CURRENT NEUROPHARMACOLOGY

Curr Neuropharmacol. 2017 Apr; 15(3): 353–358.
Published online 2017 Apr. doi: 10.2174/1570159X14666160606210811
PMCID: PMC5405618
PMID: 28503106

Depression and Mania in Bipolar Disorder

Leonardo Tondo,[a,b,c,*] Gustavo H. Vázquez,[a,d] and Ross J. Baldessarini[a,b]

Abstract

Abstract: Background: Episode duration, recurrence rates, and time spent in manic and depressive phases of bipolar disorder (BD) is not well defined for subtypes of the disorder.

Methods: We reviewed the course, timing, and duration of episodes of mania and depression among 1130 clinically treated DSM-IV-TR BD patients of various types, and compared duration and rates as well as total proportion of time in depressive versus manic episodes during 16.7 average years at risk.

Results: As expected, episodes of depressions were much longer than manias, but episode-duration did not differ among BD diagnostic types: I, II, with mainly mixed-episodes (BD-Mx), or with psychotic features (BD-P). Recurrence rates (episodes/year) and proportion of time in depression and their ratios to mania were highest in BD-II and BD-Mx subjects, with more manias/year in psychotic and BD-I subjects. In most BD-subtypes, except with psychotic features, there was more time in depressive than manic morbidity, owing mainly to longer depressive than manic episodes. The proportion of time in depression was highest among those who followed a predominant DMI course, whereas total time in mania was greatest in BD with psychotic features and BD-I. and with an MDI course.

Conclusions: Subtypes of BD patients differed little in episode-duration, which was consistently much longer for depression. The findings underscore the limited control of bipolar depression with available treatments.

Keywords: Bipolar disorder, cycle length, depression, duration of episodes, mania, polarity

1. INTRODUCTION

1.1. Background: The Bipolar Disorder Concept

Early descriptions of what is now recognized as bipolar disorder (BD) date to ancient and medieval writers, and others through the 18th century [1, 2]. In the 19th century, based on his clinical observations at Hôpital Saltpêtrière, Parisian alienist Jules Baillarger (1809-1890) first presented his concept of *Insanity of Double Form*, consisting of alternating periods of excitation and depression, at a lecture at the Académie de Médecine in 1854 [1, 3, 4]. Jean-Pierre Falret (1794-1870), who worked at the same institution, and like Baillarger was a student of Jean-Étienne Dominique Esquirol (1772-1840), claimed to have identified a similar disorder several years earlier (1851), which he termed *Circular Insanity*, with manic and depressive periods as well as intervening periods of lucidity or illness-free intervals [1, 4]. Baillarger described cases involving attacks or episodes of mania and melancholia which varied from two days to one year in duration, but averaged approximately six months. He also noted that transitions between relatively short-lasting mood states could occur quite suddenly, even during a single night's sleep, but that transitions were typically more gradual with longer-lasting attacks [3].

At the end of the 19th century, Emil Kraepelin (1856–1926) professor of psychiatry at the Universities of Heidelberg and later Munich conceptualized a broad condition, *Manic-Depressive Insanity*, that included current-day bipolar disorder and major depressive disorder [1, 2, 5]. The current concept of *Bipolar Disorder* emerged from MDI in the mid-20th century, based primarily on separation of illnesses with manic or hypomanic phases and depressions as well as conditions marked primarily with recurrent major depressive episodes [1, 6-8]. In the 1970s, a subgroup of BD patients characterized by prominent recurrences of major depressive episodes with hypomania but not mania (BD-I) was described and designated type-II (BD-II) [9].

1.2. Duration of Episodes in Bipolar Disorder

Kraepelin noted that states of manic excitation can vary greatly in duration from weeks to several months, and that more severe forms of mania with severe excitement and psychotic features tend toward relatively long episodes. He also noted that melancholic (depressive) states (of both modern bipolar and major depressive disorders) are generally longer than manic attacks, can sometimes persist for years, and tend to become more prominent than mania at older ages [2, 5].

