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Review Article

Rapid cycling bipolar disorder – diagnostic concepts

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Objectives: This paper reviews the literature to examine the DSM-IV diagnostic criteria for rapid cycling in bipolar disorder.

Methods: Studies on the clinical characteristics of rapid cycling bipolar disorder were reviewed. To identify relevant papers, literature searches using PubMed and MEDLINE were undertaken.

Results: First observed in the prepharmacologic era, rapid cycling subsequently has been associated with a relatively poor response to pharmacologic treatment. Rapid cycling can be conceptualized as either a high frequency of episodes of any polarity or as a temporal sequence of episodes of opposite polarity. The DSM-IV defines rapid cycling as a course specifier, signifying at least four episodes of major depression, mania, mixed mania, or hypomania in the past year, occurring in any combination or order. It is estimated that rapid cycling is present in about 12–24% of patients at specialized mood disorder clinics. However, apart from episode frequency, studies over the past 30 years have been unable to determine clinical characteristics that define patients with rapid cycling as a specific subgroup. Furthermore, rapid cycling is a transient phenomenon in many patients.

Conclusions: While a dimensional approach to episode frequency as a continuum between the extremes of no cycling and continuous cycling may be more appropriate and provide a framework to include ultra-rapid and ultradian cycling, the evidence does not exist today to refine the DSM-IV definition in a less arbitrary manner. Continued use of the DSM-IV definition also enables comparisons between past and future studies, and it should be included in the next release of the ICD. Further scientific investigation into rapid cycling is needed. In addition to improving the diagnostic criteria, insight into neurophysiologic mechanisms of mood switching and episode frequency may have important implications for clinical care.

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The term 'rapid cycling' was introduced in 1974 by Dunner and Fieve (1) to denote a course of illness in which four or more mood episodes occurred in the year preceding their study of lithium prophylaxis. The number four was chosen arbitrarily to obtain a population of sufficient size to study (2). In most of the patients with rapid cycling, lithium failed to prevent recurrences, although it did attenuate the further course of illness (2). Three decades later, it is clear that this relative resistance is found to all standard pharmacologic treatments and not just lithium (3). The original definition of rapid cycling (four or more mood episodes per year) was to some degree confirmed in a multisite reanalysis (4), and included in the DSM-IV (5) as a course specifier for bipolar I and II disorders (6). It was also noted that some patients experienced very brief cycles lasting for days (ultra-rapid cycling) or <1 day (ultradian cycling) (4, 7). However, very frequent cycling was not included in the DSM-IV, as this was attributed to the inherent mood lability of bipolar disorder first noted by Kraepelin (8, 9).

Since the introduction of the term, many investigators have explored the clinical characteristics of patients who suffer from rapid cycling. In a meta-analysis, Kupka et al. (10) reviewed the studies that were published between 1974 and 2002 and directly compared patients with and without rapid cycling. Similar recently published studies (11–14) are shown in Table 1. The differences in findings may be explained in part by the varying methodologies and by the inclusion of patients who received naturalistic treatments. Recent reviews have addressed clinical characteristics (10, 15–18), pharmacologic (3, 18–20), and non-pharmacologic (21) treatments, and biological mechanisms (22). The purpose of our paper was to review the DSM-IV diagnostic criteria for rapid cycling and examine the impact of research findings that have since emerged.

Classic diagnostic validators

Phenomenology

Rapid cycling can be conceptualized in different ways: as a high frequency of separate episodes of any polarity, or as a temporal sequence of episodes of opposite polarity (4, 23–25). A simple approach to distinguish rapid cycling is to count individual episodes according to explicit duration and severity criteria and then define a cutoff point. This approach was used by Dunner and Fieve (1), incorporated in the DSM-IV, and requires four or more episodes in no particular pattern or sequence. The mood episodes are categorized by the number and severity of symptoms and by episode duration. The minimum length for a manic episode is 1 week, for a hypomanic episode 4 days, and for a major depressive episode 2 weeks. Modern studies generally recruit patients using a definition of rapid cycling based on the DSM-IV definition. In contrast, older studies typically focused on continuous cyclicity and used definitions based upon rapid alternations of episodes of opposite polarity. When evaluating results from older and newer studies, it is important to note that these two different

