

Rapid Cycling Bipolar Disorder: Systematic Review

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Abstract: *Bipolar disorder is characterized by mood episodes that are nearly always recurrent. Patients who experience at least four episodes during a 12 - month period are classified in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM - 5 - TR) as "rapid cycling". The term was first used in 1974 to describe bipolar patients who were unresponsive to lithium. However, it is now clear that any form of pharmacotherapy (including lithium) is typically less effective for rapid cycling patients than for non - rapid cycling patients. This article reviews the epidemiology, pathogenesis, clinical features, and diagnosis of rapid cycling in patients with bipolar disorder.*

Keywords: rapid cycling bipolar disorder, epidemiology, clinical correlates

1. Introduction

Definitions

Bipolar disorder is characterized by episodes of mania, hypomania, and major depression (1). The major subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes (2). Most patients suffer from multiple mood episodes over their lifetime. Patients who experience at least four episodes during a 12 - month period are classified as "rapid cycling." (3).

Epidemiology

Prevalence

The prevalence of rapid cycling bipolar disorder is based upon community surveys and clinical studies from academic medical centers.

- a) **General population** – A cross - national community study (n >54, 000 individuals in 10 countries) found that the estimated 12 - month prevalence of rapid cycling bipolar disorder in the general population was 0.3 percent (4). The prevalence ranged from 0.0 percent in Bulgaria, India, and Japan to 0.7 percent in the United States.
- b) **Patients with bipolar disorder** – The estimated prevalence of rapid cycling among bipolar patients differs across studies and is reported to be higher among individuals who are ascertained in studies of the general population than in studies conducted in clinical settings; this discrepancy probably reflects methodologic differences between population studies (which may include milder mood episodes) and clinical studies:
- c) **Community settings** – A cross - national community study found that among all bipolar patients, the one - year prevalence of rapid cycling was approximately 30 percent (5).
- d) **Clinical settings** – Studies in clinical settings indicate that the one - year prevalence of rapid cycling in patients with bipolar disorder is approximately 10 to 20 percent:
 - A review of 12 clinical studies (n >8000 bipolar patients) found that the mean one - year prevalence

of rapid cycling was 18 percent, and the lifetime prevalence was 31 percent (6).

- In a subsequent, prospective, multinational study of 726 patients who presented with bipolar major depression, 22 percent met DSM - 5 - TR criteria for rapid cycling during the past year (7).
- Retrospective studies of bipolar patients (n >2600 and n >1600) found that the one - year prevalence of rapid cycling was 8 and 10 percent (8, 9).

2. Material and Methods

This is a systematic review of the literature including search in databases Embase, MEDLINE, Web of Science, and Google Scholar for the topic Rapid Cycling Bipolar Disorder.

Sociodemographic correlates

- 1) **Age** – Age of onset of bipolar disorder may be younger in patients who develop rapid cycling bipolar disorder, compared with non - rapid cycling bipolar disorder (8). A cross - national community study found that onset of bipolar disorder occurred at a younger age among rapid cycling individuals compared with non - rapid cycling individuals (mean age 17 versus 20 years) (5).
- 2) **Sex** – It is not clear if rapid cycling occurs equally in females and males, or more often in females:
 - Based upon a cross - national community study, rapid cycling appears to equally affect females and males in the general population (5). This is consistent with the finding that the lifetime prevalence of bipolar disorder in both sexes is approximately equal.
 - However, studies in clinical settings indicate that rapid cycling is associated with female gender. A meta - analysis of 16 clinical studies with 3394 bipolar patients (including 929 with rapid cycling) found a slightly larger prevalence of rapid cycling in female bipolar patients than male patients (10), as did subsequent studies (8, 11).
- 3) **Other factors** – Neglect during childhood and parental divorce both appear to be more common in rapid cycling individuals in the general population compared to individuals with non - rapid cycling bipolar disorder (5).

Functional impairment — Psychosocial functioning is generally more impaired in rapid cycling than non - rapid cycling bipolar disorder (8). A cross - national community study found that during bipolar depressive episodes in the past year, severe role impairment occurred in more rapid cycling patients than non - rapid cycling patients (87 versus 67 percent) (5). During manic/hypomanic episodes, rapid cycling patients were unable to function for more days than non - rapid cycling patients (51 versus 21 days).

Functional impairment in patients with rapid cycling may be due to an increased number of mood episodes. In addition, a shorter time in remission between mood episodes can hinder functional recovery.

