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Research report

# Continuous circular cycling in bipolar disorder as a predictor of poor outcome



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## ABSTRACT

**Objective:** This prospective study aims to determine if patients with bipolar disorder with a continuous circular course (CCC) are significantly different on clinical characteristics and response to long-term treatment from those with a non-continuous circular course (N-CCC). CCC was defined as the alternation of depression and (hypo)mania without a completely free interval, and N-CCC as the presence of free intervals after the sequence mania–depression or depression–mania.

**Method:** The study sample includes 140 consecutive patients with bipolar I or II disorder according to DSM-IV criteria, aged 18–65 years and receiving prophylactic treatment for. Treatment was based upon international guidelines and clinical experience at the time of patient's enrollment (from January 1998 to January 2006). Primary outcome was the absence of new episodes during the follow-up. Significance level was set at  $p < 0.05$ .

**Results:** Twenty-eight percent of the sample has CCC. Compared with N-CCC, CCC patients were older, had a later onset, a higher number of total, depressive and (hypo)manic episodes, and of switches, and spent a higher percentage of time ill in the year before entering the study. Polarity at onset and subsequent recurrences were more frequently mixed in N-CCC than in CCC patients. The proportion of patients in the CCC group who had no recurrences during the follow-up was significantly lower than in the N-CCC group.

**Conclusion:** The presence or absence of a free intervals over the course of illness identifies two subtypes of bipolar disorder that differ in clinical presentation, outcome, and response to long-term treatment.

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## 1. Introduction

Melancholia and mania were considered to be two distinct disorders up to the beginning of the second half of the 19th century (for a review, see Koukopoulos et al. (2000)). At the end of the century, experts in psychiatric phenomenology began to observe and report a distinct correlation between these two mood states. In 1851 Jean-Pierre Falret and in 1854 Jules Baillarger, two insightful psychiatric phenomenologists, were the very first to argue that there was a special form of mental illness accompanied by regular cycling between melancholia and mania. They called this cyclic pattern of presentation *La folie circulaire* (“circular insanity”) and *La folie à double-forme* (“dual-form insanity”) (Falret, 1851; Baillarger, 1854, respectively). As reported more

recently by Maj et al. (2002), the influence of Falret's and Baillarger's clinical observations on Kraepelin's description of manic depressive insanity has been recognized, but one aspect is quite frequently overlooked. Unlike Falret's *folie circulaire*, Baillarger's *folie à double-forme* included a specific pattern of presentation that was accompanied by the direct transition from depression to mania, or vice versa, without an intervening free interval. In some contrast to Kraepelin's unitary hypothesis of manic depressive illness, Baillarger, as well as his followers (Ritti, 1883; Ballet, 1894), believed that there was a distinct pattern of presentation in which manic and depressive episodes occurred separately and considered this distinction as significant (Maj et al., 2002).

We submit that the clinical relevance of this observation, the absence of the free interval, has not received adequate clinical attention despite clinical observations corroborate this hypothesis. Koukopoulos et al. (1980) investigating the different patterns of manic depressive cycles, observed that 170 out of 434 bipolar patients (39%) had a course that did not include free intervals.

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Koukopoulos called this pattern “continuous circular” cycling, and was the first to argue that this presentation predicted poor response to lithium (Koukopoulos et al., 1980). Other European authors have subsequently confirmed that on average 27% (range 6%–38%) of bipolar patients experienced continuous circular cycling without free intervals (Haag et al., 1986; Grof et al., 1987; Maj et al., 1989; Azorin et al., 2011), and that this presentation was in fact associated with low response rates to long-term treatment with lithium (Haag et al., 1986; Grof et al., 1987; Maj et al., 1989; Koukopoulos et al., 1995).

### 1.1. Aim of the study

The aim of this observational study was to determine if patients with bipolar disorder characterized by a continuous circular course (CCC) were significantly different from patients with bipolar disorder who had an intervening free interval, the non-continuous circular course (N-CCC), on clinical characteristics and response to long-term treatment. Based on our clinical experience we hypothesized that CCC patients had more severe illness and a poorer response to long-term treatment compared with N-CCC patients.

## 2. Material and methods

### 2.1. Subjects

Consecutive patients seen from January 1998 through January 2006 at the *Istituto di Psicopatologia* in Rome, Italy—a private outpatient clinic specialized in mood and anxiety disorders—were screened for eligibility. Patient enrollment criteria were as follows: (1) age 18–65 years; (2) meeting DSM-IV criteria for type I or II bipolar disorder (American Psychiatric Association (APA), 2004); and (3) receiving prophylactic treatment for at least 1 year. We included only patients with at least 1 year of follow-up to confirm their pattern of cycling prospectively and to assess the effectiveness of prophylactic treatment.

