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Research report

Duration and stability of the rapid-cycling course: a long-term personal follow-up of 109 patients

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Abstract

Background: Recognition by the DSM-IV of rapid cyclicity as a course specifier has raised the question of the stability and long-term outcome of rapid-cycling (RC) patients. Data on this topic is sparse and often inconsistent. To our knowledge, these are the first personally followed patients over the long term, dealing directly with the issue of the duration of the RC course. *Methods:* We examined the evolution of the course of 109 RC patients (68 women and 41 men) followed for a minimum of 2 years and up to 36 years, beginning with the index episode when the RC course was diagnosed by the authors (A.K., G.P.M., P.G., L.P., D.R.). Patients were included in the study if they met criteria for RC as defined by ≥ 4 affective episodes per year (Dunner and Fieve, 1974). The follow-up period varied from 2–5 years for 25 patients, 6–10 years for 24 patients, 11–15 years for 24 patients, 16–20 years for 19 patients, 21–25 years for 13 patients, 30–36 years for four patients. *Results:* In 13 patients (12%), RC emerged spontaneously and in 96 patients (88%), it was associated with antidepressant and other treatments. In 19 women (28% of all women) RC course started in perimenopausal age (45–54 years). The mean duration of RC during the follow-up period was 7.86 years (range 1–32) and its total duration (including RC course prior to the follow-up period) was 11 years (range 1–40). The total duration of the affective disorder, from the first episode to the end of the follow-up, was 21.78 years (range 1–70). At the end of the follow-up, 36 patients (33%) had complete remission for at least the past year, 44 (40%) stayed rapid cycling with severe episodes (six of this group committed suicide), while 15 (14%) were rapid cycling but with attenuated episodes. The other 14 patients (13%) became long cyclers, eight with severe episodes and six with milder ones. The main distinguishing features between those who remitted from and those who persisted in the RC course were: (1) the initial cycle pattern: patients with Depression-Hypomania(mania)-Free interval cycles (53 patients) had a worse outcome: 26.4% remitted and 52.8% persisted in the RC course through to the end of the follow up period. The Mania/Hypomania-Depression-Free interval cycles (22 patients) had a significantly better outcome, with 50% remitted and 27.2% persisting RC; and (2) the occurrence of the switch process from depression to hypomania/mania and the occurrence of agitated depressions made the prognosis worse. Continuous treatment was more effective against mania/hypomania than against depression, yet in all persisting RC cases the mania/hypomania remitted only partially. *Limitations:* These data derive from clinics known for their expertise in mood disorders, and they may have

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attracted and retained patients with a more severe course. Treatment was uncontrolled and consisted more of lithium than divalproex, lamotrigene and olanzapine, recently shown to be beneficial in subgroups of patients with rapid-cycling. *Conclusions:* Our findings suggest that rapid cyclicity, spontaneous or induced, once established, becomes for many years a stable rhythm in a substantial proportion of patients, linked to endogenous and environmental factors. The suggestion is made to consider as rapid-cyclers, at least for research purposes, those patients who have had a rapid cycling course for at least 2 years, borrowing the duration criterion currently employed for other chronic disorders such as Dysthymia and Cyclothymia. That our patients had poorer prognosis than some other cohorts in the literature is probably due to the shorter duration of "rapid-cycling" at entry in the latter cohorts. A true understanding of the nature of rapid-cycling will require a rigorous definition of not only duration, but also pole-switching and course patterns at entry into study.

Keywords: Rapid-cycling; Cycle pattern; Temperament; Hypomania; Stability

1. Introduction

The recognition of rapid cycling (RC) as a course specifier in the DSM-IV has fueled debate concerning the stability of this type of course and its long-term outcome. Coryell et al. (1992) in their 1–5-year follow-up study of 45 rapid-cycling bipolar patients, found that only one of the 39 patients who completed 5 years of follow-up met criteria for rapid-cycling over the entire 5 years. They remarked, "rapid-cycling is, in the large majority of cases, a transient, nonfamilial manifestation of bipolar affective disorde.". They also noted that the use of TCAs and MAOIs did not seem to anticipate rapid-cycling, and that the prognosis of patients with rapid cycling is more benign than generally assumed. Maj et al. (1994) in a 2–5-year follow-up of 37 rapid-cycling patients, found that only seven of them (18.9%) had ≥ 4 affective episodes per year throughout the follow-up period, whatever its duration. They also found that rapid-cycling patients with a pole-switching pattern during the year preceding intake were significantly more likely than other rapid-cycling patients to have ≥ 4 affective episodes during each of the first 4 years of follow-up. These authors commented: "Whether the long-term outcome of rapid-cyclers is significantly worse than that of nonrapid-cyclers remains unclear." Kilzieh and Akiskal (1999) state in their overview of the subject, "RC appears to be a temporary, complicated phase in the illness, not a stable feature."

