Rapid Cycling in Bipolar Disorder: A Systematic Review

André F. Carvalho, MD, PhD; Dimos Dimellis, MD, PhD; Xenia Gonda, MA, PharmD, PhD; Eduard Vieta, MD, PhD; Roger S. McIntyre, MD, FRCPC; and Konstantinos N. Fountoulakis, MD, PhD

ABSTRACT

Objective: The long-term course of bipolar disorder is typified by recurring mood episodes of opposite polarity as well as mixed states. Rapid-cycling bipolar disorder refers to the presence of at least 4 mood episodes in the previous 12 months that meet the criteria for manic, hypomanic, or major depressive episode. The purpose of this study was to synthesize data regarding prevalence, clinical correlates, and familial/genetic aspects related to rapid cycling in bipolar disorder.

Data Sources: We searched the MEDLINE database through September 7, 2013 for articles regarding rapid cycling in bipolar disorder. Searches were performed using the keywords *rapid cycling* or *rapid-cycling*. The search strategy was augmented through the inspection of reference lists of relevant review articles. Eligible articles included original studies in English on rapid-cycling bipolar patients according to the criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders*.

Study Selection: This study followed the recommendations of the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses statement. The initial search returned 2,715 articles; 2,594 were excluded for several reasons (not aligned with objectives, pertaining to bipolar disorder but not focusing on rapid cycling, case reports, and case series). The final review included 119 articles.

Data Extraction: Two investigators (K.N.F. and D.D.) independently reviewed articles for eligibility. Final decisions regarding eligibility were made by consensus following the full-text review.

Results: The literature suggests that rapid cycling affects a significant proportion of bipolar patients and is related to a longer course of illness, an earlier age at onset, and more illegal drug and alcohol abuse and increased suicidality. Year prevalence of rapid cycling among all bipolar patients ranges between 5%–33.3%, while lifetime prevalence ranges between 25.8%–43%. The etiology remains unclear, although a causal or triggering role for the use of antidepressants and hypothyroidism is implicated. Rapid cycling seems to represent a transitory phenomenon rather than a stable pattern that characterizes the individual patient and probably is related to a worse outcome.

Conclusions: Rapid cycling is a frequent, although underrecognized, condition in bipolar disorder, and it constitutes a worsening of the primary disorder. There is no good evidence that rapid cycling represents a discrete subtype. Early recognition of this pattern can lead to better treatment strategy and improvement of the long-term course. Conceptualizing rapid cycling according to Research Domain Criteria will be an important advance.

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Corresponding author: *Dimos Dimellis, MD, PhD, 47-49, Pontou Str, 55133, Kalamaria, Thessaloniki, Greece (dimosdimellis@hotmail.com).*

Bipolar disorder is a severe, chronic, and disabling condition typically characterized by mood alterations between major depression and mania, which usually last from days to weeks or even months. It would be reasonable to define the cycle in bipolar disorder as the period of time that starts with a mood episode of 1 polarity, followed by remission and a subsequent episode of the opposite polarity, and lasts until the complete remission of this second episode. However, today, we know that the course of bipolar disorder is rarely that symmetrical and typical. The application of such a rigid definition seems impractical. A more pragmatic approach would define a cycle as the period of time that starts with an episode of any polarity and lasts until the recurrence of the disorder with the emergence of another mood episode of any polarity.

In 1911, Eugene Bleuler described a 50-hour cycle in a patient suffering from a mood disorder,[1,2] and almost 10 years later in 1921 Emil Kraepelin underlined a relationship between illness progression and cycle length.[3] During the last 100 years, others also reported several cases of a 48-hour cycle.[4,5]