Modern estimates of the average duration of major episodes of disturbances of mood and behavior in bipolar disorder have been provided in several long-term follow up studies, mainly with ongoing treatment [7, 8]. In an early report, Kukopulos and his colleagues [10] reported average durations of 24 weeks for depression and 30 weeks for mania among BD-I subjects. In a five-year US study, the time to symptomatic recovery, or of no longer meeting diagnostic criteria for a major episode of illness, averaged 6 weeks with mania, 11 weeks with depression and 17 weeks with mixed manic-depressive states [11]. In a Zurich study, manic, depressive, and mixed episodes did not differ substantially in duration, which averaged 12-to-16 weeks [12]. A more recent US study found that episodes of major mood disorders averaged 8–12 weeks, with longer acute episodes of depression than of mania [13]. Our earlier observations found that depressive episodes in BD-I patients lasted, on average, 20–25 weeks [14]. Episodes of depres-

sion with agitation that may represent mixed-states averaged about one-third longer than non-agitated depressive episodes in BD-I patients [15]. Based on these few available reports, episode-duration averaged: bipolar depression 15.8 [CI: 7.17-24.4] weeks, mixed-episodes 15.5 weeks (with only two reports), and manic-hypomanic episodes 13.3 [CI: 0-30.7] weeks.

1.3. Course and Sequence of Manic and Depressive Episodes

An important phenomenon noted by Kraepelin is that periods of manic excitement are often followed by a period of exhaustion sometimes considered a consequence of a severe illness, which "is obviously only a case of the transition to depression peculiar to the disease" [5]. This observation indicated that periods of mania and depression can be associated, such as in *biphasic cycles* of illness in
BD.

Following this concept of paired phases of illness in BD, Athanasios Koukopoulos and his colleagues introduced the idea that many (approximately half) BD-I and BD-II patients follow predominantly paired, course-sequences or cycles of illness as depression-mania (or hypomania)–euthymic interval (DMI type) or its opposite (MDI type) [16-21].

1.4. Aims of this Study

To add further information about the timing and duration of episodes of mania and depression in BD patients diagnosed by DSM-IV criteria and treated by current community standards, we reviewed the life-charts of a large sample of types I and II BD patients who were evaluated, treated, and followed in a mood disorder center by a mood disorder expert (LT). We considered the mean duration
of manic and major depressive episodes, their annual frequency, and the total proportion of affective illness over long-term follow-up, not only for BD-I and BD-II patients, but also BD-I with prominent psychotic features or with predominantly mixed manic-depressive episodes. We also assessed BD patients with major recurrences which followed the predominant course of *mania-depression-euthymic interval* (MDI), or its opposite (DMI).

2. METHODS

The 1130 bipolar disorder study subjects were evaluated and followed prospectively at the Lucio Bini Mood Disorders Center in Cagliari and Rome between 1990 and 2015 for an average of 6.53 [95% CI: 3.01-7.05] years, with 16.7 [CI: 15.9-17.5] years of overall exposure time following illness-onset. Following review and approval by a local ethics committee and in compliance with applicable Italian law, study participants provided written, informed consent for the anonymous and aggregate analysis and reporting of their findings, with assurance that their treatment would be determined by community standards and not modified for research purposes. Data-management complied with US federal Health Insurance Portability and Accountability Act (HIPAA) regulations pertaining to confidentiality of patient records.

Participants underwent initial diagnostic assessments, treatment, and follow-up evaluations by the same mood-disorders expert (LT), based on semi-structured interviews and life-charts as well as extensive, prospective, follow-up clinical assessments, typically every 2-4 weeks for

three months, and every 2-3 months thereafter, as was reported previously [14, 22]. Clinical diagnosis and BD-I versus BD-II subtyping was updated to meet DSM-IV-TR criteria after 2008. Other subtypes were based on clinical assessments that included the presence of at least two *mixed* manic-depressive features in multiple episodes (BD-Mx), based on clinically defined criteria (not restricted by severity or duration of either polarity), or of psychotic features (delusions or hallucinations) in at least one episode (BD-P). In addition, we considered subjects separately who followed a majority of cycles of illness as depression–mania (or hypomania)–euthymic interval (DMI type) or its opposite (MDI type), based on life-charts. which supported identification of the types, duration, and sequences of episodes.

