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REVIEW ARTICLE

Continuous circular cycling as a predictor of treatment response in bipolar disorders: a comprehensive review of the current literature

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Evidence from the literature suggests that, on average, 27% of patients with a bipolar disorder (BD) experience a continuous cycling course (CCC) and that this subgroup differs significantly from patients with a noncontinuous cycling course (N-CCC) with respect to sociodemographic characteristics and clinical presentation. The aim of the present paper is to review the studies that evaluated short- and long-term treatment responses in BD patients with CCC. The retrieved studies indicate that CCC is a significant predictor of poor response to long-term treatment with lithium (the odds of a response in the CCC group were 57% less than in the N-CCC group; $p < 0.01$), as well as to polytherapies including lithium and/or an antiepileptic augmented, when necessary, with an antipsychotic and/or antidepressant. The percentage of patients without new episodes during follow-up was significantly lower in the CCC group compared with the N-CCC group (15.4 vs. 37.6% , $p < 0.01$). Compared with patients in the N-CCC group, members of the CCC group had a poorer response and lower remission rates after 12-week antidepressant treatments for a major depressive episode (82.3 vs. 50%, $p = 0.002$; 69.6 vs. 40.9%, $p = 0.013$). These findings, underlining that CCC is a predictor of poor response to short- and long-term treatment in BD, should be interpreted considering the limitations of the reviewed studies (the small sample sizes, the small number of trials and their observational nature, the lack of randomization or placebo controls, and the unblinded nature of the outcomes). Clinical trials and observational studies with larger samples are warranted to confirm the conclusions of our review.

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Key words: Bipolar disorders, course, bipolar depression, long-term treatment, antidepressant.

Introduction

In 1854, Jules Baillarger, a French psychiatric phenomenologist, identified a special form of "folie à double forme" (resembling bipolar disorders in modern nosology), characterized by a direct transition from depression to mania, or vice versa, without an intervening free interval.[1] He regarded this form as distinct from those in which mania and depression occur separately. The presence/absence of a free interval in bipolar disorder (BD) had not received the attention of clinicians until 1980, when Kukopoulos *et al.*[2] identified four patterns of manic-depressive cycles: (1) manic–depression interval (MDI; in which the cycle starts with (hypo)mania, followed by depression and then by a free interval); (2) depression–mania interval (DMI; in which the cycle starts with depression, followed by (hypo)mania, and then by a free interval); (3) continuous cycling course (CCC; in which episodes of depression and (hypo)mania alternate without a real free interval, i.e., an interval of at least one month); and (4) irregular course of cycle sequence (IRR; in which the sequence of depression–(hypo)mania–free interval is irregular).[2] The authors distinguished two subtypes of CCC: long-cycle (CC–LC), with <4 episodes per year, and short-cycle (CC–SC), with >4 episodes annually. Notably, in 1999, Maj *et al.*[3] observed that CC–SC corresponds to a severe subtype of rapid-cycling BD (stable pattern over time, poor prognosis, and poor treatment response) according to DSM–IV criteria.[3]

The studies that examined the sequence of episodes in BD showed that an average of 27% of patients experience CCC and that these patients remarkably differ from those with a free interval with respect to age at onset (later onset), polarity at onset (more likely to be depressive than

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mixed), polarity of recurrences (more (hypo)manic and depressive than mixed), and rate of switch (higher).[4] Taking into account these clinical differences, we argue that patients with CCC differ from patients with other patterns of cycling in treatment response, but, to our knowledge, no studies have reviewed the available evidence on this topic. The aim of the present paper is to review the results of studies that evaluated short- and long-term treatment response in patients with BD and CCC patterns of course.

Method

We present a detailed and comprehensive review of the current literature focusing on treatment response in CCC BD. We identified relevant literature published between 1980 and March of 2016 through searching MEDLINE/PubMed using as the search string ["continuous circular cycling bipolar disorders" OR "pattern of course in bipolar disorders") AND ("treatment")]. The title and abstract of retrieved articles were reviewed by the two authors independently, and nonpertinent papers were excluded. Of the 105 papers screened, only those including original research, clinical trials, systematic reviews, and meta-analyses that directly addressed short- and long-term treatment response in bipolar patients with CCC patterns of course were retained for review and included in this study. Other citations of interest were further identified from the references reported in the accessed articles. Our search was limited to studies written in English and carried out in adult patients. A total of eight studies, including seven observational studies and one metaanalysis, were found. The response rate was compared between N-CCC and CCC groups using logistic regression analysis.