Bauer et al. (1994), however, found that, of the 60 rapid-cycling patients who were followed for at least 12 months, the RC course persisted through the follow-up period in 39 patients (63%) while only eight patients (13.3%) had no relapses. Baldessarini et al. (2000) found that 22.2% of their RC patients showed no improvement and only 29.4% had no recurrences of mania or depression during treatment. Wehr et al. (1988) in their 5-year follow-up study had found that only 31% of the patients had complete remission while 41% persisted in RC course.

In order to contribute to the debate regarding the stability and long-term outcome of the rapid-cycling course of manic-depressive patients, we examined the evolution of the course of 109 RC patients who were followed and treated by the authors for at least 2 years and as long as 36 years at the Centro Lucio Bini in Rome. We also examined the clinical characteristics of affective patients which make them more liable to be rapid-cyclers for many years.

2. Patients and method

The present study included 109 patients (68 women and 41 men) followed for a period of 2 to 36 years, beginning with the index episode when rapid cycling was diagnosed by the authors (A.K., G.P.M., P.G., L.P., D.R.). Patients were subtyped as rapid cycling according to Dunner and Fieve's (1974) criteria of four or more episodes per year. The gradual shift or switch from one polarity to the opposite one was taken to indicate the start of a new episode. The two cases of recurrent major depression had four episodes per year and met the criterion of at

least 2 weeks of interval. Since many patients experienced considerable acceleration of their cyclicity throughout the follow-up period (one reached 48-h cycles), we waived the duration criterion. In many of these patients, rapid cyclicity was established prior to presentation to our clinic. Patients' initial course and onset of rapid cyclicity was based on information collected from the patients, their relatives and from all available medical records. Table 1 shows the gender distribution and nosologic diagnosis of the patients, and Table 2 shows the age at onset of the first affective episode and of the RC course according to polarity.

Course of illness was evaluated by use of a life chart in which the type, duration and intensity of the episodes, treatments and major life events were recorded. The number of consultations was determined by the patient's clinical requirements. In the event of recurrence or change of treatment, the patient was seen at least once. Cases in which patients achieved complete clinical remission, consultations took place at longer intervals (i.e., 2–3 times or even once a year). At the end of the follow-up period, patients were categorized by outcome: (1) *Fully Recovered*: those patients who experienced no recurrences for a period of ≥ 1 year at the end of follow-up; (2) *Persisting RC Course*: those patients still meeting criteria for rapid cyclicity at the end of the follow-up with episodes of unmodified severity; (3) *Persisting RC Course in Partial Remission:* those patients who, although rapidly cycling, had no hospitalization, no suicide attempts and a $\geq 50\%$ reduction on Hamilton Rating Scale for Depression (HAM-D) score and (4) *Modified Course in Long Cycles*: the episodes were severe or attenuated, but the cycles and intervals were longer and did not meet the criteria for rapid cyclicity.

Table 1
Gender distribution according to nosologic diagnosis

	RC patients ($n = 109$)			
	BPI	BPII	UP	Total
Women	26	40	2	68 (62%)
Men	14	27	0	41 (38%)
Total	40 (37%)	67 (61%)	2 (2%)	109 (100%)

Table 2
Mean age at onset

	BPI	BPII
First episode	23.2 (9–39)	31.2 (11–61)
RC course	34.7 (16–55)	42.1 (17–77)

