CNS Spectrums (2017), **22**, 120–125.
doi:10.1017/S1092852916000493

OPINION

What is the role of conventional antidepressants in the treatment of major depressive episodes with Mixed Features Specifier?

Gianni L. Faedda,[1]* *and Ciro Marangoni*[2]

[1] Lucio Bini Mood Disorders Center, New York, New York, USA
[2] Centro Lucio Bini, Rome, Italy

The newly introduced Mixed Features Specifier of Major Depressive Episode and Disorder (MDE/MDD) is especially challenging in terms of pharmacological management. Prior to the publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, the symptoms of the mixed features specifier were intradepressive hypomanic symptoms, always and only associated with bipolar disorder (BD).

Intradepressive hypomanic symptoms, mostly referred to as depressive mixed states (DMX), have been poorly characterized, and their treatment offers significant challenges. To understand the diagnostic context of DMX, we trace the nosological changes and collocation of intradepressive hypomanic symptoms, and examine diagnostic and prognostic implications of such mixed features.

One of the reasons so little is known about the treatment of DMX is that depressed patients with rapid cycling, substance abuse disorder, and suicidal ideation/attempts are routinely excluded from clinical trials of antidepressants. The exclusion of DMX patients from clinical trials has prevented an assessment of the safety and tolerability of short- and long-term use of antidepressants. Therefore, the generalization of data obtained in clinical trials for unipolar depression to patients with intradepressive hypomanic features is inappropriate and methodologically flawed.

A selective review of the literature shows that antidepressants alone have limited efficacy in DMX, but they have the potential to induce, maintain, or worsen mixed features during depressive episodes in BD. On the other hand, preliminary evidence supports the effective use of some atypical antipsychotics in the treatment of DMX.

Received 10 May 2016; Accepted 22 July 2016; First published online 10 November 2016

Key words: Antidepressant, bipolar disorder, major depression, mixed features, mixed states.

Introduction

Depressive mixed states (DMX) are phenomenologically different from pure major depression due to the presence of excitatory (hypomanic) symptoms, and they have been extensively characterized by the works of Emil Kraepelin and Wilhelm Weygandt. In the classic medical literature, DMX, and mixed states in general, have always been considered as part of manic-depressive illness.

DMX are characterized by motor agitation (such as pacing; handwringing; inability to sit still; pulling or rubbing hair, skin, clothing, or other objects; outburst of complaining or shouting), inner psychic tension (which makes the patient very anxious and fearful), racing or crowded thoughts (which generally are not expressed verbally), talkativeness, mood lability/irritability, inhibition of purposeful activity, and marked anhedonia.[1] Some DMX present with pronounced psychomotor agitation, while in others anxiety and/or inner psychic agitation dominate the clinical picture.

Although the Research Diagnostic Criteria[2] recognized and described agitated major depression as a separate category, the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) and following editions did not consider irritability, psychomotor agitation, and distractibility as hypomanic symptoms, but rather as depressive symptoms.

The introduction of the Mixed Feature Specifier in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) represents a very significant

* Address for correspondence: Gianni L. Faedda, Lucio Bini Mood Disorders Center, 245 E. 50th St., New York, NY 10022, USA.
(Email: moodcenter@gmail.com)

conceptual shift that affects nosology, research, and clinical practice. In order to understand this shift, it is necessary to appreciate the phenomenology of mixed states as well as the changes in their classification across successive editions of the DSM (Table 1).

The clinical characteristics of DMX are very similar to those of bipolar mixed states.[3] Bipolar mixed states, including DMX, are found more often in patients with greater rates of recurrence, complex comorbidities, and suicidality.[1,4,5] A history of past mixed states also increases the risk of having future mixed states, and is usually associated with poor treatment response and outcome. Prospective and retrospective studies have confirmed that bipolar mixed states are difficult to treat, with poor response to monotherapy with antidepressants or mood stabilizers and improvement with combined treatment with antipsychotics and mood stabilizers.[4,6]

The Third, Third Revised, Fourth, and Fourth Text Revision editions of the DSM all recognized a narrow definition of mixed states as "mixed mania," a period of time (at least 1 week) in which the criteria are met for both a manic episode and a major depressive episode. However, it is now clear that among mixed states, most do not meet full criteria for mania.[5]

With the introduction in the DSM-5 of the Mixed Feature Specifier, which is applicable to hypomanic, manic, and depressive episodes, both in major depressive disorder (MDD) and bipolar disorder (BD) (Table 1), hypomanic symptoms are no longer specific to BD. This change might allow for a more frequent recognition of mixed features during episodes of major depression, but does not guarantee appropriate treatment.