### 2.2. Assessments

All subjects underwent initial diagnostic assessments by the first author (AT), based on semi-structured interviews that followed the mood disorder components of SCID-I (First et al., 1996). Approximately 30% of subjects also underwent full, structured, SCID-I based diagnostic assessment to confirm findings of semi-structured clinical examinations. During the first visit demographic (age, sex, marital status and employment) and clinical characteristics were collected, including age at onset, polarity of the first episode, duration of illness, number and polarity of previous episodes, delusional episodes of any polarity, the occurrence of switch, the course of illness, lifetime Axis I comorbidities, and bipolar disorder type (I or II). Wherever possible, collateral clinical data, including information obtained from other informants as well as any available past medical records, were used to corroborate the presence or absence of CCC vs. N-CCC.

During the follow-up visits, which occurred a minimum of 4 times per year, information on treatment and course of illness (number, polarity and duration of recurrent episodes, hospitalizations, suicide attempts) was collected from patients. Typically, family members/close friends provided supplemental clinical information. We assessed mania, hypomania, major depression and mixed states using DSM IV criteria (American Psychiatric Association (APA), 1994). We defined “treatment adherent” patients as those who reported a 75%–100% adherence to the prescribed medication regimen. Severity of illness and improvement were

assessed using the Clinical Global Impressions scale modified for bipolar disorder (CGI-BP) (Spearing et al., 1997), at each follow-up visit. CGI-BP scale was always administered by the first author (AT).

Consistent with the findings of Koukopoulos et al. (1980), we identified four patterns of course: (1) MDI (in which the cycle starts with (hypo)mania, followed by depression and then by a free interval), (2) DMI (in which the cycle starts with depression, followed by (hypo)mania and then by a free interval), (3) CCC (in which episodes of depression and (hypo)mania alternate without a real free interval, i.e. an interval of at least 1 month), (4) IRR (in which the sequence of depression-(hypo)mania-free interval was irregular). As suggested by Koukopoulos et al., we also distinguished long-cycle CC (CC-LC), i.e. less than 2 cycles per year, from short cycles (CC-SC), i.e.,  $\geq 2$  cycles per year. For the purpose of this study we included under the CCC definition patients with long or short continuous cycles and under N-CCC patients with DMI, MDI and IRR pattern of course.

All patients gave written informed consent for the anonymous use of their clinical records, and a local ethical committee approved the research project.

### 2.3. Treatment

Treatment was chosen by the first author (AT) based upon the international guidelines and clinical experience at the time of patient's enrollment (American Psychiatric Association (APA), 2004; Frances et al., 1996; Bauer et al., 1999; Goodwin, 2003). First-line treatment was one mood stabilizer, mainly lithium or divalproex or carbamazepine. If patient's response was inadequate, a combination of two mood stabilizers was utilized. If the response continued to be inadequate, either a third mood stabilizer was added or one of the drugs was replaced with lamotrigine (for prevalent depressive recurrences), nimodipine (for prevalent manic recurrences), gabapentin (for anxiety comorbidity), or topiramate (for eating disorder comorbidity).

If necessary, mood stabilizer(s) were augmented with an antidepressant (acute depressive episode or prevalent depressive recurrences) or an antipsychotic (acute manic or mixed episode or prevalent manic or mixed recurrences). We used antidepressants in N-CCC and CC-LC but not in CC-SC patients, according to the view that antidepressants could worsen the course of CC-SC. (Koukopoulos et al., 1983; Wehr et al., 1988; Baldessarini et al., 2000).

### 2.4. Response to long-term treatment

This primary outcome was measured as the absence of new episodes during the follow-up. Secondary outcomes were based upon: (1)  $\geq 50\%$  reduction in the number of episodes in the last year of follow-up compared to the year prior to entering the study, (2)  $\geq 50\%$  decrease in the time spent in an episode in the last year of follow-up compared to the year prior to entering the study, and (3) CGI-BP overall bipolar illness severity  $\leq 2$  (minimal or less) in the last year of follow-up.

### 2.5. Statistical analysis

CCC and N-CCC patients were compared on demographic and clinical characteristics. The  $\chi^2$  test was used to compare categorical variables and the *t*-test or the Mann–Whitney (M–W) test was used to compare continuous variables when appropriate. In particular, the M–W test was used when the distribution of the variable was skewed. Because of the exploratory nature of the study, the significance level was set to 0.05. Post-hoc tests were

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