, lifetime number of depressive episodes, duration of untreated illness, prevalent polarity, prevalent course, lifetime psychotic symptoms, lifetime attempted suicide;
- cluster 3 (clinical variables-last year of observation): presence of hypomanic episodes, psychotic symptoms, hospitalizations, presence of insight, attribution of symptoms to a psychiatric disorder, treatment adherence, psychoeducational interventions (according to Colom's model) [34], acceptability of treatment by patients.

Prevalent polarity was calculated according to the definition provided by the Barcelona Bipolar Disorder Group [35]. Manic prevalent polarity is characterized by at least two-thirds of past episodes complying with DSM-IV criteria for manic/hypomanic episodes, while depressive prevalent polarity is defined as at least two-thirds of a patient's past episodes fulfilling DSM-IV criteria for a major depressive episode [35].

Exclusion criteria were the following: (1) patients who had not been examined in the last 12 months for the impossibility to collect data of cluster 3 variables (last year of observation); (2) patients whose the information about the bipolar type diagnosis was not available; (3) patients with a diagnosis of dementia, mental retardation or other medical conditions (e.g., untreated endocrine disorders) associated with an increased risk of psychotic symptoms.

Descriptive analyses of the total sample were performed. The subgroups (divided according to the diagnostic subtype) were compared by Student's *t* tests for quantitative variables and Chi-square tests for qualitative ones. Owing to the large number of variables statistically related to the dependent variable (bipolar subtype) at the univariate analyses, preliminary multiple logistic regression analyses (one for each above-mentioned cluster) were performed including only statistically significant variables. Finally, statistically significant variables from these final models were then inserted in a new starting multivariable logistic regression model to obtain the variables independently associated with the outcome.

The selection of the variables has been done according to a backward procedure; in the last multivariable logistic model, the gender and the age (not statistically significant) have been kept into the model to obtain the estimates adjusted for these two variables. The goodness of fitting has been assessed by the Hosmer–Lemeshow test.

The level of statistical significance was set at $p < 0.05$. Statistical analyses have been performed by SAS® 9.2 version.

Results

The sample included 1500 patients: 648 males (43.2%) and 852 females (56.8%). Patients had an age between 18 and 80 (mean: 48.61 ± 13.43). Nine hundred and sixty-three patients were affected by BD I (64.2%) and 537 by BD II (35.8%). One hundred and nine patients have been excluded from the analysis as a result of missing data about bipolar type diagnosis. Twenty-seven centers scattered throughout the Italian territory contributed to the final sample: 8 centers (29.6%) enrolled about 100 patients each, 7 centers (26.0%) enrolled about 50–80 patients each, and 12 centers (44.4%) enrolled about 10–50 patients each.

Descriptive analyses of the total sample and of the two groups, divided according to bipolar subtype, are reported in Tables 1, 2 and 3. Of note, age at first pharmacological

prescription is earlier than age at onset of BD: this is probably due to psychiatric comorbidity (e.g. with anxiety disorders with onset before BD) or alternatively delayed diagnosis.

Patients divided according to diagnostic subtype were not different in terms of years of education ($\chi^2 = 2.49$, $df = 2$, $p = 0.28$).

