



Should cyclothymia be considered as a specific and distinct bipolar disorder?

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Practice points

- Besides typical forms of bipolar disorders, clinical experience and recent epidemiological studies have revealed a high prevalence of cyclothymia.
- Despite the fact that more than 30% of patients with major depression are cyclothymics, most clinicians remain blind to correct diagnosis.
- Cyclothymia should not be considered as a soft form of bipolar disorder, but taken as an exaggeration of a special, basic cyclothymic temperament.
- Within the bipolar spectrum, cyclothymia is characterized by specific phenomenology: age of onset, family history, recurrence, mixed states, distinct clinical picture of hypomanic episodes and comorbidities.
- Related risks are augmented in cyclothymia (e.g., suicide behavior, alteration of quality of life and functioning).
- Misdiagnosis represents a high risk of transforming cyclothymia to severe, complex, borderline-like bipolarity, especially with chronic and repetitive exposure to antidepressants.

SUMMARY Current research is mainly focused on 'classical episodic' forms of bipolar disorder (I and II). Despite its historical roots, cyclothymia is still neglected among the bipolar spectrum disorders. Contrary to DSM definition, based on the recurrence of low-grade episodes, cyclothymia is better defined as an exaggeration of cyclothymic temperament: early onset, complex temperament structure, high mood instability and reactivity, and rapid switching. Current epidemiological and clinical research has demonstrated the high prevalence and the validity of cyclothymia as a distinct form of bipolarity. In this article, the authors discuss their own clinical research and expertise on the understanding and medical management of cyclothymia. This is the beginning of challenging work concerning psychoeducation, clinical, pharmacological and genetic research.

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Among mood disorders, cyclothymia has received the least attention in epidemiological studies. Reviews of over 100 epidemiological studies on bipolar disorders (BDs) found that only eight reported on cyclothymia, which showed rates ranging from 0.4 to 2.5% in the general population [1]. Prevalence rates for brief episodes of hypomania associated with brief depression ranged between 5 and 8% [2], and for subsyndromal bipolarity between 6 and 13%. Higher rates of cyclothymia can be observed in the clinical population: more than 30% of depressed patients are seen in psychiatric outpatient settings [3] and 50% of patients have obsessive–compulsive disorder (OCD) [4]. A similar figure was confirmed in the general practice setting [5].

Most clinicians are blind to cyclothymia and very few use this diagnosis in their practice, probably because BDs are considered according to rigid and narrow conceptions requiring the observation of typical (hypo)manic episodes. In other words, clinicians do not accept the subtyping of BD. Therefore, the first source of confusion is to consider cyclothymia as a continuum of intensity of a manic episode, which is the statement accepted in the DSM. Further confusion is due to the young age of onset (early adolescence) of cyclothymic features (e.g., mood instability and extreme emotional reactivity), which are usually reported as markers of the cluster ‘B’ of personality disorders: histrionic or borderline personality disorders [6].

From historical roots to the current definition of cyclothymia

The term ‘cyclothymia’ was proposed by Ewald Hecker, a pupil of Ludwig Kahlbaum, in 1877 [7]. Interestingly, the term ‘cyclothymia’ referred to recurrent mood disorder and existed 20 years before the term ‘manic-depressive insanity’ was created by Emil Kraepelin. According to Kraepelin, cyclothymia will be considered as part of manic-depressive illness, nowadays designated as BD, precisely as a soft or attenuated form (i.e., episode of lower intensity) [8]. Indeed, this conception is due to Karl Willmams, Hecker’s student, who presents cyclothymia as a mild presentation [9]. Similarly, in France, Khan, defended the hypothesis that cyclothymia should not only serve to designate the mild forms of manic-depressive insanity [9], but that it is also an exaggeration of a special constitution, which preceded the onset of episodes and survives to their disappearance. This psychic constitution

is currently described within the operational criteria of ‘cyclothymic temperament’ [10].

