CNS Spectrums (2017), **22**, 141–146. © Cambridge University Press 2016
doi:10.1017/S1092852916000547

REVIEW ARTICLE

Treatment of mixed features in bipolar disorder

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Mood episodes with *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5)–defined mixed features are highly prevalent in bipolar disorder (BD), affecting ~40% of patients during the course of illness. Mixed states are associated with poorer clinical outcomes, greater treatment resistance, higher rates of comorbidity, more frequent mood episodes, and increased rates of suicide. The objectives of the current review are to identify, summarize, and synthesize studies assessing the efficacy of treatments specifically for BD I and II mood episodes (ie, including manic, hypomanic, and major depressive episodes) with DSM-5–defined mixed features. Two randomized controlled trials (RCTs) and 6 post-hoc analyses were identified, all of which assessed the efficacy of second-generation antipsychotics (SGAs) for the acute treatment of BD mood episodes with mixed features. Results from these studies provide preliminary support for SGAs as efficacious treatments for both mania with mixed features and bipolar depression with mixed features. However, there are inadequate data to definitively support or refute the clinical use of specific agents. Conventional mood stabilizing agents (eg, lithium and divalproex) have yet to have been adequately studied in DSM-5–defined mixed features. Further study is required to assess the efficacy, safety, and tolerability of treatments specifically for BD mood episodes with mixed features.

Received 23 May 2016; Accepted 29 June 2016; First published online 13 September 2016

Key words: Antipsychotics, bipolar disorder, DSM-5, mixed episode, mixed features, mixed states, mood stabilizers.

Introduction

Bipolar disorder (BD) is a severe and persistent mental illness defined by the presence of recurrent mood episodes.[1] As per the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), BD is characterized by the presence of mood episodes, namely, major depressive, manic, hypomanic, and mixed episodes.[2] The previous DSM-IV-TR criteria for mixed episodes required the contemporaneous presence of a threshold manic and major depressive episode (MDE).[2] With the updated Fifth Edition of the DSM (DSM-5), significant changes were made to how mixed mood states were defined.[1]

Empirical evidence has revealed that the rare occurrence of fully meeting criteria for both mood states (ie, a DSM-IV-TR–defined mixed episode) lacked sufficient clinical utility to remain included in the diagnostic manual.[3–5] Rather, mood states in which a patient met criteria for *either* a MDE, manic episode, or hypomanic episode with *some* symptoms, but not necessarily meeting full criteria, of the opposite mood state had greater clinical and scientific relevance.[3–5] As such, the DSM-5 introduced the "with mixed features" specifier, which is defined by the presence of a mood episode wherein criteria for either a MDE or manic/hypomanic episode is met while simultaneously having 3 or more criteria from the opposite mood state. The mixed features specifier may have significant clinical relevance given that approximately 30–40% of patients with BD experience mood episodes with mixed features during the course of illness.[6–8] Moreover, mixed features are associated with more severe symptomatology, mood episode recurrence, higher rates of comorbidity, poorer clinical outcomes, and suicidality.[9–12]

Given the relative recency of this new nosological entity (May 2013), only a limited number of studies has directly examined the efficacy of treatments for mood states with DSM-5–defined mixed features.[13–22] Further, to date, only the Florida Medicaid Guidelines have specifically addressed the treatment of mixed features.[23] At the current time, inadequate evidence exists to adequately inform evidence-based treatment guidelines for mixed features in BD, as randomized controlled trials (RCTs) assessing the efficacy of various treatments specifically for BD mood

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episodes with mixed features have yet to be conducted. Numerous RCTs have assessed the efficacy of treatments of DSM-IV–defined mixed episodes[3,9,24–27]; however, the translational application of these results to the treatment of DSM-5–defined mixed features is speculative, as the DSM-IV overlaps but is distinctly different.

The objectives of the current article are to identify, summarize, and synthesize clinical studies specifically assessing the treatment of DSM-5–defined BD mood episodes (ie, including mania, hypomania, and bipolar depression) with mixed features. Of note, there is inadequate evidence for definitive evidence-based treatment recommendations; however, in the absence of rigorously controlled trial data, this review attempts to provide decision support until the execution of RCTs that may appropriately assess the efficacy of treatments specifically for DSM-5–defined mixed features.