Since most of the information on the use of antidepressants in DMX is based on bipolar subjects, we will review evidence regarding the safety, tolerability, and efficacy of antidepressant drugs for patients with symptoms now included in the Mixed Features Specifier definition.

Clinical Characteristics of Major Depression with Mixed Features

The presence of hypomanic symptoms during an episode of depression has been described in the phenomenology of mixed states since the 19th century. Up to 2013, most data on mixed states was collected in patients with BD[3]; few studies investigated the role of intradepressive hypomanic symptoms in patients with MDD.

DMX, in contrast to pure major depression, are characterized by earlier age at onset, high frequency of depressive recurrences, longer episode duration, increased risk of suicide attempts, psychotic symptoms, comorbid anxiety and substance abuse disorders, and antidepressants-induced mania/hypomania, as well as greater illness severity, functional disability, and poorer prognosis.[7–12]

Among those patients with MDD, 22% to 50% have had at least 1 manic symptom, and 7% to 23% had 3 or more manic symptoms; similarly, in BD-I and BD-II patients, more than 50% experience at least 1 manic symptom and 10–16% at least 3 manic symptoms during depression.[13]Additionally, the presence of hypomanic symptoms during major depression has been found to be a significant risk factor for the development of BD in prospective studies.[14]

In the DSM-5 (Table 1), core features of DMX, such as irritability, distractibility, and psychomotor agitation, have been excluded from the Mixed Features Specifier criteria because they are present both in MDE and manic episode; this decision is questionable, however, since clinical studies show that these core hypomanic symptoms are very frequent compared to euphoric/grandiose mood in patients with DMX.

Koukopoulos *et al*[13] systematically reviewed the papers used as reference by the DSM-5 Mood Disorders Work Group in defining the symptoms of major depression with mixed features. They found that the clinical picture proposed by DSM-5 criteria is extremely rare in DMX and does not target the great suffering linked to the disorder. In fact, the most common intradepressive hypomanic symptoms reported in the papers were irritability, motor agitation/restlessness, distractibility, racing thoughts, and flight of ideas. Less than 10% of the patients reported euphoric mood or inflated self-esteem/grandiosity. Additionally, some recent studies[6,12] have confirmed the clinical characteristics of major depression with mixed features.

Treatment Issues in Major Depression with Mixed Features

Antidepressants

The safety, tolerability, and side effect profile of antidepressants for the treatment of the Mixed Features Specifier is limited to retrospective data obtained in BD patients.[15–17]

Using the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) data, Goldberg *et al*[18] examined the 3-month outcomes of patients with bipolar mixed depression who were treated with antidepressants plus mood stabilizing drugs. Adjunctive antidepressant use did not reduce time to recovery relative to treatment with mood stabilizers alone, and was associated with significantly higher mania symptom severity at the 3-month follow-up.

In an independent sample, the Bipolar Collaborative Network, Frye *et al*[16] found that a subset of baseline hypomanic symptoms predicted treatment-emergent

https://doi.org/10.1017/S1092852916000493 Published online by Cambridge University Press

TABLE 1. ***Diagnostic and Statistical Manual of Mental Disorders*** **(DSM) criteria for mixed states**

DSM edition	Notes	Criteria
III (1980)	Mixed states are part of BD.	A. Current (or most recent) episode involves the **full symptomatic picture** of **both manic** and **major depressive** episodes, intermixed or rapidly alternating every few days. B. Depressive symptoms are prominent and last at least a full day.
III-R (1987)		Same criteria as DSM-III except for the duration requirement of 2 weeks for depressive symptoms.
IV (1994)	Mixed states are only part of BD-I.	A. The criteria are met **both** for a **manic episode** and for a **major depressive episode** (except for duration) nearly every day during **at least a 1-week period**. B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. C. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism). Note: Mixed-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of BD-I.
IV-TR (2000)		Same criteria as DSM-IV
5 (2013)	Mixed features specifier applies to manic, hypomanic, or depressive episode in BD-I, BD-II, and MDD.	Depressive episode, with mixed features: A. **Full** criteria are met for a **major depressive episode**, and **at least 3** of the following **manic/hypomanic symptoms** are present during the majority of days of the current or most recent episode of depression: – Elevated, expansive mood – Inflated self-esteem or grandiosity – More talkative than usual or pressure to keep talking – Flight of ideas or subjective experience that thoughts are racing – Increase in energy or goal-directed activity (either socially, at work or school, or sexually) – Increased or excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments) – Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia) B. Mixed symptoms are observable by others and represent a change from the person's usual behavior. C. **For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features.** D. The mixed symptoms are not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment). Note: Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of BD-I or BD-II. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment. Manic or hypomanic episode, with mixed features: A. **Full** criteria are met for a **manic** episode or **hypomanic episode**, and **at least 3** of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania: – Prominent dysphoria or depressed mood as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful) – Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others) – Psychomotor retardation nearly every day (observable by others; not merely subjective feelings of being slowed down) – Fatigue or loss of energy – Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick) – Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide B. Mixed symptoms are observable by others and represent a change from the person's usual behavior. C. **For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features,** due to the marked impairment and clinical severity of full mania. D. The mixed symptoms are not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, other treatment).