Data accumulated in computer spreadsheets, summarizing the course of illness in each case were analyzed by standard bivariate methods for associations of selected parameters of illness (counts and annual rates of major depressive and manic or hypomanic episodes, estimated proportion of time-at-risk in depression or mania, as well as total episode counts, episode durations and rates allowing for calculation of average duration of depressive and manic episodes); diagnostic or course-type subgroups also were assessed as already defined. Continuous measures were assessed by ANOVA methods; *t*-scores and *p*-values are presented. Averages are presented as means ± standard deviation (SD) or with 95% confidence intervals (CI). Statistical analyses were based on use of Staview-5 (for spreadsheets; SAS Institute; Cary, NC) or STATA-13 (StataCorp; College Station, TX) commercial software.

3. RESULTS

3.1. Episode Duration

Initially, we estimated the duration of major depressive and manic (or hypomanic) episodes for each BD diagnostic and cycle-pattern subtype (Table **1**). A total of 56.8% of subjects could be characterized for major course-patterns as either DMI or MDI, which occurred in similar proportions for each type. As expected, depressive episodes averaged
5.2 months, and were 50% longer than manic-hypomanic episodes which lasted 3.5 months (overall, t=8.21, p<0.0001). In addition, depressive episodes were longest in BD-II, and similarly longer with DMI and MDI than other course-types, whereas manic episodes were significantly longer (33%) in MDI than DMI cases. Of note, however, episode duration for each polarity did not vary significantly among the diagnostic or course-type subgroups (Table **1**). On average, depressions were 81% longer than manias among BD subjects with a DMI course and 41% longer with an MDI course (Table **1**).

Table 1

Months/episode of mania or depression in bipolar disorder types.

Clinical Subgroups	Subjects (n)	Months/Episode		
		Depressions	Manias	D/M
A. Diagnosis				
BD-I	215	4.53 [4.11-4.95]	3.25 [2.70-3.80]	1.39
BD-II	464	5.46 [4.91-6.01]	3.63 [3.09-4.17]	1.50
BD-Mx	186	5.30 [4.60-6.00]	4.12 [3.40-4.84]	1.29
BD-P	265	5.07 [4.44-5.70]	2.98 [2.66-3.30]	1.70
Total	1130	5.18 [4.87-5.49]	3.46 [3.18-3.73]	1.50
p-value [*t*-score]	---	0.24 [1.19]	0.09 [1.47]	---
B. Course-type				
DMI	313	4.53 [4.11-4.95]	2.50 [2.13-2.87]	1.81
MDI	329	4.70 [4.14-5.26]	3.33 [2.89-3.77]	1.41
p-value [*t*-score]	---	0.69 [0.40]	0.02 [2.41]	---

Episode duration = total time ill/total episode-count. *Abbreviations*: *BD* = bipolar disorder, *D* = depression; *DMI* = depression–mania-euthymic interval; *M* = mania or hypomania; *MDI* = mania–depression–interval; *Mx* = mainly with mixed-episodes; *PD-P*, with prominent psychotic features in at least one episode. Of all 1130 subjects, 21.8% followed a DMI, and 21.6%, an MDI course-pattern. Note: depressive episodes were consistently longer than manias (by 39%–81%), but in both depression and mania, episode-durations were very similar among the clinical subgroups.