BPI cases were included in category 3, *Persisting RC Course in Partial Remission*, if the manias had turned into hypomanic episodes and the depressive phases were also attenuated. If the manias had turned into hypomanias but the depressive phases were still severe and invalidating, they were classified as 2, *Persisting RC Course* cases. In order to identify clinical features that may distinguish RC patients with a poor prognosis from those with a favorable one, groups 1 and 2 were compared (i.e., those *Fully Recovered* versus those with *Persisting RC Course*) with respect to the following parameters: gender, bipolar type, age at onset of first episode and of rapid cycling course, frequency of episodes and the pattern of the manic-depressive cycle during the previous course. We also examined the occurrence of a switch from depression to mania or hypomania, the occurrence of agitated depression, and the elapsed time from the onset of rapid cyclicity to the start of adequate treatment. By adequate treatment we mean the suspension of antidepressants and the administration of either lithium, antiepileptics, benzodiazepines, or typical and atypical antipsychotic agents as main treatment.We discuss the relevance of temperament, based on our clinical experience and literature review, on the origin and course of rapid-cycling.

Statistics—means were compared with the t-test, and frequencies were compared with the Chi-square test (χ^2) or the Fisher's exact test. STATA Statistical Software, Release 7, was used (Stata Corporation, College Station, TX, USA). P values were two-tailed, and the probability level was $P < 0.05$.

3. Results

3.1. Onset of RC course

The onset of the rapid cyclicity occurred about 10 years later than the first episode of the affective disorder for both women and men: 28.1 vs. 38.8 and

30.1 vs. 41.2 years, respectively. BPI patients had a younger age at onset of the first episode (23.2 years) and at onset of rapid cyclicity (34.7 years) than the BPII patients: 31.2 and 42.1 years, respectively.

This paper does not investigate the factors related to the onset of the rapid cyclicity. We would like, however, to mention the association of treatments and of menopause with the onset of this condition. Eighty-four patients (77%) developed rapid cyclicity while they were receiving antidepressants (TCA 62, MAOI 10, SSRI 9 and other AD 3), lithium 7, ECT 2, steroids 1, cocaine 1 and caffeine 1. Of the 68 women, 19 (28%) developed rapid cyclicity during the perimenopausal age (45—54 years).

3.2. Duration of RC course

The total duration of the affective disorder from the first episode to the end of the follow-up period, whatever its duration, was 21.78 years (range 1–70, S.D. = 12.33). The mean duration of the initial course prior to the beginning of the RC course was 11.36 years (1–38, S.D. = 8.16). The total duration of rapid cyclicity, including RC course prior to follow-up period, was 11.04 years (1–40, S.D. = 8.39 years). In 34 patients, RC lasted 1–5 years, in 31 it lasted 6–10 years, in 15 it lasted 11–15 years, in 13 it lasted 16–20, in eight it lasted 21–25, in five it lasted 26–30 years, in two it lasted 32 years, and in one it lasted 40 years. The mean duration of rapid cyclicity during the direct observation and treatment period was 7.86 years (range: 1–32, S.D. = 7.84). For the patients who fully recovered (group 1), the total duration of the affective disorder was 15.27 years (2–44, S.D. = 9.47), the initial, non RC course, was 9.48 years (1–30, S.D. = 7.45), the total duration of RC was 6.05 years (1–25, S.D. = 5.03),the duration of RC during follow-up was 2.61 years (1–12, S.D. = 3.02).

For those who persisted in RC course (group 2) for the entire follow-up period, whatever its duration, the above mean values were: total duration of the affective disorder 26.38 years (9–70, S.D. = 12.40), the initial, non RC course, 12.27 years (2–38, S.D. = 7.97), the total duration of RC course 15.22 years (3–40, S.D. = 8.75), the duration of RC during follow-up 12.04 years (1–32, S.D. = 8.08).

All 109 patients had completed at least 2 years of follow-up (mean duration = 12.65 years, range 2–36, S.D. = 7.46). Twenty-five patients had 2–5 years of follow-up, 24 had 6–10 years, 24 had 11–15, 19 had 16–20, 13 had 21–25 and four had 30–36 years.

3.3. Outcome

Of the 109 patients, 36 (33%; 21 women and 15 men), were fully recovered at the end of the follow-up. The mean duration of recovery was 11.3 years (range 4–23). In another 44 patients (40%; 26 women and 18 men), the RC course persisted throughout the follow-up period. Six of this group (three women and three men) committed suicide. In another 15 cases (14%, 10 women and five men), the intensity of the episodes was attenuated but the course was still RC. In 14 patients (13%; 11 women and three men), the course was modified into long cycles. Three remained chronically depressed despite intensive treatment. No statistically significant difference was found regarding gender and outcome.