Table 1. Overview of recent studies comparing rapid cycling (RC) and non-rapid cycling (N-RC) bipolar disorder[a]

Study (year)	Primary focus	Subjects	Diagnosis	n RC (%) n N-RC	n (%) Females	n (%) Bipolar II	Mean Age Onset (SD)
Vo & Dunner (11) (2003)	Treatment response	n = 152 treatment-resistant outpatients	DSM-III-R/IV Lifetime RC	102 RC (67) 50 N-RC	RC: 63 (62) N-RC: 28 (56)	RC: 55 (54) N-RC: 30 (60)	n/r
Coryell et al. (12) (2003)	Descriptive (NIMH-CDS)	n = 345 outpatients; long-term follow-up for 14 years	DSM-IV Current RC	89 RC (26) 256 N-RC	RC: 62 (70) N-RC: 137 (54) [p = 0.008][b]	RC: 29 (33) N-RC: 89 (35)	RC: 21.6 (8.9) N-RC: 24.4 (10.6) [p = 0.03][b]
Schneck et al. (13) (2004)	Descriptive (STEP-BD)	n = 456 outpatients	DSM-IV Previous year	91 RC (20) 365 N-RC	RC: 61 (67) N-RC: 210 (58)	RC: 22 (24) N-RC: 89 (24)	RC: 16.7 (8.7) N-RC: 20.0 (8.5) [p = 0.01][b]
Kupka et al. (14) (2005)	Descriptive (SFBN)	n = 539 outpatients; follow-up for 1 year	DSM-IV Current RC	206 RC (38) 333 N-RC	RC: 129 (63) N-RC: 173 (52) [p = 0.02][b]	RC: 29 (14) N-RC: 75 (23) [p = 0.03][b]	RC: 17.6 (9.1) N-RC: 23.1 (10.0) [p < 0.0001][b]

Percentages are rounded off to whole numbers.

[a]A similar table presenting all studies published between 1974–2002 that compared rapid cycling and non-rapid cycling bipolar disorder is given in a meta-analysis by Kupka et al. (15).

[b]Statistically significant differences between rapid cyclers and non-rapid cyclers reported in original studies are indicated by p-values in brackets.

n/r = not reported in original study; NIMH-CDS = National Institute of Mental Health-Collaborative Depression Study; STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorders; SFBN = Stanly Foundation Bipolar Network.

concepts of rapid cycling may result in different although overlapping patient groups (25).

To validate the proposed DSM-IV criteria for rapid cycling, Bauer et al. (4) reanalysed available data from 239 patients at four research sites. In this analysis, a lifetime diagnosis of rapid cycling was given if the patients had ever experienced rapid cycling. The authors also differentiated between 'full rapid cycling' (meeting the DSM-III-R criteria, n = 120) and 'truncated-episode rapid cycling' (patients with four or more episodes that lasted at least one day at full severity). The latter group included 19 of the 119 patients without rapid cycling. For two sequential episodes to be considered as separate, they had to be separated by either a switch to the opposite pole or by a period of remission that was at least as long as the proximate episode. Of the sample, 89 patients were prospectively followed for at least one year. The primary results of this study were: (i) patients with rapid cycling were likely to be female and had more previous and prospectively observed episodes. These findings were not impacted by the inclusion of patients with truncated episodes; (ii) the relationship between female gender and episode frequency became nonlinear at 4–8 observed episodes per year supporting the cutoff at four or more episodes, although the sample size was relatively small; (iii) inclusion of truncated episode rapid cyclers had little impact on the validators of rapid cycling as they shared characteristics with both the full-duration rapid cyclers and the non-rapid cyclers; (iv) rapid cycling was antidepressant induced in 20% of patients. The authors reported that these findings validated the proposed DSM-IV diagnostic criteria for rapid cycling and that the definition of remission periods should be further refined.

Two other clinical studies specifically addressed the validation of the DSM-IV definition of rapid cycling. Maj et al. (26) used the DSM-IV-draft criteria but included a euthymic period of at least eight weeks to separate mood episodes of the same polarity. They reported that patients with at least one direct switch to an episode of the opposite polarity within 24 hours were more likely to have a rapid cycling pattern during four years of follow-up. Additionally, they found that rapid cycling was unrelated to clinical characteristics including female gender, family history, or hypothyroidism.