Pathogenesis- The pathogenesis of rapid cycling bipolar disorder is not known.

Genetics – Although there is considerable evidence for the genetic transmission of bipolar disorder (9), support for the heritability of a rapid cycling course is lacking. A meta - analysis of four family history studies (693 bipolar patients, including 146 with rapid cycling) found that rapid cycling did not aggregate within families; a subsequent study (305 bipolar patients, including 46 with rapid cycling) also failed to find evidence that rapid cycling is a familial trait. In addition, linkage studies have not consistently identified any specific genes associated with rapid cycling (10).

Endocrinopathies

- **Diabetes** – Diabetes may possibly be involved in the pathogenesis of some cases of rapid cycling. A prospective study of bipolar patients with type 2 diabetes (n = 26) and euglycemic bipolar patients (n = 56) found that rapid cycling occurred in more patients with type 2 diabetes than euglycemic patients (39 versus 18 percent).
- **Hypothyroidism** – Hypothyroidism does not appear to cause rapid cycling bipolar disorder; a meta - analysis of six studies (275 bipolar patients, including 121 with rapid cycling) found that hypothyroidism was present in a comparable number of rapid cycling and non - rapid cycling patients.
- **Neurobiologic correlates** – Although biomarkers specific for rapid cycling bipolar disorder have not been established, different biologic correlates of rapid cycling bipolar disorder have been identified; however, it is not clear whether these findings represent etiologic causes or sequelae of the disorder because the studies investigated patients who already met criteria for rapid cycling. Neuroimaging studies have found several correlates of rapid cycling. As an example, magnetic resonance imaging (MRI) studies have found that the ventral prefrontal cortex is significantly smaller in rapid cycling patients than in non - rapid cycling patients and healthy controls. Other gray matter structures that are significantly smaller in rapid cycling patients compared with healthy controls include the medial orbital prefrontal cortex, anterior cingulate, insula, and parahippocampus (11).
- **Psychosocial factors** – A history of childhood maltreatment is associated with rapid cycling. As an example, a meta - analysis of eight studies (n >3000 patients with bipolar disorder) found that the risk of rapid cycling was greater in bipolar patients with a history of

childhood maltreatment (physical, sexual, or emotional abuse; neglect; or family conflict), compared with patients without a history of maltreatment (odds ratio 1.9, 95% CI 1.5 - 2.5).

Antidepressants — Although some authorities think that antidepressants (particularly tricyclics) can trigger and prolong rapid cycling bipolar disorder, this is not established and remains a point of contention, due to the low quality, limited evidence that is available. A few prospective observational studies have found an association between antidepressants and rapid cycling; as an example, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP - BD) study followed 1191 bipolar patients for up to one year and found that rapid cycling occurred nearly four times more often in patients who received antidepressants compared with patients who did not. In addition, a prospective study compared 159 rapid cycling patients with 567 non - rapid cycling patients and found that treatment with antidepressants was associated with greater irritability and treatment resistance in rapid cycling patients. By contrast, other studies refute the association between antidepressants and the emergence of rapid cycling; in one study that followed 345 bipolar patients for a mean of 14 years, antidepressants were not associated with onset of rapid cycling and resolution of rapid cycling was not associated with discontinuation of antidepressants. Contrary to the idea that antidepressants precipitate rapid cycling, it has been suggested that it is frequent episodes of major depression that are associated with rapid cycling (as well as administration of an antidepressant) (12).

Additional indirect evidence suggests that adjunctive antidepressants may not cause or exacerbate rapid cycling and are safe to use in many patients with rapid cycling. Both short - term (eg, ≤6 months) and long - term (>6 months) (13) randomized trials have found that adjunctive antidepressants do not increase rates of switching from major depression to mania/hypomania. In so far as patients are not switching from one pole to the other, they may not be at increased risk of rapid cycling.

Clinical Manifestation

Number of mood episodes — The essential feature of rapid cycling is the occurrence of four or more bipolar mood episodes within a 12 - month period. The mood episodes consist of mania, hypomania, and major depression; these mood episodes can occur in any combination and order. The episode symptoms that occur as part of a rapid cycling pattern are no different from those that occur as part of a non - rapid cycling pattern. However, the episodes may be of shorter duration, and the beginning and end of an episode may be more abrupt.