Despite these observations, rapid mood alterations and fluctuations were not usually described during the 1960s in bipolar patients, but, on the other hand, they were frequently reported during the 1970s and 1980s.[6] The concept of rapid cycling was introduced by Dunner and Fieve[7] in the early 1970s as a course specifier for bipolar illnesses. According to the authors,[7] rapid cycling was defined as a condition in which at least 4 distinct mood episodes occur (including major depressive, manic, hypomanic, or mixed) within a 12-month period, and this approach stands until today. Generally speaking, the cycles can last from weeks to months. When cycles occur in a frequency of days to weeks, then this condition is referred to as ultrarapid cycling, while ultradian cycling refers to the presence of significant mood variations occurring in a 24-hour period.[8] Other course specifiers include, but are not limited to, "ultra-ultra rapid" or "ultradian rapid," which, respectively, refer to weekly or daily cycling, conditions that are not uncommon in patients suffering from bipolar spectrum disorders.[8] However, the limited existing data do not allow unequivocal conclusions regarding the clinical phenomenology, prevalence, and clinical correlates associated with rapid cycling.[8–12]

The concept of rapid cycling overlaps with other clinical phenotypes including mixed specifiers, which provide a source of diagnostic uncertainties. For instance, both contemporary classification systems tend to classify ultrarapid patients within the category of mixed episodes rather than rapid cycling. In fact, the only condition in which a manic or hypomanic episode coexists in the same

Clinical Points

- Rapid cycling is not uncommon among bipolar patients and represents a transitory phenomenon rather than a stable phase of the disorder.
- Rapid cycling can complicate the clinical picture, worsens the long-term outcome by increasing the suicide rate, and has a profound influence on the strategic treatment design.
- The only confirmed close relationship of rapid cycling is that to female gender, while connections to specific bipolar subtype, depressive predominant polarity, treatment with antidepressants, and several biological factors are not universally accepted or documented beyond doubt.

patient and in the same period of time along with a full-blown major depressive episode (as this is required by the modern classification systems) is within the nosologic entity recognized as ultrarapid cycling.[13] This fact direct contrasts the principle proposed by Kraepelin[3] regarding the 3 independent factors that underlie any mood episode (volition, mood fluctuations, and cognition).

The National Institute of Mental Health developed the Research Domain Criteria project as a framework to provide a means to develop a research classification system for mental disorders based on fundamentals of neurobiology as well as observable behaviors.[14] This project aims to characterize the full range of behaviors from normal to pathological and to integrate fundamental genetic, environmental, biological, and experiential components that comprise mental disorders.[15] This approach is also supposed to lead to the modern concept of "personalized medicine," which has been labeled as "stratified psychiatry" in the field of mental health.[16] To the extent that the rapid-cycling phenotype may represent the ultimate expression of a distinct affective instability with unique biological, familial/genetic, and behavioral components remains unknown. Furthermore, little is known regarding the temporal stability of this phenomenon and the role of environmental factors on its pathogenesis, such as antidepressant exposure.[17] The understanding of the unique clinical correlates and the underlying neurobiology/genetics of the rapid cycling may provide a means to understand the true nature of disorders characterized by affective dysregulation.[18,19]

Thus, it is evident that the concept of rapid cycling remains controversial regarding its value as a course specifier and its influence in the treatment planning and long-term prognosis of bipolar disorder. Therefore, the purpose of the present study was to perform a systematic review of the available studies regarding the phenomenology, course, and other clinical correlates of rapid cycling.

METHOD

Articles for review were identified from the MEDLINE database through September 7, 2013. MEDLINE was searched by using the keywords *rapid cycling* or *rapid-cycling*. This study followed the recommendations of the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses statement.[20] The search strategy was augmented through the inspection of reference lists of relevant review articles. Eligible articles included original studies in English on rapid-cycling bipolar patients according to the criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders*.

Two investigators (K.N.F. and D.D.) independently reviewed articles for eligibility. If either investigator deemed an article as potentially eligible on the basis of title and abstract review, then a full-text review was performed. The references of retrieved articles were hand-searched for further relevant articles, and other relevant data were included. Final decisions regarding eligibility were made by consensus following the full-text review.