In contrast, BD II patients were found to be more frequently females ($\chi^2 = 5.21$, $df = 1$, $p = 0.02$), older ($t = -4.98$, $p < 0.0001$), employed ($\chi^2 = 7.20$, $df = 1$, $p < 0.01$), at least married once or partnered ($\chi^2 = 11.56$, $df = 1$, $p < 0.001$) and to live with someone ($\chi^2 = 3.8$, $df = 1$, $p = 0.05$). In addition, BD II vs I patients showed a later age at onset ($t = -6.21$, $p < 0.0001$), age at first psychiatric diagnosis ($t = -6.12$, $p < 0.0001$), age at first pharmacological prescription (including benzodiazepines) ($t = -6.13$, $p < 0.0001$), age at first contact with psychiatric services ($t = -7.07$, $p < 0.0001$), age at first diagnosis of BD ($t = -11.11$, $p < 0.0001$), and age at first Mood Stabilizer/Atypical Antipsychotic ($t = -10.91$, $p < 0.0001$). BD II vs I individuals had also a more frequent misdiagnosis with major depressive disorder (MDD) ($\chi^2 = 43.97$, $df = 2$, $p < 0.0001$), depressive polarity of first episode ($\chi^2 = 101.4$, $df = 2$, $p < 0.0001$), depressive prevalent polarity ($\chi^2 = 147.7$, $df = 2$, $p < 0.0001$), prevalent course depression/hypomania ($\chi^2 = 14.44$, $df = 2$, $p = 0.0007$), absence of lifetime psychotic symptoms ($\chi^2 = 245.81$, $df = 1$, $p < 0.0001$), absence of lifetime suicide attempts ($\chi^2 = 10.7$, $df = 1$, $p = 0.001$), a longer duration of untreated illness (>2 years) ($\chi^2 = 29.36$, $df = 1$, $p < 0.0001$), a higher number of depressive episodes ($\chi^2 = 43.55$, $df = 3$, $p < 0.0001$) and a lower number of hypomanic/manic episodes ($\chi^2 = 538.68$, $df = 3$, $p < 0.0001$). Finally, in the last year of observation, BD II vs I subjects showed more frequently the presence of insight ($\chi^2 = 27.52$, $df = 2$, $p < 0.0001$), attribution of symptoms to a psychiatric disorder ($\chi^2 = 22.06$, $df = 2$, $p < 0.0001$), treatment adherence ($\chi^2 = 62.08$, $df = 2$, $p < 0.0001$) and probability of satisfaction with antidepressant treatment ($\chi^2 = 29.88$, $df = 2$, $p < 0.0001$). On the other hand, BD II vs I patients showed less frequently the presence of hypomanic episodes ($\chi^2 = 50.40$, $df = 1$, $p < 0.0001$), psychoeducational interventions ($\chi^2 = 7.36$, $df = 2$, $p = 0.025$), psychotic symptoms ($\chi^2 = 85.67$, $df = 1$, $p < 0.0001$) and hospitalizations ($\chi^2 = 24.25$, $df = 1$, $p < 0.0001$). No differences were found in terms of major depressive episodes in the last year of observation between BD I and II patients ($p = 0.23$).

The goodness-of-fit test results (Hosmer and Lemeshow Test: $\chi^2 = 13.33$, $df = 8$, $p = 0.1$) showed that multivariable logistic regression model including socio-demographic/clinical variables as possible predictors of BD II subtype was adequate. In particular, the absence of lifetime attempted suicides (OR = 1.58, $p = 0.01$) (Fig. 1), a later age of BD diagnosis (OR = 1.03, $p < 0.01$) (Fig. 2), less hypomanic episodes in the last year (OR = 2.29, $p < 0.0001$) and absence of psychoeducational interventions in the last year (OR = 0.51, $p < 0.01$) were all found to be predictors of BD II (Table 4).

Discussion

To date and to authors' knowledge, the present study is the first national report conducted on the largest Italian sample of bipolar patients, assessing related differences in terms of socio-demographic and clinical variables.

The main results of this study (as shown by binary logistic regression) indicate that BD II patients have fewer lifetime suicide attempts, a later psychiatric diagnosis and are treated less frequently with psycho-educational interventions than BD I patients. In addition, BD I patients were found to have more hypomanic episodes in the last year than BD II patients, similarly to what has been reported in previous researches [36], although without statistical significance. Of note, in the paper by Kupka and collaborators [36], the lack of statistical significance might have been due to the distinct sample size, type of patients (only outpatients vs outpatients plus inpatients), distinct way of assessing hypomania (time spent in this state vs number of hypomanic episodes).

With regard to attempted suicides, available data are contrasting with regard to a difference in suicide attempts between BD I and II. Some researches did not find significant differences according to bipolar subtype [7; 21]; others found a higher frequency of suicide attempts in bipolar 2 patients [18] as a result of more probable mixed depressed episodes [37], while further researches found a higher frequency of suicide attempts in bipolar 1 subjects than in bipolar 2 ones [38]. Severity of depression and dysphoric-agitated mixed phases of illness have been indicated as strong predictors of suicidal behavior in BD [39]. Some studies reported more severe depressive episodes such as the psychotic ones [40] and more frequent mixed depression in bipolar 1 patients [41] thus supporting the findings of the present research. However, our results may be biased by other factors such as different distribution of ethnicity [42] and female gender in the two groups of patients as well as distinct duration of illness, all variables that are considered to be associated with increased suicidal behavior in BD [43, 44, 45]. However, our sample was almost exclusively composed by Caucasians, the two sub-groups of patients had a similar duration of illness (17.6 years in BD I subjects and 17.22 years in BD II subjects) and BD II group showed a greater representation of females. Despite these observations, other factors could be influenced the result of a higher risk of suicide attempts in bipolar 1 vs bipolar 2 patients, such as the inclusion of inpatients [29] and bipolar subjects with a severe clinical presentation (e.g. with psychotic symptoms associated with increased suicide risk) [46, 47]. Of note, reasons for hospitalization include high suicidal risk and in our sample bipolar 1 subjects presented more hospitalizations in the last year with respect to bipolar 2 patients. This means that bipolar inpatients might be more represented by BD I subjects who have a high suicidal risk [48].