Of the 40 BPI patients, 14 (35%) recovered and 18 (45%) persisted in RC course. Of these last 18 BPI patients, eight had severe depressions but their manias were reduced to hypomanias. They ran their course like BPII. Another two BPI patients had an outcome in persisting RC course in partial remission and six had a course modified into long cycles. Also of these last patients, four had turned into BPII type of bipolarity. On the whole, of the 40 BPI RC patients only 12 (30%) ran as BPI until the end of their follow-up. The antimanic efficacy of treatment was recorded in 70% of the cases; the antidepressant efficacy of anticycling treatment occurred in 47.5% of the cases.

Of the 67 BPII patients 20 (30%) recovered and 26 (39%) persisted in RC course. Another 13 BPII patients had an outcome in persisting RC course in partial remission and eight had a course modified into long cycles. The antidepressant efficacy of anticycling treatment occurred in 49.2% of the cases, and the hypomanias disappeared or substantially improved in 54% of the cases.

Differences between BPI and BPII groups were not statistically significant. The two unipolar depressive RC recovered fully.

In many patients with persisting RC course there was an acceleration of the course. Of the 44 patients

with persisting RC course, at the end of the follow-up period, 14 still had four episodes per year, eight had six, two had eight, 13 had 12, one had 18, four had 24, one had 48 episodes per year, and one woman had developed 48-h cycles.

3.4. Initial frequency of episodes

Another clinical feature we should underline concerning patients who became rapid-cyclers is the frequency of 0.88 episodes per year (range 0.03–2, S.D. 0.63) during the previous course. This frequency is higher than in the general bipolar or unipolar population. Angst (1986) found that annually bipolar patients had 0.37 episodes and Marneros (1999) found 0.22. However, we did not find any statistically significant difference in the frequency of the episodes during the previous course between the patients that persisted in the RC course (0.95, range 0.11–2.33) and those who recovered (0.80, range 0.03–2) (Table 3).

3.5. Initial cycle pattern

The clinical feature that most distinguished those patients who remitted from those who persisted in the RC course was the initial cycle pattern, prior to the establishing of the RC course. Fifty-three patients with depression-hypomania-interval (DmI), and depression-mania-interval cycles (DMI), had the worst outcome: 14 patients (26.4%) remitted while in 28 (52.8%) the RC course persisted throughout the follow-up period, whatever its duration. Twenty-two patients with mania-depression-interval (MDI), and hypomania-depression-interval (mDI) cycles had a significantly better outcome: 11 patients (50%) remitted and the RC course persisted in only six (27.2%). This difference was found to be statistically significant ($P = 0.0267$).

The 30 patients that initially had a "unipolar" depressive course occupied an intermediate position, with 37% recovered and 27% persisting RC (Table 4).

Table 3
Outcome of 109 RC patients

Persistent RC	44 (40%)
Complete remission	36 (33%)
Persistent RC in partial remission	15 (14%)
Modified course	14 (13%)

Table 4
Initial cycle pattern and outcome

	Recovered	Persistent RC
Dm/DM ($n = 53$)	14 (26%)	28 (53%)
MD/mD ($n = 22$)	11 (50%)	6 (27%)
UP ($n = 30$)	11 (37%)	8 (27%)
CC ($n = 4$)	0	2 (50%)

Dm = Depression-hypomania-free interval cycle; DM = depression-mania-free interval cycle; MD = mania-depression-free interval cycle; mD = hypomania-depression-free interval cycle; UP = recurrent major depression; CC = continuous circular course.

3.6. RC and the switch process

Fifty-nine (54%) of the total 109 RC patients had switches from depression to mania or hypomania before or during the RC course. Examining the outcome of our RC patients, according to the presence or absence of a switch in their course, we found that 12 (20%) of the 36 patients with full recovery had one or more switches while 24 did not have any. Thirty-one (52.5%) of the 44 patients with persisting RC course had one or more switches compared to 13 who did not have any. This difference though clinically important, did not reach statistical significance.