hypomania in bipolar depression: increased motor activity, speech disorder, distractibility, and racing thoughts.

Further adding to this evidence, in the STEP-BD,[15] 3 clinical features were identified that conferred a greater risk of switch in antidepressant exposed vs unexposed individuals: history of suicide attempt, younger age, and bipolar-I subtype; also, a greater number of past depressive episodes, greater mania severity, recent or lifetime rapid cycling, alcohol use disorder, previous suicide attempt, and history of switch while treated with antidepressants were risk factors for treatment-emergent mania.

The presence of a pharmacological or iatrogenic precipitant to DMX is well illustrated by Koukopoulos *et al*.[1] In a large chart review study, in 56% of the cases of agitated depression, with psychic/motor agitation, insomnia, impulsivity, and suicidality, the onset of agitation was associated with pharmacological treatments, mainly antidepressants, and took place either immediately or within a few days to a few weeks. Such states can be managed effectively by discontinuing antidepressants and using mood stabilizers or other antimanic agents.[4] The contribution of antidepressants to the development or worsening of suicidal ideation and behaviors has been attributed to disinhibition and impulsivity.[19]

These findings were confirmed in a cohort of 219 consecutively assessed outpatients with DMX, who were diagnosed using Koukopoulos's criteria: a diagnosis of BD type-II, greater depression severity and older age at index episodes were predictors of DMX, and antidepressants were associated with half of the cases diagnosed with DMX.[20]

Additional data were provided in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[21] Among 2397 subjects with MDD, 18.7% endorsed at least 2 of 6 self-reported mania subscale items of the Psychiatric Diagnosis Screening Questionnaire: the presence of expansive mood and cheerfulness were associated with a greater likelihood of remission, pointing to the cycling potential of these depressive states compared to those subjects with MDD without such mixed features. Indeed, this study systematically excluded cases of overlapping manifestations, such as increased psychomotor agitation, irritability, and distractibility, therefore selecting for subjects with a "less severe" illness.[21]

The International Society for Bipolar Disorder Task Force on Antidepressant use in BD[22] recommends that (1) antidepressants should be avoided during manic and depressive episodes with mixed features; (2) antidepressants should be avoided in bipolar patients with predominantly mixed states; (3) antidepressants should be discontinued in patients currently experiencing a mixed state.

Antipsychotics

Atypical antipsychotics have been shown to have mood-stabilizing properties, and selected agents have demonstrated antidepressant efficacy in bipolar depression. Currently quetiapine, olanzapine + fluoxetine, and lurasidone have been approved in the US for the treatment of major depressive episodes in BD-I, while aripiprazole and olanzapine + fluoxetine have been approved also for treatment-resistant MDD.

Additional evidence of efficacy comes from a recent systematic review and meta-analysis of placebo-controlled clinical trials of atypical antipsychotics in bipolar depression with mixed features that demonstrated significant improvements in both Montgomery–Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) scores.[23] Finally, a randomized, double-blind, placebo-controlled study found lurasidone to be effective and well tolerated in patients with MDD with mixed features.[6]

Discussion

In summary, the treatment of intradepressive hypomanic symptoms has been limited to (1) bipolar depression and (2) depressive episodes with mixed features. It appears that antidepressants alone have limited efficacy in bipolar depression,[24] but they have the potential for inducing, maintaining, or worsening mixed features during depressive episodes in BD.[1,4,16,18,20,22,25] On the other hand, preliminary evidence supports the effective use of atypical antipsychotics in the treatment of DMX.