With regard to the delayed diagnosis in BD II patients, several studies in the literature confirm this finding [49]. A delayed diagnosis of this subtype of bipolar patients may be due to a lower recognition by patients and their relatives of hypomanic episodes with a delay in access to psychiatric services [50], or alternatively to a misdiagnosis with recurrent MDD [51] or substance misuse disorders by clinicians [52]. Of note, the consequences of a delayed diagnosis or a misdiagnosis of these patients may lead to an

improper treatment (e.g. antidepressant mono-therapy) and to a worse outcome consisting of more relapses [53] and more suicidal attempts [54]. In addition, improper prolonged antidepressant mono-therapy may explain high frequency of dysphoric-agitated depression [55] and suicide attempts in bipolar 2 patients [21].

Purposes of psychoeducation include the improvement of illness insight and treatment adherence, early symptom identification and development of coping strategies [56]. The finding of a higher frequency of psychoeducation in BD I patients is not surprising because available data indicate poorer insight and less treatment adherence in BD type 1 than in type 2 (also as a consequence of manic episodes and more frequent psychotic symptoms) [57, 58, 59, 60]. In addition, a recent systematic review reported that psychoeducation seems to be more effective for prevention of manic/hypomanic episodes than for depressive ones, perhaps representing an intervention more targeted for bipolar 1 than bipolar 2 subjects [61].

Limitations

The following limitations of the present research need to be taken into account:

1. 1.

   patients were treated with different drugs which might have influenced reported results;

2. 2.

   the different settings of care (in several Italian regions) may have influenced the clinical and demographic characteristics of the sample;

3. 3.

   some data were collected retrospectively (e.g. duration of untreated illness or number of mood episodes) so that they might have not been always as accurate as in controlled studies;

4. 4.

the heterogeneity of number of subjects in the two sub-groups of patients as a consequence of the naturalistic and retrospective design of the study.

Compliance with ethical standards

Conflict of interest

The authors do not have any conflicts of interest with the present manuscript. Local ethics committees have approved the present research.

References

1.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th Edition, (DSM-5). American Psychiatric Press, Washington DC.

2.

Wittchen HU, Mhlig S, Pezawas L (2003) Natural course and burden of bipolar disorders. Int J Neuropsychopharmacol 6:145–154.

3.

Ketter TA (2010) Handbook of diagnosis and treatment of bipolar disorder. American Psychiatric Publishing, Inc., Washington, DC.

4.

Ghaemi SN, Dalley S (2014) The bipolar spectrum: conceptions and misconceptions. Aust N Z J Psychiatry 48:314–324.

5.

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W (2003) Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 73:133–146.

6.

Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, Young AH (2013) Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur Arch Psychiatry Clin Neurosci 263:663–673.

7.

Judd LL, Akiskal HS (2003) 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 73:123–131.

8.

Dell'Osso B, Holtzman JN, Goffin KC et al (2015) American tertiary clinic-referred bipolar II disorder compared to bipolar I disorder: More severe in multiple ways, but less severe in a few other ways. J Affect Disord 188:257–262.

9.

Endicott J, Nee J, Andreasen N, Clayton P, Keller M, Coryell W (1985) Bipolar II. Combine or keep separate? J Affect Disord 8:17–28.

10.

Judd LL, Akiskal HS, Schettler PJ et al (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 60:261–269.

11.

Judd LL, Schettler PJ, Akiskal HS et al (2003) Long-term symptomatic status of bipolar I vs. bipolar II disorders. Int J Neuropsychopharmacol 6:127–137.