In the DSM-IV-TR, cyclothymic disorder is defined as alternating states of hypomanic and depressive symptoms for at least 2 years in adults and 1 year in children and adolescents [8]. During this initial period, the individual cannot be symptom free for more than 2 months. If symptoms become more severe after this period, a concurrent diagnosis of BP I or II plus cyclothymia may be assigned. Therefore, the DSM definition of cyclothymic disorder is based on ‘episode recurrence’ without any mention of temperament or predisposition. According to the authors, cyclothymia is better defined as a ‘temperamental style’ [6,7], present during a large part of life and starting from childhood to adolescence, with:

- Excessive emotional sensitivity and mood reactivity
- Ups-and-downs in activity, energy and mood
- Rapid shifts in energy and/or mood
- Persistent circularity (continuous cycling without free intervals)

These are the essential components of cyclothymic temperament. Negative consequences (e.g., school, work, love and family) and repetitive sabotage of opportunities to become stable and have a serene lifestyle are needed to designate ‘cyclothymic disorder’. The initial operational criteria by Akiskal and Akiskal were transformed in The Temperament Evaluation of the Memphis, Pisa, Paris and San Diego project with the feasibility of assessing affective temperament by clinicians and through self-rating [11]. The Temperament Evaluation of the Memphis, Pisa, Paris and San Diego autoquestionnaire has been translated in several languages and is used in large epidemiological and clinical studies [12].

Validation of cyclothymia

Since cyclothymia begins early in life, it is important to show its validity in youth. Two large studies in outpatient samples indicated that cyclothymic disorder shares many characteristics with other bipolar subtypes: mood symptoms, age of onset, irritability, sleep disturbances, family history of psychopathology and poor functioning [13]. In a prospective 2–4-year follow-up, cyclothymic temperament is revealed as a strong predictor of BD in youths with major depression: 64 versus 15% of depressive youths without

cyclothymia [14]. These results support the bipolar nature of cyclothymic temperament as a major risk factor for developing BP I/II disorder, for switching to hypomania with antidepressants and to have positive family history for BD [2,9,15].

Cyclothymia also suggests a special phenomenology. The Italian research by Perugi *et al.* has helped to show the specificity of cyclothymia within BP I and II disorders [16]. In fact, when exploring the temperament dominance in BP I patients, two subgroups were clearly identified [16]:

- ‘Hyperthymic/stable’ group: male dominance, late onset, admissions for manic episodes, drug abuse and antisocial behaviors;
- ‘Cyclothymic/unstable’ group: female dominance, young onset, separation anxiety, anxious and impulsive comorbidity, borderline features, suicide behaviors and a family history of bipolarity and anxiety disorders.

In the same way, cyclothymia is able to separate two subgroups of BP II patients according to high levels of interpersonal sensitivity and separation anxiety, and high rates of comorbidity with panic disorder, OCD, social phobia, bulimia and alcohol abuse [17].

The pathoplastic effect of cyclothymia on the clinical expression of mood episodes is shown in other studies. In hypomanic episodes, the presence of cyclothymia is linked with increased global severity, higher recurrence and is especially correlated with the ‘dark’ side of hypomania: irritability, risk-taking behaviors and substance abuse. In depressive episodes, the presence of cyclothymia is linked with increased global intensity and a higher frequency of symptoms, such as guilt, psychomotor agitation, suicidal thoughts, early age of onset, higher recurrence, more suicidal attempts and a shorter delay to switch under antidepressants (Table 1) [18–21].

Recent studies confirm the validity of cyclothymia through its correlations with clinical validators and functional impairment, especially home management, private leisure and social activities [22]. Moreover, high scores on cyclothymia predicted depressive recurrence even when controlling for medication nonadherence [23]. Cyclothymic temperament also influences suicide risk in depressive patients. In fact, 64% of the cluster ‘cyclothymic anxious–depressive’ temperament received a score of nine or more on Beck’s Hopelessness Scale versus only 13% in the cluster ‘hyperthymic’ [24].

In a nonclinically ascertained sample of young adults at risk for BD, cyclothymic/irritable temperament was associated with a range of deleterious outcomes, including mood disorders and impaired functioning. It was negatively associated with agreeableness and conscientiousness, and positively associated with current depressive symptoms, neuroticism, borderline symptoms, impulsivity and grandiosity [25].