RESULTS

The initial search returned 2,715 articles. Of those articles, 2,594 were excluded after a title and abstract review. Of those 2,594 excluded articles, 1,946 were not aligned with objectives and 593 pertained to bipolar disorder but did not focus on rapid cycling, while 55 were either case reports or case series and 2 publications were duplicated. The remaining 119 articles were reviewed (Figure 1). The articles were organized in thematic domains as follows: etiology; relationship with previous history and genetic loading; prevalence rate; age at onset; relationship with the episode polarity; substance use, abuse, and suicidality; and long-term course and outcome. Subdomains were also utilized for etiology (hypothyroidism, role of antidepressant treatment, and general medical conditions) and relationship with previous history and genetic loading (family studies and specific genes) in order to further organize the data.

CORRELATED FEATURES OF RAPID CYCLING

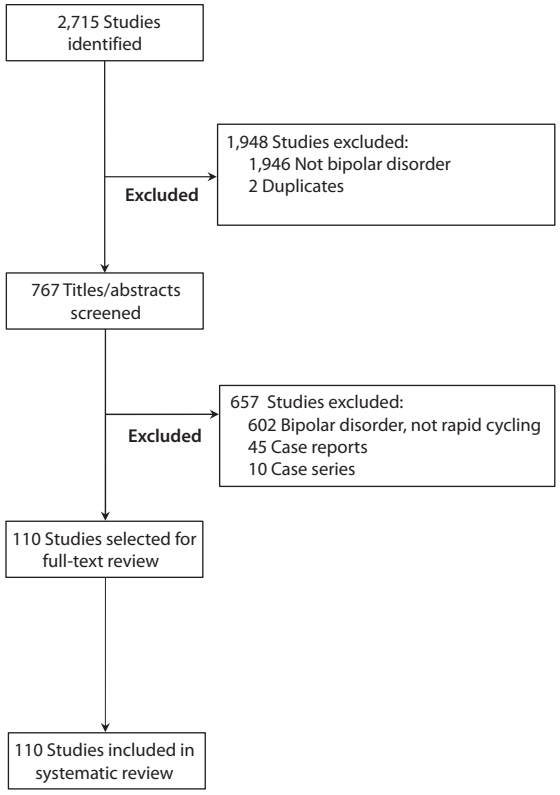
Etiology

Hypothyroidism. Many authors consider hypothyroidism to be highly correlated with rapid cycling, with almost 50% of rapid-cycling patients manifesting peripheral hypothyroidism.[21–24] The first report on a possible relationship between hypothyroidism and rapid cycling was published in 1979 in patients receiving lithium and thyroid substitution therapy.[25]

In the following years, several authors disputed this correlation,[26–33] and a subsequent meta-analysis supported their thesis.[29] Subclinical hypothyroidism has been associated not only to rapid cycling but also to cognitive impairment.[34] The possible usefulness of thyroid augmentation therapy has been a matter of debate.[24,35]

Previous treatment with lithium does not always emerge as a valid explanation for the relationship of rapid cycling with hypothyroidism.[36,37] The literature supports a correlation between lithium treatment, female gender, hypothyroidism, and rapid cycling.[23,36,38] This intercorrelation is complex since even short-term lithium treatment might be the cause of grade III hypothyroidism in euthyroid rapid-cycling patients but not in controls.[39] Furthermore, the occurrence

Figure 1. Flow Chart of the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses Procedure in the Selection of Articles



of thyroperoxidase antibodies is associated with rapid cycling.[31] It should be noted that another study did not confirm the association between latent hypothyroidism and rapid cycling.[28]

The Role of Antidepressant Treatment

The majority of experts in bipolar disorder accept the notion that chronic antidepressant treatment might not only cause a switch into mania or hypomania but also induce cycle acceleration,[40] although definite evidence is lacking.[41] In 1956, the first case report implicating the monoamine oxidase inhibitor iproniazid with a probable induction of rapid cycling was published.[42] Many years later, this topic was put forward by Wehr and Goodwin.[43] Although, since then, a lot of studies addressed this issue, in both a retrospective and a prospective manner, the fact that many publications mix switching with the induction of rapid cycling limits the validity of the respective conclusions.