In a second study, Maj et al. (24) used four definitions of rapid cycling: *Definition no. 1* was the DSM-IV criteria; *Definition no. 2* was the DSM-IV criteria plus all episodes with at least one day of severe symptoms; *Definition no. 3* further required at least one direct switch to an episode of the opposite polarity; and *Definition no. 4* was *Definition no. 2* plus at least eight weeks of affective illness in the prior year. They found that the DSM-IV definition, although reliable, covered only part of the rapid cycling spectrum. The inclusion of brief mood episodes and the requirement for a direct switch in polarity defined a group with the highest association with female gender, bipolar II subtype, and stability of rapid cycling over time. However, it remains unclear as to whether ultra-rapid and ultradian cycling are distinct from rapid cycling in bipolar I and II disorders as defined by the DSM-IV criteria.

Prevalence

The prevalence of rapid cycling in patients with bipolar disorder in the general population or in non-specialized treatment settings is unknown. A meta-analysis of studies, which included patients consecutively admitted to an inpatient or outpatient facility without *a priori* selection of rapid cycling or matching with controls without rapid cycling, reported an overall prevalence of rapid cycling of 16.3% (range between studies: 12–24%) (10). This corresponds with most reviews that suggest a prevalence of 13–20% (15–20). Nevertheless, this may still be at the upper limits of the true prevalence because of the selection bias of research clinics. There are some indications that rapid cycling has become more frequent in recent years, especially in inpatient settings (27, 28). This may reflect the complexity of patients who are treated in specialized centers. Alternatively, widespread treatment with antidepressants may have increased the incidence of rapid cycling in bipolar disorder (29). Finally, better awareness after the inclusion of rapid cycling in the DSM-IV may also have contributed to an apparent increased prevalence.

Genetics

Endophenotypes. Multiple candidate endophenotypes have been studied in the field of bipolar disorders in general (30, 31) but as yet none has been specifically linked to rapid cycling. One possible exception is the age of onset of bipolar illness since an earlier onset (< 21 years) was associated with a greater rate of drug abuse, alcoholism, obsessive-compulsive disorder, eating disorders, suicide attempts, and rapid cycling (32).

Family studies. A meta-analysis of studies that investigated the impact of a family history of mood disorders on the prevalence of rapid cycling (10) reported that only one study found a significantly increased prevalence of mood

disorders among first-degree relatives of patients with rapid cycling when compared to patients without rapid cycling (33), while six studies (24, 26, 34–37) found no or non-significant differences. Furthermore, three studies (38–40) that were specifically designed to assess the morbidity risk among first-degree relatives and had a more rigorous methodology also found no differences. Although Fisfalen et al. (41) determined that episode frequency was a highly familial trait after investigating 407 subjects with affective disorder from 86 families of probands with bipolar disorder, they also reported that there was no evidence that DSM-IV rapid cycling was a familial trait. These results suggest that a family history of mood disorders does not substantially increase the risk for rapid cycling.

Molecular studies. Using molecular genetic techniques, to study candidate genes that may be related to the development of rapid cycling, one study found an association with low catechol-*O*-methyltransferase activity allele (chromosome 22q11.2) (36). A similar association was found in six patients with ultra-rapid cycling (42), but not in prepubertal and adolescent subjects with ultradian cycling (43). However, if rapid cycling, ultra-rapid, and ultradian cycling (22) all constitute different entities, this would decrease the likelihood of finding a common set of genetic predisposing factors.

The long allele polymorphism of the serotonin transporter gene-linked functional polymorphic region (5-HTTLPR) was found to be more prevalent in patients with rapid cycling when compared with controls and patients with other forms of bipolar and remitting mood disorders (44). In contrast, another group found an association between a lifetime history of rapid cycling and the short form of the 5-HTTLPR (45). Two recent studies (46, 47) reported that variations at the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene were associated with the susceptibility for rapid cycling but not with bipolar disorder in general.

