

Treatment of Cyclothymic Disorder: Commentary

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Psychotherapy Trial by Fava and Colleagues

This commentary was occasioned by the reporting of what appears to be the first randomized, controlled trial of psychotherapy in DSM-IV cyclothymic disorder [1]. It involved 62 untreated patients, randomized to psychiatrist-conducted psychotherapy versus usual (supportive, advisory) clinical care without antidepressant or mood-stabilizing medication (benzodiazepines could continue at reduced doses). Importantly, the treatment conditions were closely matched for intensity at ten 45-min sessions every 2 weeks for 5 months, with the exception of additional ‘exposure homework’ required for cognitive-behavioral therapy (CBT). The experimental intervention involved sequential use of CBT (first 6 sessions) aimed primarily at treating subsyndromal depression and anxiety symptoms [1, 2], followed by well-being therapy (final 4 sessions) originally designed to supplement mood-stabilizing treatments in more severe bipolar disorder (BPD) and to reduce anxiety [1, 3]. At baseline, participants were generally well-matched: average age 40 years, 50% were married, with an average of 5 years from estimated illness onset of DSM-IV cyclothymic disorder. By chance, initial ratings of depression severity were 15% higher among psychotherapy cases (42.3 ± 6.2 vs.

36.9 ± 4.4 ; $p < 0.001$), but hypomania scores were only 0.76% greater (9.26 ± 3.10 vs. 9.19 ± 2.52) [1]. In addition, a small proportion (14.5%) of subjects met DSM-IV criteria for type II BPD at some time, presumably after at least 2 years of cyclothymic disorder (table 1), indicating the presence of major depressive episodes and sustained hypomania [1]. Additional comorbidity involved anxiety disorders, but substance abuse and personality disorders were excluded.

Most participants (82.3%) completed all 20 weeks of treatment (83.5% given psychotherapy vs. 80.6% randomized to usual care). Depression ratings declined by 34.0% after 20 weeks of experimental treatment versus 15.2% among controls (a 2.2-fold difference). At the final assessment at 2 years of follow-up, these beneficial effects were sustained (37.1 vs. 18.7%, respectively, a 2.0-fold difference favoring psychotherapy). Hypomania ratings similarly improved by 36.3 versus 14.0%, respectively, at 20 weeks (2.6-fold), and by 48.1 versus 15.5% at 2 years (3.1-fold difference). These differences between treatment arms were highly statistically significant [1]. The findings support the hypothesis that cyclothymic disorder is a treatable condition, and that the 5-month psychotherapy intervention offered showed substantial benefits that persisted for at least 2 years.

Table 1. Current international diagnostic criteria for cyclothymic disorder

WHO International Classification of Diseases, Tenth Revision (ICD-10, since 1990)

F34.0. Cyclothymia

Persistent instability of mood involving numerous periods of depression and mild elation, none of which is sufficiently severe or prolonged to justify a diagnosis of bipolar affective disorder (F31) or recurrent depressive disorder (F33). This disorder is frequently found in the relatives of patients with bipolar affective disorder. Some patients with cyclothymia eventually develop bipolar affective disorder. Can be diagnosed as a personality disorder in some cases.

APA Diagnostic and Statistical Manual, Fourth Edition (DSM-IV, since 1994)

301.13. Cyclothymic disorder

- 1 A chronic mood disorder characterized by numerous depressive and hypomanic symptoms over at least 2 years (at least 1 year in children and adolescents), typically starting insidiously in adolescence or early adulthood.
- 2 No symptom-free period lasting 2 or more months.
- 3 At least 2 years without a major depressive, manic or mixed manic-depressive episode, although these sometimes emerge later.
- 4 Lack of explanation by another disorder or substance abuse.
- 5 Clinically significant distress from symptoms, or impairment in work, social or other important functions.

DSM-IV criteria allow for major depressive episodes (comorbid bipolar II disorder), typically after ≥ 2 years of cyclothymic disorder.

at least 2 years (1 year for juveniles) of mood shifts without major depression or mania, either as a distinct diagnosis, or as a precursor to major recurrences of depression or mania in BPD. From early reports, however, some patients with only cyclothymia and without major episodes of affective illness have been recognized.