Typically, it is reported that the use of antidepressants may precipitate the onset of rapid cycling in more than 70% of cases and that rapid cycling is maintained even after antidepressant discontinuation.[33,44] More recently, published rates of this antidepressant-induced rapid cycling fall into the range of 3%–50%,[33,45,46] although there are reports disputing the role of antidepressants in the switching of poles.[47] Methodological variations across studies might explain this wide range in the incidence of rapid cycling following antidepressant exposure. This induction is more probable within the first year of antidepressant treatment.[48] Nevertheless, drawing solid conclusions is not feasible. While all shorter-duration retrospective studies pose an association between rapid cycling and antidepressant use[33,48,49] and only one of them limits this association to women,[50] long-term trials are inconclusive.[6,51–54] Regarding the prospective studies, 3 support the presence of this association,[43,55,56] while the remaining 3 are negative.[50,57,58] This population of supposedly antidepressant-induced rapid-cycling patients does not differ from the rest of the rapid-cycling population in terms of general clinical profile,[59] although females[50] and especially those suffering from bipolar II disorder might be overrepresented.[48] Conclusively, this risk concerning antidepressants seems to apply only to a subset of patients, and definite data are not available to support or refute.

A plausible explanation for the complex relationship between rapid cycling, female gender, and possibly bipolar II disorder is merely explained by the predominance of depression in rapid-cycling patients, which probably leads to an increased use of antidepressants.[27,60]

General Medical Conditions

Finally, various different general medical conditions were reported to be possible causes of rapid-cycling bipolar disorder in previously mentally healthy individuals. These conditions include subarachnoid hemorrhage,[61] closed head injury,[62] focal temporal pole damage,[63] homocystinuria,[64] and mild immune activation, which appears to normalize with lithium treatment.[65] Another condition related to rapid cycling was the effect of environmental temperature and its changes,[66] while 1 study correlated rapid cycling in bipolar II disorder patients to changes in the ventromedial prefrontal cortex.[67]

Overall, the data to support a direct linkage between hypothyroidism and rapid cycling are insufficient, and this fact brings up the need for more rigorous research, especially regarding lithium-naive patients. In a similar manner, the association between the use of antidepressants and rapid cycling lacks strong evidence and is not supported by the major reviews.[35,68–70]

Relationship With Previous Family History and Genetic Loading

Family studies. The literature does not support any difference between rapid cyclers and the rest of the population of bipolar patients concerning family aggregation. Only a few publications recognize a stronger family loading of bipolarity in rapid-cycling patients[33,71] and a close relationship to the presence of panic disorder, substance abuse, and suicidality in the family,[72–74] but the majority of studies clearly do not support this association.[1,27,35,59,75,76] A previous meta-analysis confirmed a lack of familial load for rapid-cycling bipolar patients.[29]

Specific genes. In the field of genetics, the Val66Met polymorphism,[77,78] the single-nucleotide polymorphisms (SNPs) hCV11592756, rs2049045, and GT(n) of the brain derived neurotrophic factor (*BDNF*) gene,[78] the low activity

Table 1. Current and Lifetime Prevalence Rates of Rapid Cycling in Bipolar Disorder

	N		Prevalence		
Publication	Current Prevalence	Lifetime Prevalence	Current, N (%)	Lifetime, N (%)	Comments
Kukopulos et al, 1980[49]	434		86 (20.0)		
Nurnberger et al, 1988[76]	195		29 (15.0)		
Coryell et al, 1992[27]	919		46 (4.9)		
Schneck et al, 2004[89]	456		91 (20.0)		STEP-BD
Azorin et al, 2008[21]	1,090		86 (9.0)		
Cruz et al, 2008[87]	3,089		535 (17.3)		EMBLEM
Garcia-Amador et al, 2009[88]	305		55 (18.0)		
Coryell et al, 2003[58]		345		89 (25.8)	13.7 ± 6.1–y follow-up
Dittmann et al, 2002[91]		152		41 (26.5)	2.5-y follow-up
Hajek et al, 2008[92]		240		80 (33.3)	Primary care sample
Yildiz and Sachs, 2004[50]		197		84 (43.0)	Tertiary care sample
Schneck et al, 2008[56]	1,742		562 (32.0)		STEP-BD
Total	8,230	934	1,490 (18.1)	294 (31.5)	