Separate mood episodes are demarcated from each other by either (14):

- Switching from one pole to the other
- Full or partial remission for at least two months

Manic and hypomanic episodes are counted as being on the same pole; thus, a switch in polarity involves one of these episodes and an episode of major depression. As an

example, a patient with mania may remit and subsequently develop major depression. The time frame for switching poles is less than two months between the point that the patient has remitted from a mood episode on one pole and the point that the patient becomes ill with an episode on the other pole. In some cases, the switch occurs suddenly.

Although there is no established definition for partial remission, most authorities define it as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of psychotic and mood symptoms. Partial remission can be quantified with standardized rating scales that assess psychosis.

Most authorities think it is arbitrary to use a cut - off of four mood episodes to define rapid cycling bipolar disorder. Although this cut - off was confirmed to some degree in studies that examined the validity of rapid cycling, subsequent studies that examined the stability, course of illness, and heritability of rapid cycling did not support this cut - off. In addition, the number of mood episodes observed in bipolar patients during a specific time period is distributed monotonically along a continuum (15). Thus, rapid cycling appears to represent one extreme on the spectrum of episode frequency that occurs in bipolar disorder (15).

Duration: Prospective studies indicate that rapid cycling bipolar disorder is generally a transient phenomenon (state) rather than a stable characteristic (trait):

- A study of 356 bipolar patients with rapid cycling in the previous year found that during follow - up lasting 12 months, 91 percent converted to non - rapid cycling.
- Among 89 bipolar patients who developed rapid cycling during follow - up lasting a mean of 15 years, rapid cycling resolved within two years of onset in 78 percent of the patients and within three years in 92 percent.
- A study of 58 rapid cycling bipolar patients followed for at least 12 months found that 53 percent converted to non - rapid cycling (16)

However, rapid cycling can persist for many years. In a prospective study that followed 109 rapid cycling bipolar patients for up to 36 years, the mean duration of rapid cycling was eight years [50]. One factor associated with persistent rapid cycling is a depression - (hypo) mania - interval course; the interval is characterized by full or partial remission. Other factors associated with worse outcomes include a sudden "switch" from depression to (hypo) mania, and the occurrence of agitated/mixed depressions.

Other features — Rapid cycling can occur at any point in the bipolar patient's course of illness. A review of four studies, which included 181 rapid cycling patients, found that rapid cycling was present at the onset of bipolar disorder in 27 percent (17). A study of 109 bipolar patients with past - year rapid cycling found that onset of rapid cycling followed onset of bipolar disorder by a mean of 11 years. In addition, case reports describe onset of rapid cycling in geriatric bipolar patients (18).

The sequence of mood episodes observed during rapid cycling varies greatly; a few examples include:

- Individual mood episodes that are each followed by a period of euthymia
- Continuous cycling – Alternating episodes of opposite polarity (major depression on one pole and manic/hypomanic episodes on the other pole) with no intervening period of euthymia
- Numerous mood episodes that form no discernible pattern

The predominant psychopathology in rapid cycling bipolar disorder is generally depression, rather than mania or hypomania. As an example, among 206 bipolar patients who suffered rapid cycling during prospective follow - up lasting for one year, depressive symptoms were present for twice as many days as were manic/hypomanic symptoms (145 versus 73 days). This is consistent with the finding that depression is the predominant mood state for bipolar patients in general (19).

Rapid cycling bipolar disorder often includes brief mood states or "truncated episodes" with manic, hypomanic, and/or depressive symptoms that meet DSM - 5 - TR symptom criteria but not duration criteria for a mood episode:

- A study prospectively followed 206 rapid cycling patients for 12 months and found that an average of nine truncated episodes occurred per year, in addition to full mood episodes.
- A study prospectively followed 96 rapid cycling patients for at least 12 months and found that an average of four to eight truncated episodes occurred per year, in addition to full mood episodes

However, it is difficult to distinguish multiple truncated episodes from a single episode with mixed features (concurrent symptoms of major depression and mania/hypomania).

The frequency of rapid cycling in bipolar I and bipolar II disorder does not appear to differ substantially. A cross - national community study found no difference in the 12 - month prevalence of rapid cycling among individuals with bipolar I or bipolar II disorder. Although a meta - analysis of 11 clinical studies (2686 bipolar patients) and a subsequent study (1225 bipolar patients) each found a history of rapid cycling in more bipolar II patients than bipolar I patients, another subsequent study (500 bipolar patients) found that the prevalence of rapid cycling in bipolar I patients and bipolar II patients was nearly identical, and yet another study (539 bipolar patients) found that the prevalence of rapid cycling was greater in bipolar I patients (20).