3.7. Agitated depression in RC patients

Forty-two (38.5%) of our 109 RC patients had one or more episodes of agitated depression during the follow-up period. The agitation lasted either the entire episode or part of it, especially during the transition between two episodes of opposite polarity. We define as agitated depression here not only the depressions with motor agitation according to the RCD criteria but also the cases of major depression with intense psychic agitation and racing or crowded thoughts (Koukopoulos and Koukopoulos, 1999). Thirty patients were women (44.1% of 68) and 12 (29% of 41) were men. This is in line with the fact that women suffer from agitated depression more than men. Only 19% of these patients recovered while 52% continued their rapid cycling course. It is noteworthy that out of 25 patients who had both

agitated depression and switches, only three patients (12%) recovered and in 17 (68%) RC persisted.

4. Treatment

This study does not investigate the efficacy of the various treatments for rapid-cyclers. We provide, however, the following information regarding the treatments these patients received during the follow-up period.

The administration of antidepressant drugs was suspended in all cases. (Only six patients received SSRIs, MAOI or TCA at a later stage in their course in order to alleviate depressive symptoms when all efforts to stop cyclicity had failed). Lithium was the basic treatment and all except five patients received lithium prophylactic treatment. It contributed substantially to the recovery of 30 (11 BPI, 18 BPII and one UP) of the 36 completely recovered RC patients. Eleven of these 30 were treated and maintained successfully on lithium monotherapy. Ten patients were treated with ECT and maintained on lithium monotherapy. Two patients were treated with neuroleptics and lithium and maintained on lithium monotherapy. Of six other patients who recovered, two did so on carbamazepine, one on valproic acid, one on clozapine, one on olanzapine monotherapy and one unipolar woman by simple suspension of antidepressants. Sixty RC patients received polypharmacy treatment (lithium, ECT, anticonvulsants, benzodiazepines, neuroleptics and atypical antipsychotics). Seven (four BPI and three BPII) recovered, 36 persisted in RC course, 11 persisted in RC course but with milder episodes and eight had a modified course. Out of 43 patients who received ECT, 11 recovered and were maintained stable on mood stabilizers whereas the others improved only temporarily. Three patients accepted ECT maintenance treatment: two men recovered and after 2 years could be maintained on mood stabilizers without ECT; in one woman, it failed to stop cyclicity. Lamotrigine was used in eight cases of treatment failure: two of them improved partially. Sleep deprivation, applied to two women, gave only temporary improvement of the depression. One woman accepted hospitalization and a substantial reduction of external stimuli while continuing lithium and valproic acid. She improved partially. A forty-seven-year old woman recovered after the addition of estrogens to lithium; she had been a rapid-cycler for 20 years.

Twenty women and six men (24% of all patients) received thyroid supplementation treatment for lithium induced hypothyroidism.

We compared the time from the onset of the rapid cyclicity to the beginning of an adequate treatment. In those who recovered, the mean duration of this period was 3.7 years (range 1–13, S.D. = 3.49) versus 4.6 years (range 1–29, S.D. = 5.40) in those who persisted cycling rapidly. This difference is not statistically significant. Of the 36 patients who fully recovered, 24 (66.6%) recovered within 1 year of treatment. The other 12 recovered within 2–12 years. The mean duration of the treatment required was 2.6 years, but the median was 1 year.

5. Discussion

Rapid cycling is not a rare type of bipolar course. It is generally estimated to affect approximately 15% of bipolar patients. In 1997 we examined 812 bipolar patients who had been treated by the authors over the years 1990–1997 (Koukopoulos, 1997). The proportion of RCs was 17%. In psychiatric practice it is often overlooked, due mainly to the difficulty patients have recalling past episodes as distinct when they are not separated by long intervals as well as to the lack of attention paid by many practitioners to the course of affective disorders.

The present study is naturalistic in design and thus carries with it the biases inherent to such studies. On the other hand, it contains valuable, long-term (up to 36 years) follow-up data collected by the authors (A.K., G.S., G.P.M., P.G., L.P., and D.R.) while they were treating the patients. The advantages of this approach, in becoming intimately acquainted with the patients and the evolution of their disorder, are considerable and obvious.

The first thing to note is that the long-term outcome of rapid-cyclers is not benign in a substantial proportion of cases. At the end of the follow-up, 33% had fully recovered while 40.4% were still cycling rapidly with unmodified severity. The results of our follow-up investigation are strikingly similar to those of Wehr et al. (1988) in their study on the

outcome of 51 RC patients, after 5 years of follow-up: persisting RC was 41 vs. 40% in our study, while complete remission was 31 vs. 33% in ours; the percentage of patients who had a modified course, i.e., changed from RC to long cycles, was 16 vs. 13%.