The major lesson from our clinical expertise is the importance of a clinical differentiation based on symptom stability and dynamic course of illness, rather than polarity and intensity of mood episodes. In favor of this approach, the study by Nwulia *et al.* demonstrates that rapid switching in bipolar patients appears to be linked with a more complex clinical course, early emergence of bipolar symptoms, antidepressant activation, anxiety comorbidity, and suicidal and self-harm behaviors [26]. This profile is often observed in cyclothymic patients where the intensity of mood swings is generally limited, although in some cases major affective episodes of both polarities may appear. The unpredictability of mood swings is a major cause of distress, as it weakens self-esteem and produces a considerable instability in terms of vocation, behavior and relations. Instable work adjustment, sexual promiscuity, substance abuse, impulsiveness and the strong self-harming tendencies could be interpreted as the result of long-lasting affective instability and excessive mood reactivity [17,27].

Treating cyclothymia: reasons for difficulties

There is a long list of reasons for difficulties in treating cyclothymia. First, there is a lack of consensus on the definition of the bipolar spectrum and the difficulties in the diagnosis of hypomania, both representing major obstacles to the correct diagnosis. Moreover, a complex clinical picture of cyclothymia, lack of clear-cut episodes, high comorbidity, early onset and an overlap with personality disorders can also be responsible for a very long diagnostic delay (more than 10 years in 50% of cyclothymic patients). Complicated patient–doctor relationships and a weak response to conventional approaches produces further difficulties in the recognition of cyclothymia.

Even when properly identified, there is no evidence-based treatment and no consensus on the strategy to treat cyclothymia. The lack of adequate research in this area is even more

Table 1. Characteristics of cyclothymic disorder compared with episodic bipolar disorder.

Clinical features	Classical bipolar disorder (episodic)	Cyclothymic disorder (persistent circularity)
Manic/major depressive episodes	Present	Absent during the first 2 years in adults (first year in youths)
Free intervals between episodes	Present	Absent (or less than 2 months duration) – presence of continuous mood swings between the episodes
Age of onset	>20 years	Early in childhood or adolescence
Basic temperament	Stable, rather hyperthymic	Instable, cyclothymic and complex (associated with traits of anxious, depressive or irritable temperaments)
Separation anxiety and interpersonal sensitivity	Low-to-moderate	High
Gender dominance	Male	Female
Frequency of episodes	Low-to-moderate	High tendency to rapid cycling and rapid switching
Sequence of episodes	(Hypo)mania followed by depression	Depression followed by (hypo)mania
Mixed episodes	Low rate	High rate
Dimensions of (hypo) manic episodes	Dominance of ‘sunny side’ (hyperactivity)	Dominance of ‘dark side’ (irritability, risk-taking behavior)
Suicidal and self-harm behaviors	Low-to-moderate	Frequent
Comorbidity	Substance abuse, antisocial personality features	Anxiety disorders, eating disorders (bulimia), impulse–control disorders, personality disorders (borderline features)
Response to lithium	Excellent	Mitigated

astonishing, considering that the intensity and recurrence of depressive and hypomanic episodes are higher in cyclothymia, and related risk of suicide, substance abuse and pejorative impact on functioning are also significantly augmented [18,19,28,29].

Owing to all the facts listed above, cyclothymia requires more sophisticated treatment than other classical bipolar forms. The diagnosis of cyclothymia needs to be achieved with adapted psychoeducation in order to facilitate acceptance of the disorder.

Need for an adapted psychoeducation

Most cyclothymics do not match with the psychoeducation proposed for BD I. The classical description of BD, characterized by manic and depressive episodes followed by a period of remission and with different algorithms for the treatment of different episodes, does not apply to cyclothymia, where depression and excitement are strongly related and interepisodic mood instability is the rule. Initiated by Hantouche *et al.*, a psychoeducation group therapy has been elaborated by the Anxiety and Mood Center team

(Paris, France) [30]. The format is weekly based with six, 2 h sessions:

- Session 1: clinical characteristics of cyclothymia, causes and medications determined;
- Session 2: monitoring of mood swings, assessment of warning signs, strategies to cope with early relapses and planning of ‘positive’ routines;
- Sessions 3 and 4: psychological vulnerabilities assessed (e.g., emotional dependency, sensitivity to rejection, excessive need to please, testing limits, need for control and compulsive behaviors);
- Session 5: cognitive processes linked to ups-and-downs determined;
- Session 6: interpersonal conflicts discussed.