Results

Long-term treatment response

Five studies from the 1980s analyzed the relationship between episode sequence and long-term response to lithium.[2,5–8] All studies adopted Kukopoulos's criteria for subtyping the course of illness by the sequence of episodes and the presence or absence of a free interval,[2] and overall included 531 patients, 481 with BD (90.5%) and 50 (9.5%) with schizoaffective bipolar disorder. The cycle patterns were MDI in 157 (29%) patients, DMI in 133 (25%), IRR in 83 (16%), and CCC in 158 (30%) (CC–LC in 86, CC–SC in 62, unspecified in 10). All patients received lithium treatment, with serum levels ranging between 0.5 and 1.0 mMol/L in two studies,[2,5] >0.7 mMol/L in one study,[6] and not specified in two studies,[7,8] and treatment duration was at least a year in three studies[2,7,8] and at least two years in two studies.[5,6] The outcomes were heterogeneous: average reduction in morbidity as compared to the pre-lithium period in three studies,[2,5,7] decrease in mean number of hospitalizations per year as compared to the pre-lithium period in one study,[6] and no recurrences during the follow-up in another study.[8]

For the purposes of this review, we combined the cycle patterns into two categories: noncontinuous circular cycling (N-CCC) ($n = 373$) (including the DMI, MDI, and IRR patterns of course) and CCC ($n = 158$) (including the CC–LC and CC–SC patterns of course). Comparing the response rate between the two groups with logistic regression analysis, we found that the odds of response in the CCC group were 57% less than those in the N-CCC arm, with a 95% confidence interval ($CI_{95\%}$) between 38 and 84% (Table 1). This result was statistically significant at $p < 0.01$. The inadequate response to lithium in patients with BD and a CCC pattern of course emerged also in a metaanalysis,[9] including four of the five studies included in our analysis,[2,5,7,8] showing that, of the 42 clinical variables investigated, CCC is one of the 5 identified predictors of poor response to long-term treatment with lithium.

More timely information could be derived from a recent prospective observational study using well-defined outcomes and modern prophylactic treatment strategies.[4] The study examined the response to long-term treatment in bipolar patients with CCC or N-CCC followed for at

TABLE 1. Response to lithium according to the presence/absence of free interval

		CCC		N-CCC				
Study	Total	Responders	Nonresponders	Responders	Nonresponders	OR	95% CI	p
Kukopoulos *et al.*[2]	294	40	66	88	100	0.69	0.41–1.15	0.14
Grof *et al.*[6]	50	1	2	36	11	0.15	0–3.34	0.16
Haag *et al.*[7]	48	0	7	12	29	cannot be computed		
Maj *et al.*[5]	99	8	13	48	30	0.38	0.12–1.15	0.08
Faedda *et al.*[8]	40	12	9	12	7	0.78	0.18–3.30	0.76
Total	531	61	97	196	177	0.57	0.38–0.84	<0.01

Abbreviations: CCC = continuous circular course; N-CCC = noncontiuous circular course.