3.2. Episode Recurrence Rate

We also considered depressive and manic morbidity as average recurrence rates (episodes/year). Recurrences of depression and mania both averaged just under one episode per year overall (total of nearly two episodes/year). The rate of all episodes/year ranked: BD-P ≥ BD-I ≥ BD-II ≥ BD-Mx. BD subjects with prominent psychotic features, BD-I subjects, and those who followed a majority MDI course had more manic than depressive episodes (D/M ratio <1.0; Table 2). In contrast, subjects with BD-II and BD-Mx syndromes had more depressions per year than manias (Table 2).

Table 2

Mania and depression in bipolar disorder types: proportion of time ill and recurrence rates.

Clinical Subgroups	Cases (n)	% of Time in Episodes [95% CI]				Episodes/year [95% CI]		
		Total	Depression	[Hypo]Mania	D/M	Episodes	Depressions	[Hypo]M
A. Diagnosis								
BD-I	215	33.8 [24.5-38.1]	17.9 [14.9-20.9]	15.9 [12.7-19.1]	1.13	2.00 [1.43-2.57]	0.90 [0.48-1.32]	1.11 [0 1.48
BD-II	464	36.3 [33.5-39.1]	26.7 [24.4-29.0]	9.55 [8.14-11.0]	2.80	1.65 [1.42-1.90]	1.08 [0.91-1.25]	0.57 [0 0.68
BD-Mx*	186	36.5 [31.9-41.1]	24.5 [20.9-28.1]	12.6 [9.91-15.3]	1.94	1.58 [1.06-2.10]	0.97 [0.68-1.26]	0.61 [0 0.86
BD-P	265	41.9 [37.8-46.0]	20.8 [17.9-23.7]	21.6 [18.4-24.8]	0.96	2.47 [1.85-3.09]	0.81 [0.58-1.04]	1.66 [1 2.20
Total	1130	37.2 [35.3-39.1]	23.3 [21.9-24.7]	14.1 [12.9-15.3]	1.65	1.90 [1.68-2.12]	0.96 [0.83-1.10]	0.94 [0 1.10
p-value [*t*-score]	---	0.03 [1.70]	<0.0001 [4.45]	<0.0001 [2.75]	---	0.03 [1.75]	0.41 [0.98]	<0.00 [3.2
B. Course-type								
DMI	313	35.6 [32.1-39.1]	28.9 [25.9-31.9]	6.97 [5.64-8.30]	4.15	1.45 [1.11-1.81]	1.06 [0.77-1.35]	0.40 [0 0.52
MDI	329	38.9 [35.3-42.5]	18.7 [16.4-21.0]	20.4 [17.5-23.3]	0.92	1.98 [1.55-2.41]	0.69 [0.55-0.83]	1.29 [0 1.67
p-value [*t*-score]	---	0.20 [1.29]	<0.0001 [5.43]	<0.0001 [8.04]	---	0.06 [1.87]	0.02 [2.29]	<0.00 [4.3

3.3. Proportion of Time Ill

We also considered morbidity as proportion of time-ill during prolonged periods of exposure averaging 12 years. Differences in total percent time ill differed little among diagnostic and course-type subgroups, but there were significant differences in time spent in depression versus mania (Table 2). The greatest proportion of total time ill, and the highest overall recurrence rate was found among BD-P subjects. There was a consistent excess of time spent in de-

pression over mania (D/M) in DMI, BD-II, and mixed-episode subjects, but there was an excess of time in mania over depression among subjects with psychotic features or an MDI course (Table 2).