Several studies suggest that the frequency of psychosis in rapid cycling and non - rapid cycling bipolar patients does not differ. As an example, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP - BD) study found that a lifetime history of psychotic mood episodes was roughly comparable in rapid cycling and non - rapid cycling patients (39 and 46 percent) (21). However, other studies have found that psychotic features occurred more often in rapid cycling bipolar disorder than non - rapid cycling bipolar disorder.

The rate of attempted suicide in rapid cycling and non - rapid cycling bipolar disorder appears to be similar. In a meta - analysis of six studies (1171 bipolar patients, including 454 with rapid cycling), a history of attempted suicide was found in a comparable number of rapid cycling and non - rapid cycling patients (35 versus 30 percent). Subsequently, a retrospective study of 128 patients with rapid cycling bipolar disorder and 1547 with non - rapid cycling bipolar disorder also found that a similar proportion had attempted suicide (8 and 7 percent). However, one study found that the mean lifetime number of suicide attempts was greater in rapid cycling patients (n = 159) than non - rapid cycling patients (n = 567; 1.0 versus 0.6).

Hospitalization is more likely to occur in rapid - cycling bipolar disorder than non - rapid cycling bipolar disorder (22).

Comorbidity — Comorbid psychiatric and general medical disorders are common in patients with rapid cycling bipolar disorder.

Rapid cycling bipolar patients are significantly more likely than non - rapid cycling patients to have a lifetime history of comorbid psychopathology, including:

- Anxiety disorders (eg, panic disorder, generalized anxiety disorder, social phobia, and specific phobia)
- Attention - deficit hyperactivity disorder
- Bulimia nervosa
- Obsessive - compulsive disorder
- Substance use disorders

In addition, impulsivity (evaluated by a rating scale) is greater in rapid cycling bipolar disorder than non - rapid cycling bipolar disorder.

Multiple general medical illnesses are frequently observed in patients with rapid cycling; one study (N = 225) found that the mean number of medical comorbidities was 2.5. Organ systems that are commonly affected include respiratory, musculoskeletal, neurologic, endocrine/metabolic, and genitourinary. As an example, rapid cycling may be associated with migraine headaches and neurodevelopmental disorders.

Course of Illness — In patients with bipolar disorder, rapid cycling is generally a transient phenomenon; however, some patients manifest rapid cycling for many consecutive years before it resolves. Once rapid cycling resolves, the risk for a subsequent period of rapid cycling is not known. The persistence of rapid cycling is discussed separately.

Bipolar patients who suffer rapid cycling at some point in their course of illness have a poorer long - term prognosis (with more lifetime affective morbidity), compared with non - rapid cycling patients (23):

- A cross - national community study found that the number of lifetime mood episodes was greater in rapid cycling than non - rapid cycling patients (103 versus 28 episodes), as was the number of lifetime years with at least one episode (15 versus 6 years).
- A study prospectively followed 345 bipolar patients for a mean of 14 years, during which 89 developed rapid cycling at some point. The number of weeks with

depressive symptoms was greater in rapid cycling than non - rapid cycling patients (42 versus 30 percent of follow - up weeks).

- A study prospectively followed 37 rapid cycling and 74 non - rapid cycling bipolar patients for up to five years (24). During each year of follow - up, the number of recurrent mood episodes was greater in the patients initially classified as rapid cyclers, even after rapid cycling resolved.

One form of rapid cycling is continuous cycling, which consists of alternating episodes of opposite polarity (major depression on one pole and manic/hypomanic episodes on the other pole) that are immediately contiguous with each other or separated by less than eight weeks of remission. These patients may have a poorer prognosis than rapid cycling patients with intermittent periods of euthymia and non - rapid cycling patients.

Bipolar patients who at one point experience rapid cycling may recover from bipolar disorder. In a study of 109 bipolar patients with rapid cycling who were followed prospectively for up to 36 years, 33 percent recovered (defined as no recurrent mood episodes for at least one year); the mean duration of recovery was 11 years (25).

Assessment — The initial clinical evaluation of patients with a possible diagnosis of rapid cycling bipolar disorder includes a psychiatric and general medical history, mental status and physical examination, and focused laboratory tests. The psychiatric history should emphasize the number of major depressive, manic, and hypomanic episodes during the previous 12 months (current rapid cycling), as well as any previous 12 - month period (lifetime rapid cycling). Patients may have difficulty distinguishing past mood episodes when they are not separated by long intervals of euthymia; interviewing family members may help to determine the number and type of mood episodes that have occurred.