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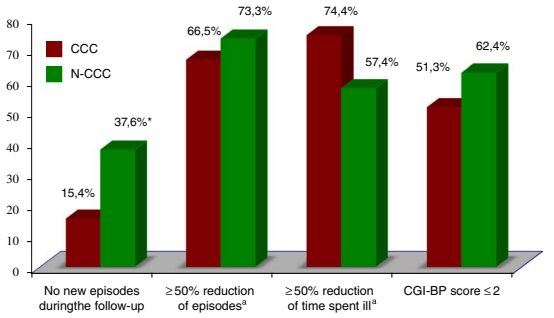
least 12 months (49.0 + 32.3 and 45.4 + 25.0 months, respectively). It included 140 consecutive patients (aged 18–65 years) with BD I ($n = 77$, 55%) and II ($n = 63$, 45%) (DSM–IV criteria).[10] The pattern of course was CCC in 39 (28%) (20 CC–LC and 19 CC–SC) cases and N-CCC in 101 (72%) (24 MDI, 35 DMI, and 42 IRR). The treatment was based on international guidelines and clinical experience at the time of the patient's enrollment (January of 1998 through January of 2006) and varied from a first-line mood stabilizer (lithium, divalproex, or carbamazepine) to complex polytherapy (including two mood stabilizers and/or a putative mood stabilizer, and/or an antipsychotic) in patients without an adequate response. If necessary, mood stabilizers were augmented by antidepressants (ADs) in patients with N-CCC and CC–LC but not in patients with CC–SC, because, as reported by the present authors, this cycle could be worsened by the ADs.[11–13] The primary outcome was the absence of a new episode during follow-up. The secondary outcomes were as follows: (1) ≥50% reduction in the number of episodes in the last year of follow-up compared to the year prior to entering the study; (2) ≥50% decrease in time spent in an episode during the last year of follow-up compared to the year prior to entering the study; and (3) a Clinical Global Impression (CGI) scale modified for bipolar disorder (CGI–BP)[14] overall bipolar severity <2 (minimal or less) in the last year of follow-up.

Compared to those in the N-CCC group, patients in the CCC group were more likely to be treated with divalproex during follow-up (61.1 and 33.7%, respectively, $p = 0.003$); lamotrigine (10.3 and 2%, respectively, $p = 0.03$); and nimodipine (12.8 and 1%, respectively, $p = 0.002$). No significant differences were found between the two groups regarding lithium (84.6 and 72.2%, respectively, $p = 0.334$); carbamazepine (30.8 and 33.7%, respectively, $p = 0.744$); gabapentin (12.8 and 21.8%, respectively, $p = 0.142$); topiramate (5.1 and 9.9%, respectively, $p = 0.366$); a combination of two or more mood stabilizers (25.6 and 21.8%, respectively, $p = 0.14$); adjunctive use of tricyclic antidepressants (TCAs) (33.3 and 19.8%, respectively, $p = 0.091$) or selective serotonin reuptake inhibitors (SSRIs) antidepressants (33.3 and 35.6%, respectively, $p = 0.797$); and/or typical (7.7 and 13.9%, respectively, $p = 0.316$) or atypical (17.9 and 30.7%, respectively, $p = 0.128$) antipsychotics. The findings of the study showed that significantly fewer patients in the CCC group than in the N-CCC group achieved the primary outcome, that is, absence of a new episode during follow-up. No significant differences between the two groups were found regarding secondary outcomes (Figure 1).

The authors concluded that CCC characterizes a bipolar subpopulation of poor responders to lithium and to modern polypharmacy. They underline that a low remission rate does not mean a lack of response,



[a]in the last year of follow-up compared to the year prior to entering the study

*p 0,01

Abbreviation: CCC= CCC= Continuous Circular Course; N-CCC= Non-Continuous Circular Course
CGI-BP= Clinical Global Impression scale modified for bipolar disorder

FIGURE 1. Response to maintenance therapy in CCC ($n = 39$) and N-CCC ($n = 110$) patients.[4]

as demonstrated by the absence of differences between the CCC and N-CCC groups regarding secondary outcomes. Although available long-term treatments reduce the number and duration of recurrences in CCC patients, these treatments are not sufficient to induce remission.

Short-term antidepressant response

To our knowledge, only one study has investigated the response to treatment with short-term ADs according to the presence/absence of a free interval in bipolar patients.[15] This practice-based clinical study included 101 consecutive patients (49/48.5% with BD I and 52/51.5% with BD II [DSM–IV criteria][10]) with a current major depressive episode (MDE) (DSM–IV criteria)[10] and a 21-item Hamilton Depression Rating Scale ($HDRS_{21}$)[16] total score >14. Patients with rapid-cycling BD, a broadly defined mixed state, high mood instability, a previous course with predominantly mixed states, and a history of past (hypo)manic or mixed episodes emerging within eight weeks after introducing an AD were excluded. Patients meeting the inclusion criteria were treated according to the International Society for Bipolar Disorders guidelines for AD use in BD.[17] Specifically, serotonin–norepinephrine reuptake inhibitors (SNRIs) and TCAs were prescribed only if other antidepressants had been tried.