Abbreviations: EMBLEM = European Mania in Bipolar Longitudinal Evaluation of Medication, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

allele variation in the catechol-O-methyltransferase (*COMT*) gene,[79,80] the serotonin (5-HT) transporter gene,[81] and the haplotype GGAC of the circadian gene *CRY2*[82] have been associated with rapid cycling in bipolar disorder. On the other hand, there are data that dispute any relationship between the low activity allele of the *COMT* gene and rapid cycling.[83]

Conclusively, the hypothesis of a specifically increased familial load for bipolar disorder in rapid cyclers is not supported, although some markers of broad familial severity have been reported. Genetic studies are limited and deserve replication before rapid cycling can be definitely characterized as a valid endophenotype for bipolar spectrum disorders. Furthermore, a number of factors should be controlled for (eg, exposure to antidepressants, temperament) in genetic studies. Essentially, a hypothesis that deserves further exploration is that possibly temperament is the determining endophenotype, while rapid cycling serves as an intermediate phenotype.[84–86]

Prevalence rate. The available literature is inconclusive regarding the exact prevalence of rapid cycling in bipolar disorder. Dunner and Fieve[7] initially reported a prevalence of 13%. In keeping with this first publication, 12 studies reported a 5%–33.3% cross-sectional prevalence[21,27,49,56,76,87–90] and a 25.8%–43% lifetime prevalence.[50,58,90–92] The prevalence rates vary as a function of definitions and setting of the study. Prevalence rates are reported to be 30% for "frequent mood episodes,"[93] 33.3% in primary care and 26.9% for tertiary care samples,[92] 43% in another tertiary care sample,[50] and 56% in a convenient clinical sample,[23] but this, as always, depends on the site where research was conducted, the sample, the methodology, and the definition (Table 1). In the large, multinational WAVE-bd study (Wide AmbispectiVE study of the clinical management and burden of Bipolar Disorder), prevalence rates ranged from 6.6% (Romania) to 28.7% (Turkey).[94]

When the data from the National Comorbidity Survey Replication study were analyzed, a 12-month prevalence of 33.3% was reported.[95] Interestingly, in a separate publication, it was reported that, while 32% of the bipolar patients were manifesting rapid cycling at study entry, only 5% of them were diagnosed as rapid cyclers after 1 year of follow-up,[56] showing that when convenience clinical samples are followed, a gradual improvement can be manifested, and this improvement can contaminate epidemiologic data.

Several lines of evidence suggest that female bipolar patients have a higher prevalence of rapid cycling,[33,50,59,87,89,96,97] and their proportion tends to be as high as 92%.[33] However, more conservative and realistic estimations suggest that the median prevalence is around 72%.[59]

A variety of factors might explain this relationship between rapid cycling and female gender, including hormonal changes associated with the menstrual cycle and the higher prevalence of hypothyroidism. Also, it should be taken into account that there is a correlation of female gender with factors like depression and cyclothymic temperament,[35] along with a stronger effect of antidepressants in inducing rapid cycling in women.[50] There is a controversy regarding the possible interaction between the bipolar disorder type and gender; the female preponderance for rapid cycling was stronger for bipolar I,[50,89] even though rapid cycling in type II bipolar disorder is also strongly related to female gender.