Early, but relatively modern, descriptions of cyclothymia were provided by Karl Kahlbaum (1829–1899) as fluctuating conditions (*cyclic partial insanity*) including ‘dysthymia’ and ‘hyperthymia’ as milder forms of more typical cyclic insanity involving manic and melancholic phases; cyclothymia could either persist or evolve into more severe cyclic insanity [6]. Further descriptions were provided by Kahlbaum’s associate Ewalt Hecker (1843–1909), who ascribed the concept to Kahlbaum from as early as 1877 [7]. This condition was also included among milder forms of illness or personality types within a broad range of *manic-depressive disorders* by Emil Kraepelin (1856–1926) by the end of the 19th century [8]. More recently, cyclothymia was considered a personality disorder in DSM-III (1980), and as a distinct disorder in both ICD-10 (since 1990) [9] and DSM-IV (since 1994) [10], provided that clinically significant distress and disability were present so as to support the designation of ‘disorder’. ICD-10 considers the possibility of cyclothymia as either a disorder or a personality type [9]. DSM-IV criteria allow for the possibility of evolution of cyclothymic disorder into (or comorbidity with) BPD, perhaps most often as bipolar II disorder (with major depression and hypomania) at later times [10] (table 1).

History of Cyclothymia

The concept of cyclothymia dates at least to the mid or late 1800s, although it had been largely ignored through most of the past century. It is one of several aspects of a current ferment in conceptualizations of mood disorders and in their nosological distinctions, including a widening range of BPD-like disorders and fragmentation of the broad ‘major depression’ concept into subtypes [4]. Usually, cyclothymia has been conceived as involving mild or moderate fluctuations of mood, thought, and behavior in what would now be considered ‘subsyndromal’ mild hypomanic or depressive-dysthymic directions, without meeting formal diagnostic criteria for either major depressive disorder (MDD) or hypomania. However, the sharp differentiation of cyclothymia as a discrete psychopathological syndrome (cyclothymic disorder) rather than a temperament or personality type, or mild phases of BPD, has been a challenge [5]. DSM-IV criteria require

Current Status of Cyclothymia

There is considerable remaining ambiguity regarding cyclothymia as a distinct disorder, a temperamental or personality type, a precursor state to BPD, or as lying within a ‘bipolar spectrum’ of related disorders [5, 10, 11]. Even the diagnosis can be clinically difficult since many cyclothymic patients do not recognize mild hypomania as psychopathological, and the distinctions between subsyndromal and syndromal hypomania and depression can be unclear. Cyclothymic disorder can be difficult to distinguish from type II BPD, and can resemble personality disorders including ‘borderline’ states [5, 10, 11]. Many basic epidemiological, clinical, and therapeutic characteristics of cyclothymia remain remarkably underdeveloped for a condition that has been widely recognized for more than a century. Estimates of the lifetime prevalence of DSM-IV cyclothymic disorder or temperament have been reported at 0.4–1.0% of nonclinical pop-

ulation samples [10–13]. Cyclothymia may represent a precursor state or a comorbid characteristic in an uncertain proportion (15–50%) of cases of types I or II BPD [10, 14]. Risks for cyclothymic disorder and temperament appear to be similar in men and women, to have a minor female preponderance and a greater chance of women to present for treatment [10, 13]. First-degree relatives of cyclothymic disorder probands have an excess of BPD or MDD and, conversely, there is an excess of cyclothymia among relatives of identified BPD patients [10, 15]. However, there is a lack of clarity about: (1) the stability of the disorder over time, (2) the proportion of early subsyndromal and later major hypomanic, depressive, or mixed states in the course of disorders considered primarily cyclothymic, (3) typical cycling rates as well as the frequency and duration of intervening periods of stability, and (4) risks of suicidal behavior. Typically, mood shifts appear to be more or less continuous in cyclothymia [5, 10, 11] with parallels to rapid-cycling forms of BPD [16–18], and a close association with type II BPD [19, 20]. Early cyclothymia in childhood may have predictive utility in anticipating later development of BPD [21, 22].