Methods

The MEDLINE/PubMed and Google Scholar databases were searched from inception through April 2016 for peer-reviewed published studies assessing the efficacy of treatments for DSM-5–defined BD mood episodes with mixed features. The search was not limited to RCTs and included secondary and tertiary analyses, such as post-hoc analyses. Search strings included various combinations of the following terms: bipolar disorder (BD), mixed features, mixed episode, treatment, antipsychotic, anti-convulsant, mood stabilizer, antidepressant, olanzapine, risperidone, paliperidone, illoperidone, aripiprizole, asenapine, ziprazidone, lurasidone, quatiapine, haloperidol, clozapine, cariprazine, lithium, epival, valproate, carbamazepine, oxcarbazapine, lamotrigine, electroconvulsive therapy (ECT), psychotherapy, Interpersonal and Social Rhythm Therapy (IPSRT), cognitive behavioral therapy (CBT), and interpersonal therapy (IPT). Reference lists from included articles were also manually searched for additional pertinent references. Of note, primary studies assessing treatments of DSM-IV-TR-defined mixed episodes were not systematically retrieved or reviewed in the current article, as this has been done by numerous other authors previously[3,9,24–27] and the focus of the current article is on studies specifically evaluating the treatment of DSM-5–defined "mixed features" rather than DSM-IV-TR–defined "mixed episodes."

Results

Search results

The initial search to identify articles specifically assessing the efficacy of treatments of acute mood episodes with mixed features yielded 5 studies assessing treatments of bipolar depression with mixed features. Only 1 study was a primary RCT assessing treatment of depression with mixed features (using ziprasidone) a priori, while the remaining studies were post-hoc analyses assessing the efficacy of lurasidone, olanzapine, and the olanzapine-fluoxetine combination (OFC).[13–17] Three studies assessed the efficacy of treatment of manic/hypomanic episodes with mixed features with 2 post-hoc analyses assessing olanzapine and asenapine for mania with mixed features and 1 RCT assessing adjunctive quetiapine for hypomania with mixed features.[18–20]

Treatment of mania with mixed features

As summarized in Table 1, only 2 studies were identified that specifically assessed the treatment of DSM-5–defined mania with mixed features.[18,19] Both studies were post-hoc analyses identifying subjects with mania with mixed features retrospectively. McIntyre *et al*[18] conducted a post-hoc analysis using data from 2 identically designed 3-week, randomized, double-blind, flexible dose, placebo- and olanzapine referenced clinical trials (NCT00159744; NCT00159796) in patients with bipolar I disorder (BD-I). This post-hoc analysis used proxies for the DSM-5 mixed features specifier by using Montgomery–Åsberg Depression Rating Scale (MADRS) and Positive and Negative Syndrome Scale (PANSS) items. Of the 960 subjects analyzed, 34%, 18%, and 4.3% of patients, respectively, had ≥3 depressive features with mild (score ≥ 1 for MADRS items and ≥2 for PANSS item), moderate (score ≥ 2 MADRS, ≥3 PANSS), and severe (score ≥ 3 MADRS, ≥4 PANSS) symptoms. In all subjects with ≥3 depressive features and independent of treatment, the MADRS remission rate decreased with increasing severity. Young Mania Rating Scale (YMRS) remission was similar for mild and moderate patients (36–37%), but higher for severe patients (54%). In asenapine-treated subjects, the MADRS remission rate was stable regardless of baseline depressive symptom severity (range 64–67%), whereas remission decreased with increasing severity with olanzapine (63–38%) and placebo (49–25%). Reduction in YMRS was significantly greater for asenapine compared with placebo at day 2 across the 3 severity cut-offs and continued to decrease throughout the treatment period. The difference in YMRS change between olanzapine and placebo was only statistically significant in subjects with mild to moderate symptoms.