4. DISCUSSION

A major finding was strong confirmation of an overall excess of time spent in depressive over manic morbidity in BD despite similar rates of recurrence of each major polarity. This difference reflects the longer average duration of depressive than manic episodes (Table **1**), and confirms Kraepelin's observations of a century ago [2, 5, 23]. As expected, the excess of recurrences and time spent in depressions over manias was particularly high among BD-II and BD-Mx subjects (Table 2) [19, 20, 24-28]. Of note, in the present data, both BD-II and BD-Mx diagnostic types were more likely to follow the DMI than the MDI course (not shown). The distribution of rates and time spent in depressions and manias and their sequence-patterns in BD is related to, but to be distinguished from, the concept of "predominant polarity," in which there is a clear excess (typically ≥2:1) of episodes of either depression or mania, and can be stated for about one-half of BD-I patients [25, 29]. In general, the present findings accord with the view that BD-II, DMI, and mainly mixed types of BD patients tend to be "depression-prone." An important general conclusion arising from the present findings is that patients meeting current diagnostic criteria for BD vary markedly in their disposition to particular types of illness, based on diagnostic subtypes. Notably, in addition to the depression-proneness of BD-II and BD-Mx subjects, those with BD-P and BD-I subtypes had excesses of both recurrence rates and proportion of time in mania over depression, and those with psychotic features had the higher proportion of overall time ill (Table 2). The clinical implications of psychotic features in BD are not well evaluated, particularly with respect to recurrence rates, time in morbid states, and their severity [7].

Diagnostic subgroups are ranked by total proportion of time ill, which differed highly significantly. *Abbreviations*: *BD* = bipolar disorder, *D* = depression; *DMI* = depression–mania-euthymic interval; *M* = mania or hypomania; *MDI* = mania–depression–interval; [*] *Mx* = with repeated mixed-episodes (some mainly M or mainly D); *BD-P*, with prominent psychotic features in at least one episode. Note: BD-II subjects spent nearly 3-fold more time in depression than in hypomania, but little more time overall than BD-I cases; also, DMI subjects spent much more time in depression and much less in mania, than MDI cases.

Subjects considered to have had mainly mixed episodes are a notable exception to the rule that we followed DSM-IV-TR diagnostic criteria, in not requiring that such cases consistently fulfill criteria for full major depressive and manic episodes simultaneously. Indeed, a majority of the mixed episodes encountered in the present subjects are best described as agitated depressions, as has been proposed previously to represent mixed states of BD [30]. Such broadening of the concept of mixed states of BD is consistent with current views represented in DSM-5 [6]. An additional factor that may contribute to the excess of depression over mania in BD-Mx subjects may be the superior efficacy of available treatments against mania versus bipolar depression [27, 31, 32].

We also found striking dissimilarities in the relative distribution of depressive and manic morbidity between subjects with predominant DMI versus MDI course-sequences. The total proportion of time ill and mean episode duration did not differ between them, but DMI subjects

had a high excess of recurrences and time-ill in depression over mania, and MDI subject, the opposite (Table 2).

Overall, the present findings underscore the importance of recognizing that some types of BD patients, including those with BD-II and BD-Mx syndromes and those who follow a predominant DMI course are "depression-prone." Such cases are even more depression-prone than might be accounted for by the general tendency toward depression over mania in BD known since the time of Kraepelin, or by the differential efficacy of currently available treatments for BD, which are more effective against mania than depression.

LIMITATIONS

The present findings, as in almost all contemporary clinical observational research, are at risk for distortions
to the natural history of untreated illnesses. Given the
strong impression that modern treatments for BD are much more effective in the treatment and prevention of mania
than depression [27, 31, 32], it is possible that depressive morbidity is somewhat over-represented in the findings. In addition, it is likely that precise historical information may be less reliable for periods long before enrollment at the study site, although errors should distribute more or less randomly across the subgroups considered. Finally, an effort was made to identify episodes as mainly manic or mainly depressive in subjects with a majority of episodes with mixed features.

CONCLUSION

The present findings strengthen long-standing impressions that the depressive components of BD are more prominent than manic or hypomanic phases of the illness. This pattern of distribution of morbidity was observed well before the introduction of modern antimanic, antidepressant, and mood-stabilizing medicines and so is unlikely entirely to be an artifact of contemporary therapeutics. Other findings that evidently are not as well known include a strong excess of depression in BD-II disorder as well as in patients with a high proportion of mixed manic-depressive episodes, and in those who usually follow a DMI course-pattern. Overall, the presence of prominent psychotic features was associated with the highest proportion of time in episodes of BD illness and the highest recurrence rate.