In an effort to clarify the distribution of cyclothymic temperament with major mood disorders, we recently characterized temperament types among 1,870 mood disorder patients [type I BPD, $n = 419$; type II BPD, $n = 308$; unipolar MDD (UP-MDD), $n = 1,143$] both clinically and by application of the TEMPS-A auto-questionnaire [23] to 174 of these (type I BPD, $n = 54$; type II BPD, $n = 41$; UP-MDD, $n = 79$), all evaluated, treated, and followed at a Sardinian mood disorder center [Tondo et al., unpubl. data]. The prevalence of patients considered to be cyclothymic averaged 12.6% overall, and was only slightly higher among women (13.7%) than men (10.8%). However, the distribution of cyclothymic temperament differed highly by DSM-IV diagnosis, ranking: type II BPD (25.6%), type I BPD (17.7%), UP-MDD (7.3%); χ^2 (d.f. = 2) = 86.8, $p < 0.0001$. Moreover, DSM-IV lifetime rapid cycling (≥ 4 recurrences/year) was strongly associated with type II BPD, ranking: type II BPD (31.4%) \geq type I BPD (7.31%) \gg UP-MDD (0.00%), and the estimated cycling rate (episode recurrences/year \pm SD) ranked: type II BPD ($3.26 \pm 8.11\%$) \geq type I BPD ($2.32 \pm 3.65\%$) \gg UP-MDD ($0.98 \pm 1.55\%$). We also found a marked (4.5-fold) difference in rates of lifetime rapid cycling between patients diagnosed with (16.8%) or without (3.70%; $\chi^2 = 35.6$, $p < 0.0001$) TEMPS-A cyclothymic temperament [Tondo et al., unpubl. data]. These observations support the hypotheses that cyclothymia is strongly associated with BPD, especially type II, and with relatively rapid cycling.

Treatment of Cyclothymic Disorder

There is broad agreement that treatment of cyclothymic disorder is appropriate when there is substantial clinical distress or dysfunction associated with depressive or hypomanic phases of the illness, or with severe emotional instability itself. Many such patients are far more distressed by the depressive or dysthymic component of the disorder, and are likely to present clinically demanding antidepressant treatment. However, the value of antidepressants is not sufficiently well studied to provide firm conclusions about either benefit or risks of additional affective destabilization, especially with continued, long-term, exposure to antidepressants or other mood-elevating drugs. Moreover, mixed states involving simultaneous or rapidly fluctuating combinations of dysphoric and hyperactive states are particularly poorly characterized in cyclothymic disorder. Both the risks of inducing or worsening of subsyndromal (or syndromal) hypomanic or mixed states with antidepressants in cyclothymic disorder patients, and their treatment or prevention by mood-stabilizing drugs are very little studied. In our recent review of BPD patients in the Sardinian mood disorder center, a cyclothymic temperament was, by far, the strongest predictor of the risk of switching into mania or hypomania [Tondo et al., unpubl. data; 24]. However, in cyclothymic disorder itself, as well as in type II BPD, there appears to be a limited risk of inducing hypomania or moderate mixed states during treatment with an antidepressant, even without a mood stabilizer [24, 25]. However, this impression is not adequately studied, and may in part reflect limited ability to become potentially dangerously manic in either cyclothymic disorder or in closely related type II BPD, with a risk of mood elevation being overlooked.

There is a growing clinical impression that mood-stabilizing agents, including lithium, several anticonvulsants, and some antipsychotic drugs, may offer particular value, at least for short-term treatment of type II BPD and perhaps also cyclothymic disorder [26–30]. Support for beneficial effects of quetiapine and lithium is particularly encouraging, but evidence pertaining to lamotrigine has been limited and inconsistent [26–30].

In addition, there is a small, but growing body of studies of psychosocial treatments in both type II BPD and cyclothymic disorder [3, 31–35]. Particularly promising results have been associated with applications of CBT and supportive groups in conjunction with mood-stabilizing medication [31, 32], although efforts to adjust the scheduling of circadian activities have had less benefit on mood

stabilization [33]. Psychoeducational group treatments have demonstrated mood-stabilizing value in type II BPD [35], but require specific study in cyclothymic disorder.

Conclusions

The controlled trial of sequentially applied psychotherapies for cyclothymic disorder by Fava and his colleagues represents an important step forward in the evaluation of therapeutic implications of increasingly broad and numerous syndromes proposed to be related to BPD in both form and possibly also their therapeutics. As the complexity and subtyping of mood disorders continue to grow, there is increased challenge to support the concepts epidemiologically and clinically, with a particular need to improve matching of phenotypes with genetic and other biological assessments. Moreover, we propose that the potential clinical value of such complexity or broadening

of diagnostic concepts calls for much more extensive and coherent evidence concerning the prognostic or predictive value of the concepts, as well as the efficacy, long-term effectiveness, specificity and safety of available means of treatment, with continued efforts to develop improved treatments.

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