12.

Goodwin FK, Jamison KR (2007) Manic-depressive illness. Bipolar disorders and recurrent depression, 2nd edn. Oxford University Press, Oxford, UK.

13.

Rihmer Z, Szádóczky E, Füredi J, Kiss K, Papp Z (2001) Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. J Affect Disord 67:175–179.

14.

Henry C, Van den Bulke D, Bellivier F, Etain B, Rouillon F, Leboyer M (2003) Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. J Clin Psychiatry 64:331–335.

15.

Baldessarini RJ, Tondo L, Floris G, Hennen J (2000) Effects of rapid cycling on response to lithium maintenance treatment in 360 bipolar I and II disorder patients. J Affect Disord 61:13–22.

16.

Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA (2003) Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry 64:1483–1494.

17.

Benazzi F (2004) Bipolar II disorder family history using the family history screen: findings and clinical implications. Compr Psychiatry 45:77–82.

18.

Dunner DL, Gershon ES, Goodwin FK (1976) Heritable factors in the severity of affective illness. Biol Psychiatry 11:31–42.

19.

Rihmer Z, Pestality P (1999) Bipolar II disorder and suicidal behavior. Psychiatr Clin North Am 22:667–673.

20.

Baek JH, Park DY, Choi J et al (2011) Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. J Affect Disord 131:59–67.

21.

Novick DM, Swartz HA, Frank E (2010) Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. Bipolar Disord 12:1–9.

22.

Valtonen H, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä ET (2005) Suicidal ideation and attempts in bipolar I and II disorders. J Clin Psychiatry 66:1456–1462.

23.

Merikangas KR, Jin R, He JP et al (2011) Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68:241–25.

24.

Vieta E, Gastó C, Otero A, Nieto E, Vallejo J (1997) Differential features between bipolar I and bipolar II disorder. Compr Psychiatry 38:98–101.

25.

Bega S, Schaffer A, Goldstein B, Levitt A (2012) Differentiating between bipolar disorder types I and II: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J Affect Disord 138:46–53.

26.

Dell'Osso B, Dobrea C, Cremaschi L et al (2016) Italian Bipolar II vs I patients have better individual functioning, in spite of overall similar illness severity. CNS Spectr Online.

27.

Holtzman JN, Miller S, Hooshmand F et al (2015) Childhood-compared to adolescent-onset bipolar disorder has more statistically significant clinical correlates. J Affect Disord 179:114–120.

28.

Coryell W, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J (2001) The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. J Affect Disord 67:79–88.

29.

Goffin KC, Dell'Osso B, Miller S et al (2016) Different characteristics associated with suicide attempts among bipolar I versus bipolar II disorder patients. J Psychiatr Res 76:94–100.

30.

Tondo L, Baldessarini RJ (2016) Suicidal behavior in mood disorders: response to pharmacological treatment. Curr Psychiatry Rep 18:88.

31.

Conus P, Macneil C, McGorry PD (2014) Public health significance of bipolar disorder: implications for early intervention and prevention. Bipolar Disord 16:548–556.

32.

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th Edition, Text Revision (DSM-IV-TR). American Psychiatric Press, Washington DC.

33.

Sheehan DV, Lecrubier Y, Sheehan KH et al (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59:22–33.

34.

Vieta E, Pacchiarotti I, Valentí M, Berk L, Scott J, Colom F (2009) A critical update on psychological interventions for bipolar disorders. Curr Psychiatry Rep 11:494–502.

35.

Colom F, Vieta E, Suppes T (2015) Predominant polarity in bipolar disorders: refining or redefining diagnosis? Acta Psychiatr Scand 132:324–326.

36.

Kupka RW, Altshuler LL, Nolen WA et al (2007) Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord 9:531–535.

37.

Benazzi F (2005) The relationship of major depressive disorder to bipolar disorder: continuous or discontinuous? Curr Psychiatry Rep 7:462–470.

38.

Angst J, Angst F, Gerber-Werder R, Gamma A (2005) Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res 9:279–300.

39.

Tondo L, Isacsson G, Baldessarini R (2003) Suicidal behaviour in bipolar disorder: risk and prevention. CNS Drugs 17:491–511.

40.