ACKNOWLEDGEMENTS

Supported by the Aretæus Foundation of Rome (to LT)., and by the Bruce J Anderson Foundation and the McLean Private Donors Research Fund (to RJB). All authors contributed to all aspects of the design, analysis and presentation of the reported findings. Note that Athanasios Koukopoulos spelled his surname as Kukopulos in early publications.

CONFLICT OF INTEREST

No author or any immediate family member has financial relationships with any commercial organization that might appear to represent a conflict of interest with the material presented in this report.

REFERENCES

1. Baldessarini R.J., Pérez J., Salvatore P., Trede K., Maggini C. History of bipolar manic-depressive disorder. In: Yildiz A., Ruiz P., Nemeroff C.B., York N., editors. *The Bipolar Book: History, Neurobiology, and Treatment.* New York: Oxford University Press; 2015. pp. 3–20. [http://dx.doi.org/10.1093/med/9780199300532. 003.0001] [Google Scholar]

2. Trede K., Salvatore P., Baethge C., Gerhard A., Maggini C., Baldessarini R.J. Manic-depressive illness: evolution in Kraepelins Textbook, 18831926. *Harv. Rev. Psychiatry.* 2005;**13**(3):155–178. [http://dx.doi.org/10.1080/10673220500174833]. [PMID: 16020028]. [PubMed] [Google Scholar]

3. Baillarger J. [Notes on a type of insanity in which attacks are characterised by two regular periods, one of depression, the other of excitation (French)]: Académie de Médecine, 30 January 1854. *Acad. Med. Bull. (Paris)* 1854;**19**:340–352. [Google Scholar]

4. Cousin F-R. In: *Jules Baillarger (1809-1890). Anthology of French Language Texts. Cousin, F.-R.; Garrabe J.* Morozov D., editor. Paris: Le Plessis-Robinson; 1999. [http://dx.doi.org/10.1002/9780470986738]. [Google Scholar]

5. *Kraepelin. E. Manic Depressive Insanity and Paranoia. Edinburgh: E. & S.* Edinburgh: Livingstone; 1921. [Google Scholar]

6. Diagnostic and Statistical Manual of Mental Illnesss 2013.

7. Goodwin F.K., Jamison K.R. *Manic Depressive Illness.* 2nd ed. New York: Oxford University Press; 2007. [Google Scholar]

8. Yildiz A., Ruiz P., Nemeroff C.B., editors. *The Bipolar Book: History, Neurobiology, and Treatment.* New York: Oxford University Press; 2015. [http://dx.doi.org/10.1093/med/9780199300532. 001.0001] [Google Scholar]

9. Dunner D.L., Stallone F., Fieve R.R. Lithium carbonate and affective disorders. V: A double-blind study of prophylaxis of depression in bipolar illness. *Arch. Gen. Psychiatry.* 1976;**33**(1):117–120. [http://dx.doi.org/10.1001/archpsyc.1976.01770010073014]. [PMID: 1108832]. [PubMed] [Google Scholar]

10. Kukopulos A., Reginaldi D., Girardi P., Tondo L. Course of manic-depressive recurrences under lithium. *Compr. Psychiatry.* 1975;**16**(6):517–524. [http://dx.doi.org/10.1016/S0010-440X(75) 80014-9]. [PMID: 1192716]. [PubMed] [Google Scholar]

11. Coryell W., Endicott J., Keller M. Outcome of patients with chronic affective disorder: a five-year follow-up. *Am. J. Psychiatry.* 1990;**147**(12):1627–1633. [http://dx.doi.org/10.1176/ajp.147.12. 1627]. [PMID: 2244640]. [PubMed] [Google Scholar]

12. Angst J., Preisig M. Course of a clinical cohort of unipolar, bipolar and schizo affective patients. Results of a prospective study from 1959 to 1985. *Schweiz. Arch. Neurol. Psychiatr.* 1995;**146**(1):5–16. [PMID: 7792568]. [PubMed] [Google Scholar]