No self - report instrument is available to screen for rapid cycling or assess response to treatment.

Diagnosis

Overview — According to DSM - 5 - TR, the essential feature of rapid cycling is the occurrence of four or more bipolar mood episodes within a 12 - month period. Thus, the term rapid cycling is used to specify the course of illness, rather than a subtype of bipolar disorder. The following subtypes of bipolar disorder may warrant a rapid cycling specifier:

- Bipolar I disorder – Patients with bipolar I disorder experience manic episodes and nearly always experience hypomanic and major depressive episodes. In addition, patients who only experience manic episodes (sometimes called “unipolar mania”) are also classified as bipolar I disorder.
- Bipolar II disorder – Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes.

Any bipolar I or bipolar II patient can develop rapid cycling and then subsequently revert to a non - rapid cycling course.

Beyond bipolar I and bipolar II disorder, the rapid cycling specifier is not used to characterize the course of illness in other DSM - 5 - TR bipolar and related disorders (26).

Additional information about diagnosing each bipolar subtype is discussed separately.

Rapid cycling — According to DSM - 5 - TR, the diagnostic criteria for rapid cycling are as follows (26):

- At least four bipolar mood episodes in a 12 - month period.
- The episodes meet both the symptom and duration criteria for major depression, mania, or hypomania; the episodes that occur as part of a rapid cycling pattern are no different from episodes that occur as part of a non - rapid cycling pattern. Mood episodes that are directly caused by substance intoxication (eg, cocaine or corticosteroids) or a general medical disorder do not count toward defining a rapid - cycling pattern.
- The mood episodes can occur in any order or combination.
- The episodes are demarcated by either:

A period of partial or full remission for at least two months, or a switch to an episode of opposite polarity. Manic and hypomanic episodes are counted as being on the same pole; thus, a switch in polarity involves one of these episodes and an episode of major depression. The time frame for switching poles is less than two months between the point that the patient has remitted from a mood episode on one pole and the point that the patient becomes ill with an episode on the other pole. In some cases the switch occurs suddenly.

Although the DSM - 5 - TR does not include a definition for partial remission, most authorities define it as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of psychotic and mood symptoms (27).

Patients who manifest brief mood states in the absence of full - duration mood episodes are classified as other specified bipolar disorder, without the additional course specifier rapid cycling. Rapid shifts between mood states have been described in case reports as "ultra - rapid cycling," in which patients alternate between periods of mania/hypomania, depression, and euthymia, with each mood state lasting approximately 24 hours. "Ultradian cycling" has also been described, consisting of shifts between different mood states (lasting only several hours), occurring within one day. The mood states seen during ultra - rapid cycling and ultradian cycling do not meet duration criteria for mood episodes as defined in the DSM - 5 - TR. If these brief mood states meeting symptom criteria but not duration criteria for mood episodes were counted along with full - duration episodes, more bipolar patients would be classified as rapid cyclers. (28).

Differential diagnosis

The psychopathology of rapid cycling bipolar disorder overlaps with that of borderline personality disorder. In addition, the two disorders often co - occur in the same patient (29). The overlap between rapid cycling bipolar disorder and borderline personality disorder includes rapid

switches between mood elevation (mania or hypomania) and major depression that can occur in rapid cycling; these switches may resemble the mood lability that occurs in borderline personality disorder. However, the affective instability of borderline patients is generally a reaction to environmental triggers such as perceived rejection or failure, which is typically not the case in rapid cycling patients. In addition, borderline patients are characterized by episodic dysphoria, irritability, or anxiety, rather than mood elevation. Borderline personality disorder is also marked by unstable and intense interpersonal relationships, identity disturbance (unstable self - image or sense of self), chronic feelings of emptiness, and frantic efforts to avoid abandonment; these features are not characteristic of rapid cycling bipolar disorder (30, 31).

3. Summary

Bipolar disorder is characterized by episodes of mania, hypomania, and major depression. Rapid cycling bipolar disorder is diagnosed in patients with four or more mood episodes during a 12 - month period. These episodes can occur in any order or combination, and are no different from episodes that occur as part of a non - rapid cycling pattern. Separate mood episodes are demarcated from each other either by a switch from one pole to the other (eg, major depression to mania), or by full or partial remission for at least two months. The estimated 12 - month prevalence of rapid cycling bipolar disorder in the general population is 0.3 percent. Among bipolar patients seen in clinical settings, approximately 16 to 17 percent have rapid cycling.

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