In our study, adding the patients with persisting RC course and severe episodes ($n = 44$) to the patients with modified course but severe episodes ($n = 8$), totals 52, (48% of the group) who had a poor outcome. The patients who improved were: 36 fully recovered, 15 with persisting RC course but with milder episodes and six with modified course and milder episodes, amounting to 57 in number (52% of the group). These data signify that, despite intensive pharmacological care over many years, 48% of our RC patients had a poor outcome and 21 (19%) improved only partially.

A recent study by Calabrese et al. (2001) found that the combination of lithium and valproex administered continuously over 6 months resulted in antimanic efficacy in 85% of patients and marked antidepressant efficacy in 60%. They comment that "the management of the hypomania/mania associated with rapid cycling was not a difficult clinical challenge but that treatment of refractory depression frequently remained and tended to be a major source of human suffering." Likewise, we have found the manic phase of this illness more responsive to psychopharmacologic treatment than the depressive phase. This is to be expected given that the prophylactic treatments used (e.g., lithium and valproex) are essentially antimanic. Antidepressant use in RC patients is avoided since these agents worsen the course of the condition (Wehr and Goodwin, 1979; Kukopulos et al., 1983). In our view (Kukopulos and Reginaldi, 1973), the attenuation and prevention of depressive episodes is achieved through the attenuation and prevention of the hypomanic/manic phase. But despite intense antimanic treatment, the hypomanic phase never completely resolves in RC patients with persistent cycling rapidly. In such cases a nuance of hypomania is present between the depressions: for example, the patient sleeps 1 or 2 h less, is more talkative, more active, more intolerant, more impatient than his usual self. These signs are so subtle that they do not impair the patient's functioning or quality of life and, on the contrary, have many positive aspects. These symptoms are so mild that they are hardly noticeable during a clinical interview but they can be clearly ascertained by questioning family members. The depression that follows these very mild hypomanic periods is nevertheless a serious one. Of our 44 patients with persisting RC course five BPI women and eight BPII men had such mild hypomanias alternating with severe depressions. However strange as it may appear, it is actually the mania/hypomania—and even the mildest hypomania—that constitute the most refractory phase of the cycle in these particular cases that persist cycling rapidly. Depression is undoubtedly the major source of suffering in these patients. The relationship between hypomania/mania and depression has never been investigated systematically although it has been noticed many times since Aretaeus (1735). The very existence of the bipolar type II, in which mild and often agreeable and "creative" hypomanias are associated with severe and suicidal depressions, demonstrates that this relationship is not a simple one. Further study and insight into this problem is needed in order to improve upon our current treatments. Perhaps greater reliance on newer agents such as divalproex (Calabrese et al., 1992), lamotrigene (Calabrese et al., 2000) and olanzapine (Bhana and Perry, 2001) would have yielded better results.

As far as the stability of the RC course is concerned, 59 patients (44 persisting unchanged RCs plus 15 persisting RCs of milder intensity) remained rapid-cyclers at the end of the follow-up period, amounting to 54% of all patients. If we consider the total duration of RC course, adding the years of RC course before our observation to those during the follow-up, we find a mean duration of rapid cyclicity of 11 years (range 1–40). This long duration of the RC course in a substantial percentage of patients suggests that rapid cyclicity, spontaneous or induced, once established, becomes a special rhythm linked to endogenous and environmental factors. The very frequent seasonal pattern of the four-episodes-per-year rhythm (74 of our patients had four episodes per year) is a clear example of this. The main clinical problem is that once established, rapid cyclicity is difficult to treat in a considerable number of patients. Also the majority of those patients who recovered did so within the first year of adequate treatment

(66%). Persistence of rapid cyclicity beyond the first year of adequate treatment is a sign of poorer prognosis.

The pattern of the manic-depressive cycle is important both in the genesis of the rapid-cycling course (Kukopulos et al., 1983; Koukopoulos, 1997) and in the response to treatment. The DM and Dm cycles respond poorly to stabilizing treatments. The different response of the RC patients to prophylactic treatment, depending on the initial cycle pattern, is very similar to that of bipolar patients in general (Table 5). First described in 1980, we noted how the different cycle patterns responded differently to prophylactic lithium treatment. Sixty-one percent of patients with the MDI cycle responded to lithium treatment, whereas only 32% of the patients with DMI cycle responded. Similar data were found by Grof et al. (1987), Haag et al. (1987), Maj et al. (1989), Faedda et al. (1991) and again by the authors (Koukopoulos et al., 1995).