13. Eaton W.W., Anthony J.C., Gallo J., Cai G., Tien A., Romanoski A., Lyketsos C., Chen L.S. Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. *Arch. Gen. Psychiatry.* 1997;**54**(11):993–999. [http://dx.doi.org/10.1001/ archpsyc.1997.01830230023003]. [PMID: 9366655]. [PubMed] [Google Scholar]

14. Tondo L., Baldessarini R.J., Vázquez G., Lepri B., Visioli C. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. *Acta Psychiatr. Scand.* 2013;**127**(5):355–364. [http://dx.doi.org/10. 1111/acps.12023]. [PMID: 23121222]. [PubMed] [Google Scholar]

15. Maj M., Pirozzi R., Magliano L., Bartoli L. Agitated depression in bipolar I disorder: prevalence, phenomenology, and outcome. *Am. J. Psychiatry.* 2003;**160**(12):2134–2140. [http://dx.doi.org/10. 1176/appi.ajp.160.12.2134]. [PMID: 14638583]. [PubMed] [Google Scholar]

16. Faedda G.L., Baldessarini R.J., Tohen M., Strakowski S.M., Waternaux C. Episode sequence in bipolar disorder and response to lithium treatment. *Am. J. Psychiatry.* 1991;**148**(9):1237–1239. [http://dx.doi.org/10.1176/ajp.148.9.1237]. [PMID: 1883005]. [PubMed] [Google Scholar]

17. Grof P., Haag M., Grof P., Haag H. Lithium response and the sequence of episode polarities: preliminary report on a Hamilton sample. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 1987;**11**(2-3):199–203. [http://dx.doi.org/10.1016/0278-5846(87)90060-1]. [PubMed] [Google Scholar]

18. Haag H., Heidorn A., Haag M., Greil W. Sequence of affective polarity and lithium response: preliminary report on Münich sample. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 1987;**11**(2-3):205–208. [http://dx,doi,org/10,1016/0278-5846(87)90061-3]. [PubMed] [Google Scholar]

19. Kukopulos A., Reginaldi D., Laddomada P., Floris G., Serra G., Tondo L. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr. Neuropsychopharmakol.* 1980;**13**(4):156–167. [PMID: 6108577]. [PubMed] [Google Scholar]

20. Koukopoulos A., Reginaldi D., Tondo L., Visioli C., Baldessarini R.J. Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias. *J. Affect. Disord.* 2013;**151**(1):105–110. [http://dx.doi.org/10.1016/j.jad.2013.05.059]. [PMID: 23827534]. [PubMed] [Google Scholar]

21. Maj M., Pirozzi R., Starace F. Previous pattern of course of the illness as a predictor of response to lithium prophylaxis in bipolar patients. *J. Affect. Disord.* 1989;**17**(3):237–241. [http://dx.doi.org/ 10.1016/0165-0327(89)90005-0]. [PMID: 2529291]. [PubMed] [Google Scholar]

22. Tondo L., Lepri B., Baldessarini R.J. Suicidal status during antidepressant treatment in 789 Sardinian patients with major affective disorder. *Acta Psychiatr. Scand.* 2008;**118**(2):106–115. [http://dx.doi.org/10.1111/j.1600-0447.2008.01178.x]. [PMID: 18397362]. [PubMed] [Google Scholar]

23. Snook E., Moseley-Dendy K., Hirschfeld R.M. Presentation, clinical course, and diagnostic assessment of bipolar disorder. In: Yildiz A., Ruiz P., Nemeroff C.B., York N., editors. *The Bipolar Book: History, Neurobiology, and Treatment.* New York: Oxford University Press; 2015. pp. 35–47. [http://dx.doi.org/10.1093/med/ 9780199300532.003.0003] [Google Scholar]

24. Baldessarini R.J., Salvatore P., Khalsa H-M., Tohen M. Dissimilar morbidity following initial mania versus mixed-states in type-I bipolar disorder. *J. Affect. Disord.* 2010;**126**(1-2):299–302. [http://dx.doi.org/10.1016/j.jad.2010.03.014]. [PMID: 20427091]. [PMC free article] [PubMed] [Google Scholar]