The absolute risk seems to be rather dissimilar and is reported to be higher among females (29.6%) than among males (16.5%) but in an inconsistent fashion.[97] A meta-analysis confirmed the association between female gender and rapid cycling.[29] Only 1 publication suggested a higher prevalence in males,[28] while a few others reported identical rates between men and women.[28,30,98,99] In 1 of these studies, the sample included a large proportion of males.[98] In another, the proportion of females was higher than the proportion of males only among patients with 8 or more episodes yearly.[100]

Conclusively, the mean weighted by sample size annual prevalence rate is 18.10%, while the lifetime prevalence is estimated to be 31.48% (Table 1).

Age at Onset

Most published articles suggest that rapid cycling is associated with a younger age at onset of bipolar

disorder,[12,21,72,89,90,92,93,101–103] even before the age of 17 years.[58] Only 2 articles reported a later age at onset,[99,104] whereas some others found no difference.[27,30,49,56,59,105] In children and adolescents, very often, bipolar disorder follows a rapid or ultrarapid course,[106,107] and this might suggest a greater heterogeneity concerning how age at onset affects the development of rapid cycling. One article disputes the earlier onset notion, reporting that the duration of illness is not significantly longer among rapid cyclers.[50] Altogether, the available literature suggests that illness onset occurs earlier among rapid-cycling bipolar patients.

Relationship With Episode Polarity and Predominant Polarity

Depression is reported to be closely connected with rapid cycling through various different ways. A significant proportion of studies suggest that in the majority of patients, rapid cycling is developed from an index episode of depression[33,105,108] and that bipolar patients with a first depressive episode are at higher risk to develop rapid cycling later in the course of the illness.[21,88,105] It has also been shown that a depressive predominance of the long-term clinical course exists,[58,89,90,109] although a domination of mania has also been reported.[100] A convincing explanation describing the relationship between depression and rapid cycling is not available. However, more frequent and prolonged antidepressant treatment[56,102] and being a female patient, as it was previously mentioned, may act as mediators. It is well proven that women are more likely to manifest a predominant depressive polarity,[110–112] which in turn increases the likelihood of antidepressant exposure. In fact, this situation deconstructs any clear cause-effect relationship between depression and rapid cycling.[35]

It has been reported that rapid-cycling patients cycle more frequently between hypomania and depression within their index episode[27] and that at least salient manic symptoms are often present during their depressive episodes.[109,113] Consequently, a question is raised as to whether at least some of these episodes are truly mixed in nature, although they might not fulfill the existing official diagnostic criteria for mixed depressive episodes.[114] A conflict exists in the literature, with 1 article suggesting that patients with a mixed episode at onset are highly unlikely to develop rapid cycling,[105] while several others suggest the opposite.[21,115–117] It has been proposed that the recently released *DSM-5* fails to capture the essence of mixed depressive states (eg, agitated depression), which may add to the diagnostic uncertainties.[118,119]

It is common for rapid-cycling patients to manifest labile emotion and even a soft ultrarapid pattern.[27] In the case of ultrarapid cycling, when the cycle lasts less than 24 hours, the majority of switches (two-thirds) occur between morning and evening, and they usually follow a pattern from depression into mania/hypomania or euthymia, while only the remaining one-third follow the opposite direction. Likewise, switches that occur following the evening to the next morning pattern are correspondingly opposite.[120,121] On the other hand, when the cycle lasts more than 24 hours, the previously mentioned parameters (time of the day plus polarity of the episode) do not follow a systematic pattern anymore.[121] Finally, there is not a definite answer in the literature concerning the question of whether bipolar I or bipolar II disorder is more closely related to rapid cycling. The data from the Stanley Bipolar Treatment Network suggest that rapid cycling is weakly more closely related to bipolar I disorder,[29] producing another confliction with the general impression of a closer relationship to bipolar II,[27,29,35,49,59,92,100,104,105,122–125] while other publications suggest that there is no preference.[30,88,126]

Overall, a clear cause-effect relationship between depressive predominance and rapid cycling is not well documented, and the closer association to bipolar II disorder is also disputed, whereas there is also a signal for a possible association between these quick mood alterations with mixed (either depressive or manic) features.