Longitudinal course

Age of onset. Older studies have reported that a late age of onset was associated with shorter cycle lengths and rapid cycling (48). However, recent large studies found that patients with rapid cycling had a younger age of onset than patients without rapid cycling (12–14, 41, 49). The existence of three subtypes of bipolar disorder determined by age of onset (17, 27, and 46 years) was proposed based on genetic studies, but these were not designed to investigate if there was a specific association between age of onset and rapid cycling (50). Some evidence suggests that an onset in prepuberty or early adolescence signifies a more severe form of bipolar disorder (50). In a study of prepubertal and early adolescent children with bipolar disorder, ultradian cycling was present in 77.4%, and ultra-rapid cycling in another 9.7% (51). Recently, a large, prospective study of pediatric subjects (mean age 13 years) with bipolar disorder (n = 263) reported a mean of 15.7 shifts in polarity per year, with 61% of the total sample changing polarity five or more times per year (52). Both physical and sexual abuse during childhood have been associated with an earlier age of onset of bipolar disorder, rapid cycling, and a more severe course of illness in adulthood (53).

Pattern of illness. Data from NIMH (54), and a retrospective study of 320 subjects with bipolar I disorder (55) revealed significantly higher rates of rapid cycling in patients who presented with depression at onset and showed a predominantly depressive course. Perugi et al. (55) suggested that induction of rapid cycling by antidepressants may have contributed to this association. However, depression at onset was not significantly associated with rapid cycling later in the course of illness in a recent meta-analysis (10). Rapid cycling has also been associated with a depression-mania-free interval (DMI) course of illness more than with a mania-depression-free interval course (56, 57). Bunney et al. (58) postulated that switching from depression to hypomania involves a more active biological process than vice versa, reflecting an underlying vulnerability to rapid cycling.

Persistence of rapid cycling. Rapid cycling appears to be a transient phenomenon in most patients (12), although it can persist over many years (26, 57). There is evidence that persistent rapid cycling is associated with brief mood episodes and a pole-switching pattern [especially from depression to (hypo) mania as seen in a DMI course], and with continuous cycling (24, 25, 56). Other features that are associated with persistent rapid cycling include agitated depression and the pre-existence of a hyperthymic or cyclothymic temperament (56). While transient rapid cycling may result from intermittent treatment with antidepressants (56), another study found no evidence of this association (12). Koukopoulos et al. (57) suggested that the persistence of rapid cycling beyond the first year of adequate treatment, for a duration of at least two years, would identify 'true' rapid cycling. This is supported by the fact that most studies report the

largest reduction of rapid cycling after the first year of treatment (4, 12, 24, 26, 39, 59) (Table 2). Still, even after the rapid cycling resolves, many of these patients suffer more subsequent morbidity than those who never experienced rapid cycling (12).

Treatment factors

Antidepressants. There is a longstanding controversy as to whether antidepressants, particularly tricyclic antidepressants (TCA), and other drugs that affect monoaminergic neurotransmitter systems, can trigger and prolong rapid cycling (60). Some longitudinal, observational studies have implicated both brief and prolonged antidepressant drug use (29, 61) and some report that women have an increased risk of antidepressant-induced rapid cycling (61, 62). Koukopoulos et al. (56) noted that antidepressant use caused acceleration in the cycle frequency from 0.8 per year prior to treatment to 6.5 episodes per year. Wehr et al. (59) reported that continued administration of antidepressant drugs was responsible for rapid cycling in approximately 50% of 51 bipolar patients. Other investigators have estimated that 20% of all cases of rapid cycling are caused by antidepressant treatment and that 95% of spontaneous rapid cycling patients may worsen with the use of antidepressants, mainly TCA (4). In contrast, in a long-term follow-up study, Coryell et al. (12) found no association between TCA and either rapid cycling or switching from depression to hypomania. Furthermore, there is evidence that newer, more selective antidepressants (for example, selective serotonin reuptake inhibitors and bupropion) may have a lower risk of inducing cycling acceleration (63–65). In a recent naturalistic study using self-reported data, patients who were taking second- and third-generation antidepressants with a concurrent mood stabilizer did not experience an increase in the rate of rapid cycling (66). It has been suggested that the association between antidepressants and rapid cycling may be related more to the frequent occurrence of depression or to a natural course of mania following depression, than to the antidepressant itself (39).