25. Baldessarini R.J., Undurraga J., Vázquez G.H., Tondo L., Salvatore P., Ha K., Khalsa H-M., Lepri B., Ha T.H., Chang J.S., Tohen M., Vieta E. Predominant recurrence polarity among 928 adult international bipolar I disorder patients. *Acta Psychiatr. Scand.* 2012;**125**(4):293–302. [http://dx.doi.org/10.1111/j.1600-0447.2011.01818.x]. [PMID: 22188017]. [PubMed] [Google Scholar]

26. Baldessarini R.J., Tondo L., Visioli C. First-episode types in bipolar disorder: predictive associations with later illness. *Acta Psychiatr. Scand.* 2014;**129**(5):383–392. [http://dx.doi.org/10. 1111/acps.12204]. [PMID: 24152091]. [PubMed] [Google Scholar]

27. Forte A., Baldessarini R.J., Tondo L., Vázquez G.H., Pompili M., Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J. Affect. Disord.* 2015;**178**:71–78. [http://dx.doi.org/10.1016/j.jad.2015.02.011]. [PMID: 25797049]. [PubMed] [Google Scholar]

28. Vieta E., Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. *Bipolar Disord.* 2008;**10**(1-2):163–178. [http://dx.doi.org/10.1111/j.1399-5618.2007.00561.x]. [PubMed] [Google Scholar]

29. Colom F., Vieta E., Daban C., Pacchiarotti I., Sánchez-Moreno J. Clinical and therapeutic implications of predominant polarity in bipolar disorder. *J. Affect. Disord.* 2006;**93**(1-3):13–17. [http://dx. doi.org/10.1016/j.jad.2006.01.032]. [PMID: 16650901]. [PubMed] [Google Scholar]

30. Koukopoulos A., Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. *Psychiatr. Clin. North Am.* 1999;**22**(3):547–564. [http://dx.doi.org/10.1016/S0193-953X(05) 70095-2]. [PMID: 10550855]. [PubMed] [Google Scholar]

31. Baldessarini R.J. *Chemotherapy in Psychiatry.* 3rd ed. New York: Springer Press; 2013. [http://dx.doi.org/10.1007/978-1-4614-3710-9] [Google Scholar]

32. Pacchiarotti I., Bond D.J., Baldessarini R.J., Nolen W.A., Grunze H., Licht R.W., Post R.M., Berk M., Goodwin G.M., Sachs G.S., Tondo L., Findling R.L., Youngstrom E.A., Tohen M., Undurraga J., González-Pinto A., Goldberg J.F., Yildiz A., Altshuler L.L., Calabrese J.R., Mitchell P.B., Thase M.E., Koukopoulos A., Colom F., Frye M.A., Malhi G.S., Fountoulakis K.N., Vázquez G., Perlis R.H., Ketter T.A., Cassidy F., Akiskal H., Azorin J.M., Valentí M., Mazzei D.H., Lafer B., Kato T., Mazzarini L., Martínez-Aran A., Parker G., Souery D., Ozerdem A., McElroy S.L., Girardi P., Bauer M., Yatham L.N., Zarate C.A., Nierenberg A.A., Birmaher B., Kanba S., El-Mallakh R.S., Serretti A., Rihmer Z., Young A.H., Kotzalidis G.D., MacQueen G.M., Bowden C.L., Ghaemi S.N., Lopez-Jaramillo C., Rybakowski J., Ha K., Perugi G., Kasper S., Amsterdam J.D., Hirschfeld R.M., Kapczinski F., Vieta E. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am. J. Psychiatry.* 2013;**170**(11):1249–1262. [http://dx.doi.org/10.1176/appi.ajp. 2013.13020185]. [PMID: 24030475]. [PMC free article] [PubMed] [Google Scholar]