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**1. INTRODUCTION**

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**Depression and Mania in Bipolar Disorder**

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**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**

**1.1. 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 Hopital Saltpetriere, 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 Academie de Medecine in 1854 [1** a, **4]. Jean-Pierre Falret (1794-1870), who worked at the same institution, and like Baillarger was a student of Jean-Etienne 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 1 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)**

**[2].**

**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 [Z, 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** [n]. **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 ). 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 ). 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.**

**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.**

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| **Clinical Subgroups** | **Subjects (n)** | **Months/Episode** |
| **Depressions** |
| **A. Diagnosis** |
| **BD-I** | **215** | **4.53 [4.11-4.95]** |
| **BD-II** | **464** | **5.46 [4.91-6.01]** |
| **BD-Mx 186** | **5.30 [4.60-6.00]** |
| **BD-P** | **265** | **5.07 [4.44-5.70]** |
| **Total** | **1130** | **5.18 [4.87-5.49]** |
| **p-value [t-score]** | **0.24 [1.19]** |
| **B. Course-type** |
| **DMI** | **313** | **4.53 [4.11-4.95]** |
| **MDI 329** | **4.70 [4.14-5.26]** |

**p-value [t-score] 0.69 [0.40]**

**2.50 [2.13-2.87]**

**1.81**

**3.33 [2.89-3.77]**

**1.41**

I **Manias D/M**

 **3.25 [2.70-3.80] 1.39**

 **3.63 [3.09-4.17] 1.50**

 **4.12 [3.40-4.84] 1.29**

**I 2.98 [2.66-3.30] 1.70**

 **3.46 [3.18-3.73] 1.50**

**0.09 [1.47]**

**0.02 [2.41]**

**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 ).**