This similarity in the outcome of RC and non-RC bipolar patients might suggest that there is no difference in response between the two types. The percentages are indeed identical. But there is an important difference in the kind of treatment that was required: suspension of antidepressants and an entirely antimanic and mood stabilizing treatment. The similar outcome implies, however, that RC is not a different entity, but a particular type of course with prevailing DmI or DMI cycle pattern and higher frequency of episodes, which occurs in patients with highly energetic or oscillating temperaments. All these features contribute to the difficulty in achieving a positive response to stabilizing treatments. The Dm type of cycle is closely related to bipolar patients with hyperthymic and cyclothymic temperament (Akiskal, 1992, 1994; Koukopoulos et al., 1992; Koukopoulos and Koukopoulos, 1999). These features constitute the roots of the BPII type in general which is indeed prevalent in RC patients.

Table 5
Lithium response and cycle pattern

	MDI (%)	DMI (%)
Kukopulos et al. (1980)	61	32
Grof et al. (1987)	94	56
Haag et al. (1987)	90	48
Maj et al. (1989)	74	37
Faedda et al. (1991)	73	50
Koukopoulos et al. (1995)	43	29

MDI = Mania-depression-free interval cycle; DMI = depression-mania-free interval cycle.

The different response of the patients that start their cycle with a mania or hypomania and those that start with a depression could be explained by the different treatment situations.

1. In the Dm cycle the intensive antidepressant treatment of the depression accentuates or even triggers the ensuing hypomania or mania. This happens especially with patients of more energetic temperament. In the MDI cycle pattern, the antidepressant treatments do not cause a switch to mania/hypomania because a more or less long interval follows the depression. During this interval antidepressants are usually stopped. But if antidepressants are maintained for a long time, an early provocation of a new mania may occur and an induction of rapid cyclicity may start. Probably the "unexpected" finding by Coryell et al. (1992) that "patients who began follow-up in a purely manic episode rarely had rapid cycling" has its explanation in the fact that the majority of manias have an MDI cycle pattern (Kukopulos et al., 1980).
2. Moreover, prophylactically the MDI cycle is favored: the prophylactic treatment prevents the onset of a mania or hypomania more easily because there is no stimulating medication to counteract it. On the contrary, in the DMI or DmI cycles, the excitatory process is stimulated by the antidepressant given during the depression and this strengthens it, and also makes it more resistant to the mood-stabilizing action of the prophylactic treatment.

The role of temperament appears to be of decisive importance. Kilzieh and Akiskal (1999) state that "it would be logical to assume that RC represents a natural accentuation of the cyclothymic's tendency towards cycling on a lower plane of severity." Brieger and Marneros (1997) state that "Cyclothymic disorder operationalized as a subaffective dimension or temperament appears to be a likely

precursor or ingredient of the construct of bipolar II disorder." Kraepelin (1913), reporting that the cyclothymic disposition among almost a thousand cases observed in Munich was 3–4%, adds "but without doubt in reality it is much more frequent, as it is the invariable introduction to the slightest forms of manic-depressive insanity which run their course outside of institutions." In our study (Kukopulos et al., 1983) dealing with the premorbid temperament of rapid-cyclers we found that 44% had a cyclothymic temperament and another 44% had a hyperthymic temperament.

The preponderance of BPII patients among rapid-cyclers is evidence of the importance of cyclothymic or labile temperament in this type of course. Akiskal et al. (1995), in their 11-year prospective study of clinical and temperamental predictors in 559 patients, conclude that: "The Bipolar II subtype is best understood by such lability intruding into and possibly its accentuation during depressive episodes, thereby creating an intimate interweaving of trait and state . . . Bipolar II represents the most fascinating interface between affective episodes and temperamental instability."