The pattern of course was CCC in 22 (21.8%) patients and N-CCC in 79 (78.2%). The treatment included one or more ADs without significant differences between the CCC and N-CCC groups regarding the class of AD (SSRI: 86.4 and 79.7%, respectively, $p = 0.482$; TCA: 54.5 and 41.8%, respectively, $p = 0.286$; venlafaxine: 13.6 and 6.3%, respectively, $p = 0.262$), their doses, and combinations of two ADs of different class (31.8 and 32.9%, respectively, $p = 0.923$). ADs were combined with at least one mood stabilizer in all patients: lithium (6.9%), an anticonvulsant (48.5%), lithium and an anticonvulsant (25.7%), and an atypical antipsychotic with or without

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a mood stabilizer (15.9%). The pattern of mood stabilizer prescription differed significantly between the CCC and N-CCC groups ($\chi^2 = 24.6$, $p < 0.001$), with a more frequent use of lithium–anticonvulsant combinations in the first and anticonvulsant monotherapy in the last. After 12 weeks, the treatment response rate (50% in the CCC group and 82.3% in the N-CCC group; $\chi^2 = 9.6$, $p < 0.002$) and the remission rate (40.9% in CCC and 69.6% in N-CCC; $\chi^2 = 6.1, p = 0.013$) were significantly lower in the CCC than in the N-CCC group. A logistic regression analysis, adjusted for age, gender, comorbidity, and baseline $HDRS_{21}$ total score, indicated that CCC patients were >4 times more likely to be nonresponders ($OR = 4.35$, $CI_{95\%} = 1.47–12.87$, $p = 0.008$) and >3 times more likely to be non-remitters than N-CCC patients ($OR = 3.30$, $CI_{95\%} = 1.16–9.69, p < 0.05$).

Discussion

About one in three/four patients with BD have a continuous circular cycling course without a free interval, and these patients significantly differ from those with a free interval with respect to sociodemographic characteristics and clinical presentation, as reported in previous studies,[4] as well as treatment response, as emerged from our review. Five studies and one metaanalysis found a poor response to long-term treatment with lithium in patients with CCC patterns of course, and one recent study demonstrated that fewer patients with CCC, compared to those with N-CCC, achieve full remission by prophylactic modern polytherapies, including lithium and/or an antiepileptic augmented, if necessary, by antipsychotics and/or antidepressants. Notably, newer long-term treatments are at least partially effective in patients without a free interval, thus reducing the number and duration of recurrences as well as in patients with a free interval.

The poor response to ADs for treatment of MDE emerged in the only study conducted to date in which the difference between the CCC and N-CCC groups was very impressive. The first are more than four times more likely to be nonresponders and more than three times more likely to be non-remitters. These results underscore the need to identify new treatment strategies for CCC depressed patients alternative to classical ADS, but, to our knowledge, no studies have been conducted on this topic.

Overall, the findings of the present review indicate that patients with BD without a free interval are poor responders to short-term AD treatment or to treatment with long-term lithium and polytherapy. These findings should be interpreted keeping in mind the limitations of the reviewed studies: (1) the small number of trials; (2) their observational nature; (3) the lack of randomization or placebo controls; and (4) the unblinded nature of outcomes. Despite these limitations, the findings of our review further support the hypothesis that CCC and N-CCC are two distinct subtypes of BD with, at least in part, distinctive genetic and/or biological features,[4,15] and strongly suggest that they be differentiated for clinical and research purposes. This distinction could help clinicians to improve prognostic evaluation and to select targeted treatments, as well as assisting researchers to identify more homogeneous samples for genetic or neurobiological investigations. Unfortunately, the pattern of course of BD has still not been assessed in clinical practice as well as in research studies, and the international classification systems for mental disorders, such as the DSM or ICD, do not incorporate the absence of a free interval as a course specifier.

Future randomized clinical trials and observational studies with larger samples are warranted to confirm these findings.

Clinical implications

About 30% of patients with bipolar disorders have a continuous circular cycling course without a free interval.

The absence of a free interval identifies a distinct subtype of bipolar disorder with poor response to short-term antidepressant treatment and to long-term treatment with lithium and polytherapy.

Subtyping patients with bipolar disorders according to the presence/absence of a free interval might help clinicians to improve prognostic evaluation and to select more effective targeted treatments.

Disclosures

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