More information is available in a self-help book [31].

Drug treatment in cyclothymia

In this section, we present our own expert experience and opinions on the medical management

of cyclothymia. Treatment of cyclothymia should always be conceived and scheduled according to the followings rules [32,33]:

- Establish a hierarchy of clinical targets to treat first:
 - Nature of current episode (i.e., depressive, hypomanic and mixed); in our practice, treatment is initially focused on more than 90% of cases, on mixed depressive states with the notion of resistance to multiple antidepressants;
 - Level of emotional sensitivity, intensity and instability;
 - Present comorbidity: OCD, panic, alcohol abuse and bulimia;
 - Risks of suicide and self-harm behaviors.
- Draw principal objectives:
 - In mid-term (6–12 months): moving toward biological stability (reducing amplitude and frequency of ups-and-downs) and behavioral stability (learning positive routines);
 - On long-term (beyond clinical stabilization): moving toward better functionality, adjustment to illness and surviving dysfunctional life schemas.

We usually insist on a strategy based on targeting specific and essential dimensions, and respecting the rule of ‘go slow and stay low’. The majority of cyclothymic patients would benefit from a small dose of valproate (if mixity and mood reactivity are dominant), lamotrigine (when anxious–depressive polarity is dominant) or lithium (if affect intensity is present). Many patients received the combination of a small dose of lithium (200–400 mg) plus lamotrigine (25–100 mg) [33]. Careful attention is required for adverse effects, such as skin reactions, thyroid function, polycystic ovary syndrome and weight gain.

Considering the high risk of (hypo)manic switches, rapid cycle induction or formation of chronic mixed states, antidepressants in the treatment of cyclothymic depression should be used with caution. But in real-world practice, almost all cyclothymic patients receive antidepressants and a correct diagnosis is established in recurrent, resistant, difficult-to-treat depression. This common reality renders the treatment more complex than it should be: gradual removal of the antidepressant (which is very important as many patients will be worsened by acute removal

of antidepressants) and unnecessary drugs (e.g., antipsychotics, sedatives, anxiolytics and hypnotics) and introducing specific stabilizers. In this configuration, delays to obtain optimal stabilization are usually longer in noncyclothymics. Owing to potential complications linked to the use of antidepressants, both when they are continued (switching or cycle acceleration) or stopped (withdrawal reactions or rapid relapses), the best advice is to avoid antidepressants from the beginning in cyclothymic patients [34]. We reserve antidepressants for nonresponder depressives. A possible option is represented by quetiapine, which has been reported to be effective in the treatment of acute bipolar depression. In our practice, the rate of intolerance of quetiapine or other antipsychotics is high (more than half of patients will drop these drugs during the first 2 weeks). Therefore, an excellent ratio of benefit–risk profile should always be considered.

Another important issue concerns the frequent comorbidity in cyclothymia with anxiety, impulse–control or eating disorders, and attention deficit in youth. Each comorbid condition requires a selection of treatments, which are mostly based on open clinical experience [17,35]. For example, high anxiety, panic attacks, inner tension (usually observed in mixed depressive state) and ultra-rapid cycling would be a predictor of response to valproate rather than to lithium. Gabapentin, which has been shown to be effective in panic disorder and social phobia, seems to be helpful when anxiety disorders or alcohol abuse are comorbid. Topiramate would be indicated when hyperphagia and binge eating are prevalent or excessive weight gain is induced by antipsychotics. Less information is available for treating social phobia comorbid with cyclothymia; the same problem applies to comorbidity with post-traumatic stress disorder. Comorbid OCD is probably the most challenging to treat. A complex combination of different mood stabilizers with serotonergic drugs and antipsychotics is often applied [4,36].