It must be noted that many of the changes introduced in the editions of DSM were not based on evidence, and in the case of the Mixed Features Specifier, were not always driven by data.[25]

These changes in the nosology of mood disorders also led to an increase in the heterogeneity of major depression–a diagnostic category used in all clinical trials. By combining heterogeneous conditions, such as pure depression and DMX, in the same diagnostic category, the DSM has consistently ignored all the depressive mixed states described in the clinical literature until DSM-5.

Such heterogeneity helps to explain the variety of clinical outcomes following treatment with antidepressant agents. While a majority of patients with major depression benefits from antidepressant treatment, a significant minority does not respond, or experiences severe adverse psychiatric symptoms beyond usually reported side effects. Even the presence of depressive and manic mixed states precipitated by the use of antidepressants–a phenomenon reported as far back as the discovery of antidepressant agents[26–28]–was not

https://doi.org/10.1017/S1092852916000493 Published online by Cambridge University Press

sufficient to raise awareness and research interests in these conditions.

Some patients (possibly undiagnosed bipolar, or prone to severe side effects for metabolic causes) can experience short or prolonged periods of hypomania. Such states, if induced by the treatment, are referred to as iatrogenic. Some patients cycle rapidly either spontaneously or during exposure to antidepressants, and might enter prolonged periods of dysphoric agitation with impulsive self-harm, suicidal ideation, and gestures. In such cases, the discontinuation of antidepressants, or adjunctive treatment with typical or atypical antipsychotics, sedatives, or ECT, is usually helpful or therapeutic.[4,6,29–33]

In the DSM-5, the status of DMX is more uncertain than before.[13] This is likely to further complicate the proper diagnosis and treatment of DMX, ignoring the rich literature clearly indicating the bipolar nature of such common clinical presentations. The recent changes to the DSM classification have created a new category of patients experiencing MDD along with mixed features (hypomanic symptoms) who do not meet criteria for BD, de facto unlinking mixed features (hypomanic symptoms) from BD. This makes it possible and likely that patients with intradepressive hypomanic symptoms will be exposed to antidepressants, effectively circumventing the safety guidelines of the US Food and Drug Administration (FDA), which require demonstrated safety, efficacy, and tolerability before approval for a specific indication. As patients with BD experience significant depressive morbidity, the safety of antidepressant treatments in the acute and maintenance treatment of BD remains largely unexplored.

In the acute management of BD, and especially DMX, the use of antidepressants must be decided on an individual basis, carefully weighing the risks and benefits. Careful, frequent monitoring during antidepressant treatment, especially titration and discontinuation, should always be a part of the more comprehensive approach to the management of depressive symptomatology, within the patients' unique medical, psychological, and social circumstances. A longitudinal assessment of the effect of antidepressant treatments on morbidity and mortality seems to offer the best opportunities to identify protective and risk factors to improve both short- and long-term outcomes.

Conclusion

In summary, diagnostic and therapeutic contributions on the psychopathology and treatment of DMX can be summarized as follows:

- The clinical features of DMX and agitated depression can overlap, and intradepressive hypomanic symptoms must be considered.
- Hypomanic symptoms occurring during MDE are common and have been extensively reported in BD-I and BD-II.
- Hypomanic symptoms during MDE increase the risk of manic switch with antidepressant, rapid cycling, and also suicidal ideation and behaviors.
- The presence of hypomanic features might explain the infrequent occurrence during antidepressant treatment of a worsening of impulsivity, aggression, and suicidal ideation/gestures.
- Great caution should be used when prescribing antidepressants monotherapy and even in combination with atypical antipsychotics, especially in depressed patients exhibiting such hypomanic features.
- In the occurrence of a mixed state precipitated by antidepressant, discontinuation of treatment often improves the clinical presentation.
- The beneficial response to sedatives including mood stabilizers and antipsychotics appears to confirm the excitatory nature of such mixed presentations during bipolar depressive episodes.

Disclosures

The authors do not have anything to disclose.