Zaninotto L, Souery D, Calati R, Camardese G, Janiri L, Montgomery S et al (2015) Dimensions of delusions in major depression: socio-demographic and clinical correlates in an unipolar-bipolar sample. Clin Psychopharmacol Neurosci 13:48–52.

41.

Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB et al (2009) Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am J Psychiatry 166:173–181.

42.

Cassidy F (2011) Risk factors of attempted suicide in bipolar disorder. Suicide Life Threat Behav 41:6–11.

43.

Undurraga J, Baldessarini RJ, Valenti M, Pacchiarotti I, Vieta E (2012) Suicidal risk factors in bipolar I and II disorder patients. J Clin Psychiatry 73:778–782.

44.

Altamura AC, Buoli M, Serati M (2011) Duration of illness and duration of untreated illness in relation to drug response in psychiatric disorders. Neuropsychiatry 1:81–90CrossRefGoogle Scholar

45.

Tondo L, Pompili M, Forte A, Baldessarini RJ (2016) Suicide attempts in bipolar disorders: comprehensive review of 101 reports. Acta Psychiatr Scand 133:174–186.

46.

Ozyildirim I, Cakir S, Yazici O (2010) Impact of psychotic features on morbidity and course of illness in patients with bipolar disorder. Eur Psychiatry 25:47–51.

47.

Altamura AC, Buoli M, Caldiroli A et al (2015) Misdiagnosis, duration of untreated illness (DUI) and outcome in bipolar patients with psychotic symptoms: a naturalistic study. J Affect Disord 182:70–75.

48.

Ghanbari Jolfaei A, Ghadamgahi P, Ahmadzad-Asl M, Shabani A (2016) Demographic and diagnostic features of 3147 inpatients with mood disorders in Iran. Iran J Psychiatry Behav Sci 10:e2298.

49.

Altamura AC, Buoli M, Albano A, Dell'Osso B (2010) Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study. Int Clin Psychopharmacol 25:172–179.

50.

Serati M, Buoli M, Altamura AC (2015) Factors that affect duration of untreated illness in pregnant women with bipolar disorder. Am J Obstet Gynecol 213:876.

51.

Perlis RH (2005) Misdiagnosis of bipolar disorder. Am J Manag Care 11:271–274Google Scholar

52.

Patel R, Shetty H, Jackson R (2015) Delays before diagnosis and initiation of treatment in patients presenting to mental health services with bipolar disorder. PLoS One 10:e0126530CrossRefPubMedPubMedCentralGoogle Scholar

53.

Gigante AD, Barenboim IY, Dias RD, Toniolo RA, Mendonça T, Miranda-Scippa Â et al (2016) Psychiatric and clinical correlates of rapid cycling bipolar disorder: a cross-sectional study. Rev Bras Psiquiatr 38:270–274.

54.

Rosa AR, Cruz N, Franco C, Haro JM, Bertsch J, Reed C, Aarre TF et al (2010) Why do clinicians maintain antidepressants in some patients with acute mania? Hints from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM), a large naturalistic study. J Clin Psychiatry 71:1000–1006.

55.

Benazzi F (2005) Agitated depression in bipolar II disorder. World J Biol Psychiatry 6:198–205.

56.

Stafford N, Colom F (2013) Purpose and effectiveness of psychoeducation in patients with bipolar disorder in a bipolar clinic setting. Acta Psychiatr Scand 442:11–18.

57.

Altamura AC, Goikolea JM (2008) Differential diagnoses and management strategies in patients with schizophrenia and bipolar disorder. Neuropsychiatr Dis Treat 4:311–317.

58.

van der Werf-Eldering MJ, van der Meer L, Burger H, Holthausen EA, Nolen WA, Aleman A (2011) Insight in bipolar disorder: associations with cognitive and emotional processing and illness characteristics. Bipolar Disord 13:343–354.

59.

Depp CA, Harmell AL, Savla GN, Mausbach BT, Jeste DV, Palmer BW (2014) A prospective study of the trajectories of clinical insight, affective symptoms, and cognitive ability in bipolar disorder. J Affect Disord 152–154:250–255.

60.

da Silva Rde A, Mograbi DC, Camelo EV et al (2015) Insight in bipolar disorder: a comparison between mania, depression and euthymia using the insight scale for affective disorders. Trends Psychiatry Psychother 37:152–156.

61.

Bond K, Anderson IM (2015) Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. Bipolar Disord 17:349–362.