The role of lithium and other mood stabilizers. Tondo et al. (3) analyzed data from 16 studies regarding the effects of rapid cycling and treatment choice on clinical outcome in bipolar disorder. The 1,856 patients (905 with rapid cycling, 951 without) were treated with carbamazepine, lamotrigine, lithium, topiramate, or valproate, alone or with other agents, over an average of 47.5 months. Although only lithium and carbamazepine could

Table 2. Prospective follow-up studies of rapid cycling bipolar disorder

Study	n	Years follow-up (mean ± SD)	Persistent rapid cycling course	Converted to non-rapid cycling course	(Nearly) Complete remission	Comments
Wehr et al. (59) 1988, US	51	1–12 (4.9 ± 3.5)	21 (41%)	8 (16%)	19 (37%)	Rapid cycling assessed lifetime retrospectively
Coryell et al. (39) 1992, US	39	5	1 (3%) in all 5 years	25 (64%) after first year 7 (18%) after second year	10 (25%)	Rapid cycling assessed prospectively during first year
Bauer et al. (4) 1994, US	58	1–3 (2.9 ± 0.4)	27 (47%)	26 (45%)	5 (9%)	Rapid cycling assessed lifetime retrospectively
Maj et al. (26) 1994, Italy	37	5	22/37 (59%) in first year 16/36 (44%) in second year 8/23 (35%) after 5 years 7/37 (19%) throughout follow-up	15/37 (41%) in first year 20/36 (56%) in second year 15/23 (65%) after 5 years	n/r	Rapid cycling assessed retrospectively during previous year
Maj et al. (24) 1999, Italy	31	1	18 (58%) in first year	13 (42%) in first year	n/r	Rapid cycling assessed retrospectively during previous year
Coryell et al. (12) 2003, US	89	(15.2 ± 4.9)	20 (22%) for ≥ 2 years	69 (78%) within 2 years	n/r	Rapid cycling assessed prospectively during first year
Koukopoulos (57) 2003, Italy	109	2–36 years (12.6 ± 7.5)	55 (54%) throughout follow-up	17 (16%)	36 (33%)	Rapid cycling assessed retrospectively during previous year

Percentages are rounded off to whole numbers.
n/r = not reported in original study.

be directly compared in patients with rapid cycling, pooled recurrence rates and non-improvement rates did not suggest that any treatment was superior. Instead, rapid cycling was associated with lower effectiveness of all treatments evaluated.

This finding was recently confirmed in a randomized-controlled double-blind study comparing divalproex and lithium in the long-term treatment of rapid cycling bipolar disorder (67). Relapse rate was 51% on divalproex and 56% on lithium, and in both groups 22% of patients relapsed into manic or mixed states. No statistically significant differences were observed between treatment groups in premature discontinuation because of side effects, median time to treat emerging symptoms of any type of episode, or median survival in the study. This suggests that divalproex and lithium are equally efficacious in the long-term management of rapid cycling bipolar disorder.

A substantial portion of the poor response to mood stabilizers in patients with bipolar disorder is probably associated with a transient occurrence of rapid cycling. Nevertheless mood stabilizers, used alone or in combination, provide benefit to many patients with rapid cycling by reducing the severity and duration of episodes, even if complete remission and prevention of subsequent episodes is rare.

Neurobiology

Neuroimaging. There are only a few case reports of neuroimaging data from patients with rapid cycling. A patient presenting with ultra-rapid cycling was examined by single photon emission computed tomography (SPECT) and showed a decreased left thalamic perfusion in mania which returned to normal during depression (68). An 81-year-old patient with ultra-rapid cycling showed a moderate bilateral frontal hypermetabolism on a positron emission tomography (PET) scan during hypomania that returned to normal during depression (69). Finally, another patient with ultra-rapid cycling showed no abnormality of glucose metabolism in a PET scan (70).