REFERENCES:

1. Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. *Acta Psychiatr Scand Suppl*. 2007; **433**: 50–57.
2. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978; **35**(6): 773–782.
3. Swann AC, Lafer B, Perugi G, *et al*. Bipolar mixed states: an International Society for Bipolar Disorders task force report of symptom structure, course of illness, and diagnosis. *Am J Psychiatry*. 2013; **170**(1): 31–42.
4. Koukopoulos A, Faedda G, Proietti R, D'Amico S, de Pisa E, Simonetto C. Mixed depressive syndrome. *Encephale*. 1992; **18**(1): 19–21.
5. Sani G, Vöhringer P, Napoletano F, *et al*. Koukopoulos' diagnostic criteria for mixed depression: a validation study. *J Affect Disord*. 2014; **164**: 14–18.
6. Suppes T, Silva R, Cucchiaro J, *et al*. Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2016; **173**(4): 400–407.
7. Smith DJ, Forty L, Russell E, *et al*. Sub-threshold manic symptoms in recurrent major depressive disorder are a marker for poor outcome. *Acta Psychiatr Scand*. 2009; **119**(4): 325–329.
8. Zimmermann P, Brückl T, Nocon A, *et al*. Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. *Arch Gen Psychiatry*. 2009; **66**(12): 1341–1352.
9. Angst J, Cui L, Swendsen J, *et al*. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. *Am J Psychiatry*. 2010; **167**(10): 1194–1201.
10. Nusslock R, Frank E. Subthreshold bipolarity: diagnostic issues and challenges. *Bipolar Disord*. 2011; **13**(7–8): 587–603.

https://doi.org/10.1017/S1092852916000493 Published online by Cambridge University Press

11. McIntyre RS, Soczynska JK, Cha DS, *et al*. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: results from the International Mood Disorders Collaborative Project. *J Affect Disord*. 2015; **172**: 259–264.
12. Perugi G, Angst J, Azorin JM, *et al*. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry*. 2015; **76**(3): e351–e358.
13. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand*. 2014; **129**(1): 4–16.
14. Faedda GL, Marangoni C, Serra G, *et al*. Precursors of bipolar disorders: a systematic literature review of prospective studies. *J Clin Psychiatry*. 2015; **76**(5): 614–624.
15. Perlis RH, Ostacher MJ, Goldberg JF, *et al*. Transition to mania during treatment of bipolar depression. *Neuropsychopharmacology*. 2010; **35**(13): 2545–2552.
16. Frye MA, Helleman G, McElroy SL, *et al*. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry*. 2009; **166**(2): 164–172.
17. Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. *J Affect Disord*. 2005; **85**(3): 245–258.
18. Goldberg JF, Perlis RH, Ghaemi SN, *et al*. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry*. 2007; **164**(9): 1348–1355.
19. Fornaro M, Martino M, De Pasquale C, Moussaoui D. The argument of antidepressant drugs in the treatment of bipolar depression: mixed evidence or mixed states? *Expert Opin Pharmacother*. 2012; **13**(14): 2037–2051.
20. Sani G, Napoletano F, Vöhringer PA, *et al*. Mixed depression: clinical features and predictors of its onset associated with antidepressant use. *Psychother Psychosom*. 2014; **83**(4): 213–221.
21. Perlis RH, Cusin C, Fava M. Proposed DSM-5 mixed features are associated with greater likelihood of remission in out-patients with major depressive disorder. *Psychol Med*. 2014; **44**(7): 1361–1367.
22. Pacchiarotti I, Bond DJ, Baldessarini RJ, *et al*. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry*. 2013; **170**(11): 1249–1262.
23. Fornaro M, Stubbs B, De Berardis D, *et al*. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. *Int J Mol Sci*. 2016; **17**(2): 241.
24. Sachs GS, Nierenberg AA, Calabrese JR, *et al*. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007; **356**(17): 1711–1722.
25. Koukopoulos A, Sani G, Ghaemi SN. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). *Br J Psychiatry*. 2013; **203**(1): 3–5.
26. Michaux L, Saulnier M, Bureau G. A propos des Etats Mixtes. *Sem Hop Paris*. 1950; **83**: 4275–4286.
27. Campbell JD. Mixed and manic phases of manic-depressive psychosis. In. *Manic Depressive Disease*. Philadelphia: Lippincott; 1953.
28. Glassman AH. Depression, delusions, and drug response. *Am J Psychiatry*. 1975; **132**(7): 716–719.
29. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry*. 1979; **36**: 555–559.
30. Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr Neuropsychopharmakol*. 1980; **13**(4): 156–167.
31. Tondo L, Laddomada P, Serra G, Minnai G, Kukopulos A. Rapid cyclers and antidepressants. *Int Pharmacopsychiatry*. 1981; **16**(2): 119–123.
32. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. *Psychopharmacol Bull*. 1987; **23**(1): 68–73.
33. Faedda GL, Marangoni C, Reginaldi D. Depressive mixed states: a reappraisal of Koukopoulos' criteria. *J Affect Disord*. 2015; **176**: 18–23.

https://doi.org/10.1017/S1092852916000493 Published online by Cambridge University Press