Substance Use, Abuse, and Suicidality

Rapid cyclers tend to abuse both alcohol and illegal drugs more frequently in comparison to the rest of bipolar patients.[29,72,87,100] One publication reported that, in this subpopulation of patients, sexual or physical abuse during childhood is more common.[100] These patients also more frequently show suicidal behavior,[21,58,87,92,109,127,128] but this might be due to more frequent and more severe attempts among rapid cyclers in comparison with non–rapid cyclers.[88] A few studies dispute this relationship,[35,72,93] which could at least be partially explained by the correlation between rapid cycling and depression. Another plausible explanation, at least for some of the above characteristics, could be the fact that rapid-cycling patients (when compared to non–rapid cyclers) manifest a longer duration of illness, possibly due to an earlier onset of bipolar illness, which leads to an increased overall burden and possibly neuroprogressive changes.[21,30,71,129,130]

Thus, the majority of data support the notion that rapid cycling and substance abuse are interconnected phenomena among bipolar patients. Suicidality is also more common in this patient subpopulation.

Long-Term Course and Outcome

Kraepelin[3] was the first to discuss the relationship between cycle length and illness progression. More recent data show that, as the years pass and the episodes accumulate, the cycles might shorten.[108,131] Although, some researchers propose the existence of a ceiling effect and that the frequency of the cycle may be stabilized after 4–6 mood episodes,[45] the data from the Stanley Bipolar Treatment Network rejected the ceiling effect notion, proving that rapid-cycling characteristics continue to increase as time passes.[29] More recently, the literature suggests that rapid cycling is a manifestation of a worsening of the underlying bipolar disorder and develops later in the course of illness.[123] A possible, proposed explanation is a sensitization process, which is triggered by the frequent use of antidepressants or a

thyroid dysfunction, in patients who manifest a depression-mania–free interval course and cyclothymic temperament.[21] This sensitization process is now accepted for at least a subgroup of mood disorder patients, meaning that after recurrent mood episodes, the threshold for the appearance of new episodes is progressively being reduced, leading to more frequent relapses. Finally, the episodes are triggered spontaneously. This "kindling" phenomenon resembles the one being observed in epilepsy.[132,133] Some authors consider the kindling mechanism as the cause of rapid cycling because it evokes more frequent episodes and, consequently, shorter cycles[2,132,134,135]; however, there are studies that dispute the relationship between rapid cycling and the number of previous episodes.[136,137]

In a subpopulation of patients, rapid cycling, either spontaneous or induced, when established will become a stable rhythm for many years, linked more to endogenous than to environmental factors.[55] Conversely, apart from episode frequency, there are no solid data supporting the theory that rapid-cycling patients constitute a distinct subgroup of patients. Interestingly enough, these data suggest that in many cases, rapid cycling is actually a transitory phenomenon and not the final and stable stage of the disorder.[22,27,35,56,58,68,138]

The literature regarding the clinical correlates of rapid cycling is more consistent. It suggests that rapid cycling is related to a greater number of both total episodes and hospitalizations,[59,68,71,100] to a lack of symptom-free intervals between episodes, to cyclothymic temperament,[21] worst long-term course,[35,68,126] higher comorbidity[72,73,90,92] more severe disability,[56,89,90,93,139,140] and greater symptom severity,[56] although there is 1 study suggesting that psychotic features are more frequent in non–rapid cyclers[74] and another rejecting any relationship to increased comorbidity.[93] In female bipolar patients, the severe forms of premenstrual tension syndrome might accelerate cycling.[141] When studying rapid cycling retrospectively, severe premenstrual syndrome is found to be a credible confounding factor.[142] In their initial report, Dunner and Fieve[7] reported that rapid cycling is more frequent during menopause, yet the majority of the literature does not support the relationship between the female reproduction cycle and rapid cycling.[59,143]