Thyroid axis. There is a longstanding debate as to whether thyroid axis abnormalities contribute to the development of rapid cycling in patients with bipolar disorder. Several studies have found an association among indices of low thyroid function or clinical hypothyroidism and rapid cycling (71–74), while other studies refute this association (59, 75–79). The results from various studies are inconsistent, and the conclusions to be drawn are often limited by their retrospective design and lack of a healthy control comparison group (10). Most importantly, many studies included patients who were receiving prophylactic long-term lithium treatment. On the other hand, cross-sectional studies of unmedicated patients with rapid cycling bipolar disorder have found no abnormalities in basal thyroid-stimulating hormone (TSH) and thyroxine levels (75). Bauer et al. (73) postulated that patients with rapid cycling may manifest no thyroid abnormalities until physiologically challenged by 'antithyroid' stressors. Such stressors may include spontaneously occurring thyroid disease or goiterogenic drugs such as lithium. In a recent controlled study, when previously unmedicated patients with rapid cycling were challenged with therapeutic doses of lithium, a significantly higher delta TSH after thyrotropin-releasing hormone stimulation was found than in age- and gender-matched healthy controls who also received lithium (79). This result suggests that some patients with bipolar disorder have a dysfunction in the hypothalamic-pituitary-thyroid axis that remains latent until the axis is challenged by the thyroprivic effect of lithium, and that changes in the thyroid economy may play a modulating role in the development of the rapid cycling pattern.

Special topics

Sex/gender issues

A meta-analysis of 10 studies including 2,057 patients with bipolar disorder (including 498 with rapid cycling) concluded that women were at somewhat more risk of developing rapid cycling than men (29.6% for women versus 16.5% for men) (80). A more recent and partially overlapping meta-analysis of 16 studies totaling 3,394 patients (including 929 with rapid cycling) concluded that rapid cycling was prevalent in 32.0% of women and in 21.4% of men (10). Sixty-six percent of all patients with rapid cycling were female, compared with 53% of patients without rapid cycling (10). The preponderance of women among patients with rapid cycling had an effect size of 0.11, which was significant but less marked than often suggested. Moreover, in a study of episode frequency in patients with bipolar disorder, Fisfalen et al. (41) found that women were overrepresented among patients with a low episode frequency but not among patients with a high episode frequency in either unipolar or bipolar disorder. Additionally, as women are more prone to depression, and more likely to seek help and receive treatment for depression, women may be diagnosed more frequently with rapid cycling than men (19).

Functional impairment

With the recognition that symptom resolution does not necessarily correlate with functional improvement, the measurement of functional impairment has assumed increasing importance. Several scales have been developed to measure functional impairment separate from symptomatology. Using the Longitudinal Interval Follow-up Examination (LIFE) instrument, Coryell et al. (12) reported a greater overall functional impairment in 89 patients with rapid cycling compared with 256 patients without rapid cycling. Kupka et al. (14) analyzed patients in the Stanley Foundation Bipolar Network (n = 539) and found significantly lower scores on the Global Assessment of Functioning scale in patients with subsequent rapid cycling. In contrast, although Tsai et al. (81) reported that a more difficult prior course of illness was associated with poorer psychosocial adjustment in a 15-year outcome study of 101 bipolar patients, the presence of rapid cycling did not predict low psychosocial scores.

Quality of life

The patient perception of quality of life is an important measure of impairment in addition to clinician ratings of syndromal or functional recovery. Despite the lack of a standard definition, quality of life encompasses the domains of physical, mental, social, and occupational function, health perceptions and symptoms of disease. In a literature review, Namjoshi and Buesching (82) reported that only ten studies have adequately characterized quality of life assessments in bipolar patients, with most focusing on the euthymic and depressive phases. In the largest study of quality of life in bipolar disorder, Yatham et al. (83) showed that patients with bipolar depression present low scores on role-physical, vitality, social functioning, role-emotion, and mental health subscales for SF-36. We predict that all forms of rapid cycling will have a strong negative impact on the quality of life but this has not been systematically studied.

Cultural assumptions and influence

While most studies of rapid cycling occurred in the USA and Europe, reports have also come from Asia, Australia, and South America. However, cross-cultural studies aiming at systematically evaluating differences in clinical presentation of rapid cycling have not been reported.

Dimensional versus categorical diagnosis

In the DSM-IV, rapid cycling is a categorical course specifier restricted to bipolar I and II disorders. Several recent prospective studies have approached rapid cycling as a dimensional phenomenon, varying on a continuum between the extremes of no episodes and continuous cycling, and found a unimodal distribution of episode frequencies (4, 14, 41). While Bauer et al. (4) reported a sharp increase in the percentage of females beyond a frequency of 4–8 episodes per year, Kupka et al. (14) found a near-linear relationship between episode frequency and several clinical characteristics including female sex, supporting a dimensional concept of episode frequency. Moreover, Fisfalen et al. (41) determined that unlike the DSM-IV rapid cycling category, episode frequency was a highly familial trait.