We think that the stimulant action of antidepressants upon the nervous system of these high-energy and mood-labile patients may trigger a period of hypomania or mania, which sooner or later turns into depression and in turn, treated with antidepressants, may set off another mania/hypomania and so on until rapid cyclicity is established (Kukopulos et al., 1983). The particular resistance of these hypomanias to the effect of our stabilizing medications may be based on the combination of the patient's high nervous energy and the stimulating effect of antidepressants. Particularly harmful seems to be the prolongation of antidepressant treatment beyond the end of the depression. Eighty-seven of our patients became rapid-cyclers in association with antidepressants or other stimulating treatments. Thirty of them initially had a unipolar depressive course. After a period of 1–32 years these initially unipolars first evolved into bipolar and later into rapid cycling patients. The difference of approximately 10 years between the first episode and start of rapid cyclicity may not be due only to age related factors but to the long-term treatments believed necessary to induce a RC course. The prevalent premorbid temperament of these "unipolar" depressives was hyperthymic or cyclothymic. These unipolar depressives are probably latent bipolars and have been called Unipolar II by Kupfer et al. (1975) and pseudo-unipolar by Akiskal (1983). More recently, such terms as "cyclothymic depression" (Akiskal, 1994) and "BP-II–1/2"(Akiskal and Pinto, 1999) have been used in reference to this relatively poor-prognosis form of BP-II.

The common feature of the transformation from a previous course into a continuous circular one was the appearance, for the first time, of a hypomania after the depression. The transformation of such cases into rapid-cyclers could be avoided by limiting the use of antidepressants and administering stabilizing agents, i.e., hypomania-preventing medications.

The Dm or DM cycle is also the cycle of the very typical switch from a depression to mania or hypomania, a most striking psychopathological phenomenon and the clearest evidence of the tight link between the two phases or poles of manic-depressive illness. Indeed, the switch process is most frequent in BPII and RC patients.

Maj et al. (1994) found that of the rapid-cyclers, 67.6% had at least one switch during the previous year versus only 24.3% among the non-rapid-cyclers.

Our data suggests that the occurrence of a switch contributes to the onset of a RC course and constitutes a particular impediment to recovery. However, a great deal of effort is required to prevent the switch. Unfortunately, if the switch is prevented by diminishing antidepressants and increasing mood stabilizing agents, many patients remain in depression, not necessarily severe but lengthy. It takes all the firmness of the physician and endurance of the patient to avoid the use of antidepressants and force the switch through a gradual transition into an interval.

The presence of a considerable number of cases of agitated depression among RCs should not come as a surprise because both stem from the same high-energy, emotional and/or unstable temperaments: the hyperthymic and the cyclothymic (Akiskal, 1992; Akiskal et al., 1998; Koukopoulos et al., 1992; Koukopoulos and Koukopoulos, 1999).

Of 25 patients who had presented both agitated depression and switch in their course, only three recovered. It is understandable that the co-existence

of two clinical features expressing severe mood lability renders response to treatment more difficult.

The seven cases in which lithium treatment was associated with the development of rapid cycling could be explained by the shortening of episodes and of post manic/hypomanic intervals created by lithium (Kukopulos et al., 1975).

In conclusion, we could say that the patients more likely to remain rapid-cyclers for many years are those with a DMI or DmI cycle patterns, those with a switch process and/or agitated depression in their course and those who have not recovered after the first year of an adequate treatment. As for the somewhat contradictory data in the literature regarding the stability of the RC course, we think that due to the powerful effect of treatments on the duration of episodes and probably the intervals too, many bipolar cases may become "transient rapid-cyclers" (Kukopulos et al., 1975). These periods of transient rapid-cyclicity are mere iatrogenic artefacts of the course of bipolar disorder which do not involve endogenous rhythms. We would like to suggest that only patients who have had four or more episodes for 2 or more years should be considered rapid-cyclers, at least for research purposes. This would permit a more accurate investigation of the biological and clinical features that contribute to the creation of long-lasting rapid cycling. It is, in fact, the stable rapid-cyclers who constitute a major therapeutic problem and have a poorer outcome than the other cases and, hence, are more likely to be represented in a mood clinic which is known for its expertise in taking care of such patients. Dunner et al. (1976) in their study included patients that had had 2 years of RC course. A 2-year duration criterion would correspond to the criterion of other such chronic affective disorders as Dysthymia and Cyclothymia.

The DSM system considers Rapid Cyclicity as a course specifier. For its continuous and completely autonomous cycling in clear bipolar alternation, Rapid Cyclicity could be viewed as the core form of the entire Bipolar Spectrum.

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