Regarding the long-term outcome of rapid cycling, a significant variability is observed. One-third of patients might achieve complete remission for at least the past year, 40% might continue being rapid cyclers with severe episodes, 14% could remain in the rapid-cycling pattern but with attenuated episodes, and almost 13% might become long cyclers.[55] Nevertheless, in many cases, rapid cycling is a transitory phenomenon, and, as mentioned before, it is neither a stable feature nor the final stage of the illness.[22,27,35,58,68,144] The question of whether the initial cycle pattern of depression-mania/hypomania–free interval produces a worse outcome when compared to the mania/hypomania-depression–free interval pattern remains unresolved.[27,30,55,59]

Conclusively, although rapid cycling seems to constitute a worsening in the course of bipolar disorder, this does not happen in a predictable manner and seems to represent a transitory phenomenon rather than a stable phase or feature of the disorder in the majority of cases.

DISCUSSION

It seems that rapid cycling affects a significant proportion of bipolar patients, with a year prevalence of 17.04% and a lifetime prevalence of 32.28% (Table 1). The etiopathogenesis of rapid cycling remains elusive, although a relationship between depression, female gender, hypothyroidism, and the use of antidepressants is possible, but only in a small proportion of patients. The data from genetic studies remain weak and inconclusive, and a possible familial pattern is not clearly supported.

Conversely, there are data suggesting that rapid cycling represents a worsening of the underlying disorder, which, in turn, leads to a significant deterioration of clinical outcomes and increased suicidality. As for its long-term course, for at least a significant percentage of bipolar patients, rapid cycling represents a transitory period, which, unfortunately, not only causes complications but also demands a different treatment strategy.

The recognition of rapid cycling is crucial, but it may be difficult, especially when the clinician has not embedded this specific nosologic entity into everyday clinical practice. This is, at least partly, explained by the fact that when the frequency of mood alterations is high, the possibility that the patients will remain free of symptoms for a prolonged period is low. Rapid cyclers may not even achieve full remissions between episodes. This fact causes major disability and makes the clinical picture resemble a personality disorder,[85] resulting in an incorrect diagnosis (frequently in favor of a personality disorder diagnosis) and consequently to inappropriate treatment. The complex clinical picture and the incorrect diagnosis might be the leading reasons, among others, for which rapid cycling was rarely diagnosed before the mid-1970s, when it was officially recognized, while today one-third to one-tenth of hospitalized patients receive this specific diagnosis.

The limitations of the present study include that it is a systematic review of the literature with no access to raw data, only English-language articles were considered eligible, and only the MEDLINE database was searched.

In conclusion, rapid cycling is still an area to be further studied. It is highly likely that rapid-cycling patients constitute a significant percentage of bipolar patients and experience more severe disability and worse outcome. Several factors, like predominance of depression, treatment with antidepressants, female gender, refractoriness to lithium, and hypothyroidism seem to be involved in the etiology of rapid cycling or to shape the clinical manifestations and the long-term consequences. Furthermore, a proper and universally accepted definition is still unavailable. A significant proportion of patients with emotional lability and those with ultra or ultraultra–rapid-cycling patterns are often diagnosed as suffering from mixed episodes or personality disorders according to available diagnostic systems and on the basis of the attitude of the

clinician. The biological and genetic underpinnings of the rapid-cycling phenomenon remain largely unknown. Future studies should also investigate whether rapid cycling represents the exacerbation of emotional endophenotypes (eg, affective temperaments) linked to disorders associated with affective dysregulation such as bipolar disorder.

Drug names: lithium (Lithobid and others).

Author affiliations: Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil (Dr Carvalho); Third Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece (Drs Dimellis and Fountoulakis); Department of Clinical and Theoretical Mental Health, Faculty of Medicine and Department of Pharmacodynamics, Semmelweis University, and MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, National Academy of Sciences and Semmelweis University, and National Institute of Psychiatry and Addictions, Laboratory for Suicide Research and Prevention (Dr Gonda), Budapest, Hungary; Bipolar Disorders Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain (Dr Vieta); and Department of Psychiatry, University of Toronto, and Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada (Dr McIntyre).

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