Psychotherapy

It is very important to assess the psychological part of cyclothymia after 3–6 months of drug therapy and psychoeducation. In fact, a significant number of apparent psychological dysfunctions are linked to circularity of mood, mixity, psychic excitation, affect intensity and extreme mood reactivity. In half of the cases, a selective drug therapy with focused psychoeducation is

sufficient to obtain a rapid clinical response with significant changes in behavior and cognitions.

There is no rigid or strict format for psychological therapy. However, we insist that psychotherapy needs to consider the model in which moods swings and circularity are linked with mood reactivity, affect intensity, emotion sensitivity, interpersonal sensitivity and basic insecurity, which illustrate the endogenous cyclicity in cyclothymia [37].

In our practice, the cognitive-behavioral approach is systematically used and strategies are selected based upon the individual's needs, with principal objectives, such as:

- Recording levels of mood and energy;
- Helping 'healthy' daily routines;
- Implementing specific strategies to manage ups-and-downs by discussing dysfunctional beliefs linked to depressive and hypomanic episodes, and especially to ultra-rapid mood swings; the goal is to achieve mood repair by identifying concomitant cognitions and beliefs related to activation and inhibition [38];
- Reducing comorbid anxiety: most cyclothymics present traits of anxious temperament, but half of them suffer from anxiety disorders (panic attacks, OCD, social anxiety or post-traumatic stress disorder); therefore, psychotherapy should address this comorbid anxiety, especially to avoid the use antidepressants or to allow the minimal dose to be administered;
- Rebuilding self-esteem after reducing mood reactivity and achieving a certain degree of emotional stability [39]. This feature, partially related to weak self-esteem, determinates high sensitivity to judgment, criticism and rejection by others. In cyclothymic subjects, susceptibility to rejection and disapproval by others prevail. They are promptly offended and sensitive to the possibility of being wounded, with feelings of hostility and anger towards those who evocate these reactions and that are considered responsible for their suffering [39];
- Restoring healthy social support: cyclothymic patients suffer from difficulties in interpersonal relationships; relatives and friends point out how they often appear hostile towards people around them. In many cases they have explosions of rage following minor disputes, which have the effect of triggering

an 'avalanche' of reactions with destructive consequences on their interpersonal life [31];

- Surviving repetitive life schemas linked to cyclothymia, especially the domains of abandonment, self-sacrifice, insufficient self-control, affective dependence and the need for control with unrelenting standards. In a preliminary research conducted in 45 cyclothymic patients, we observed high scores on these five schemas [40].

Recent research demonstrated the benefits of the sequential combination of cognitive-behavioral therapy and well-being therapy when compared with clinical management. Therapeutic gains with combined psychotherapy are maintained at a 2-year follow-up [41].

Conclusion & future perspective

Cyclothymia is still a neglected disorder despite the evidence that 30–50% of depressives, anxious, impulsive and borderline patients are affected by this disorder. There are many challenging issues concerning medical education, clinical, pharmacological and genetic research [42,43]. We need to confirm the specificity of this disorder within the bipolar spectrum and to improve its recognition in the early phase of the illness, especially in youths [44].

An appropriate approach to treat cyclothymia is needed to reduce controversy surrounding the overdiagnosis of the bipolar spectrum and pediatric BD. In fact, this approach combining sub-threshold presentations of bipolarity (typical and atypical ups-and-downs) and affective temperaments, represents a clear and precise approach for complex clinical syndromes with depression, psychic excitement, anxiety, impulse-control, substance use, attention deficit and personality disorders [17,45–48].

Early recognition means instauring specific treatment and clinical management, and avoiding unnecessary complications and risks, especially those related to antidepressant exposure. It is impossible to confirm if early detection and treatment of cyclothymia can guarantee a significant change in the long-term prognosis. Prospective observations in our practice are in favor of persistent significant improvement. This is more visible when specific psychological approaches and psychoeducation is applied to children and to young patients who are drug naive.

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