However, the adoption of a dimensional definition would have a major impact upon the study of rapid cycling. Although the boundary of four episodes per year to discriminate between rapid cycling and no rapid cycling is arbitrary, there is currently no evidence for a more valid cutoff (14). Additionally, at the extreme fast end of cycle frequency, as in ultra-rapid and ultradian cycling, the DSM-IV duration criteria for individual episodes are no longer met. Consequently, these conditions cannot be classified as bipolar I or II disorder with rapid cycling, but must be classified as bipolar I disorder, mixed, or bipolar disorder not otherwise specified (NOS). In retaining a categorical approach, the addition of the specifier 'with ultra-rapid cycling' may be useful to identify those patients within the 'NOS' category who may be similar to patients with bipolar I and II rapid cycling. This would encourage research at the higher end of the cycle frequency spectrum.

If the criteria for severity of mood symptoms are also suspended, then even cyclothymia could be considered as part of this continuum. However, including cyclothymia would have the disadvantage of adding a subgroup of patients that are usually not observed in treatment settings. Moreover, there are very few studies that address the treatment of patients with cyclothymia (84).

As of now, the most useful data regarding the treatment and biological consequences of rapid cycling comes from studies that were based upon the DSM-IV criteria. With the lack of specific evidence to change the DSM-IV criteria in a manner that is less arbitrary, it is recommended that the current diagnostic criteria be retained to

facilitate comparison between past and present studies.

Distinguishing rapid cycling from other disorders

When bipolar disorder begins in childhood or adolescence, it is often characterized by continuous rapid cycling, disruptive behavior, and mixed symptoms that may also be found in attention-deficit hyperactivity disorder (ADHD) (51). Controversy exists as to the boundaries between the diagnoses of ADHD and bipolar disorder, and as to the relation between childhood and adult forms of bipolarity (85). In prepuberty and early adolescence, the very presence of ultra-rapid or ultradian cycling may be a key criterion for the diagnosis of bipolar disorder (86). The commonly occurring presentation of rapid, continuous cycling in juveniles may be a form of bipolar disorder (BP-NOS) that exists on a continuum with bipolar I and II disorders (87).

In adults, it may be difficult to distinguish very fast cycling patterns from the mood instability found in borderline personality disorder (88). The absence of other features of borderline personality disorder, such as the distinguishing interpersonal behavior and the association of mood swings with environmental stimuli, may help to differentiate between these conditions.

Rapid cycling can also be induced by illicit substance abuse, especially cocaine and stimulants (89). In patients without a history of psychiatric disorder, rapid cycling can emerge after traumatic brain injury (90–92) and brain hemorrhage (93).

Although rare, rapid cycling can also be found among patients with unipolar disorder and is usually associated with a positive family history for bipolar disorder (94, 95).

Conclusions and outlook

Rapid cycling is a course variant of bipolar illness that has been observed in the prepharmacologic era as well in modern studies, and has been associated with a relatively poor outcome and response to treatment. As the inclusion of rapid cycling as a specifier in the DSM-IV, many key issues still remain unknown or controversial. These include the minimum duration for mood episodes and interepisodic recovery, and as a consequence the boundaries between rapid, ultra-rapid, and ultradian cycling, as well as the relationship of rapid cycling to mixed states. Additional areas to be clarified include the persistence of the phenomenon beyond one or two years, the impact of antidepressants, and the role of thyroid hormones. Among numerous possible risk factors, only a modest overrepresentation in females has consistently been reported, although the pathophysiology behind this finding remains unknown. While episode cycling can be conceptualized as a dimensional phenomenon between the extremes of no cycling and continuous ultradian cycling, there is insufficient new evidence to modify the existing DSM-IV definition of rapid cycling in a manner that would be less arbitrary. Therefore, to enable comparisons between past and future studies, it is recommended that the ICD adapt the DSM-IV definition of four or more episodes per year. Additional study of the phenomena of rapid cycling in patients with bipolar disorder is needed and may yield a large amount of scientifically and clinically relevant information.

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