Tohen *et al*[19] pooled data from 3 placebo-controlled olanzapine studies in subjects with BD-I with a current manic or mixed episode (n = 228 olanzapine; n = 219 placebo). Subjects were categorized for mixed features by number of concurrent depressive symptoms at baseline (0, 1, and 2 [category A; without mixed features], and ≥3 [category B; with mixed features]). Least-squares mean change of YMRS total scores in categories A and B (olanzapine versus placebo) were –11.78 versus –6.86 and –13.21 versus –4.72, respectively, showing a greater

https://doi.org/10.1017/S1092852916000547 Published online by Cambridge University Press

TABLE 1. Clinical studies assessing the efficacy of acute treatments specifically for DSM-5–defined manic and hypomanic episodes with mixed features

Study (PMID)	Study design	Agent	Antidepressant effect	Anti-manic effect
Mania with mixed features				
McIntyre *et al*[18]	Post-hoc analysis from 2 3-week RCTs BD-I subjects (n = 960) Subjects sub-categorized by severity	Asenapine	Significant antidepressant effect with MADRS remission rates were stable regardless of baseline depressive symptom severity (remission range 64–67%) and consistently greater than placebo.	Reduction in YMRS scores was significantly greater compared with placebo at day 2 across the 3 severity cut-offs and continued to decrease throughout the 3-week trial.
		Olanzapine	Remission decreased with increasing depression severity (63–38%) and was similar to placebo with greater depressive severity.	Difference YMRS reduction between olanzapine and placebo was only statistically significant in mild and moderately symptomatic subjects.
Tohen *et al*[19]	Post-hoc analysis from 3 3-week RCTs of BD-I subjects (n = 447) subcategorized by mania with versus without mixed features	Olanzapine	For mania with or without mixed features, the olanzapine group had significantly greater mean decrease in HAMD score compared with placebo (p = 0.010, effect size = 0.25). Larger effect size in those with mixed features (effect size = 0.34) than without mixed features (effect size = 0.20).	Least-squares mean change of YMRS total scores in mania with mixed features showed a greater decrease for olanzapine (–13.21) versus placebo (–4.72) (p < 0.001).
Hypomania with mixed features				
Suppes *et al*[20]	RCT of 55 BD-II subjects with a stable medication regimen for ≥2 weeks and hypomania with mixed symptoms Subjects randomly assigned to receive adjunctive quetiapine (n = 30) or placebo (n = 25)	Adjunctive quetiapine	Adjunctive quetiapine demonstrated significantly greater improvement than placebo in Clinical Global Impression for Bipolar Disorder Overall Severity scores [F(1) = 10.12, p = .002] and MADRS scores [F(1) = 6.93, p = .0138].	No significant differences were observed for YMRS scores [F(1) = 3.68, p = .069].

RCT = randomized controlled trial; BD = Bipolar Disorder; MADRS = Montgomery–Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale; HAMD = Hamilton Depression Scale.

decrease in manic symptoms in subjects treated with olanzapine versus placebo. Subjects in the olanzapine-treated group compared with the placebo group experienced a greater decrease in YMRS total score for mania with or without mixed features ($p < 0.001$).

Treatment of hypomania with mixed features

Only one study was identified that assessed treatments specifically for hypomania with mixed features.[20] Participants included 55 BD-II subjects with a stable medication regimen for ≥2 weeks and hypomania with mixed symptoms (>12 on the YMRS and >15 on the MADRS at 2 consecutive visits 1–3 days apart). Participants were randomly assigned to receive adjunctive quetiapine (n = 30) or placebo (n = 25). Adjunctive quetiapine demonstrated significantly greater improvement than placebo in Clinical Global Impression for Bipolar Disorder Overall Severity scores [$F(1) = 10.12$, $p = .002$] and MADRS scores [$F(1) = 6.93$, $p = .0138$), but no significant differences were observed for YMRS scores [$F(1) = 3.68$, $p = .069$].[20] As such, the study suggested that either quetiapine is ineffective for treating hypomania with mixed features, or the study was underpowered.

McElroy *et al*,[28] while not exclusively studying hypomania with mixed features, conducted an RCT of divalproex in 60 subjects with hypomania or mild mania, including participants with mixed hypomania and mixed mania, which consisted of 55% of the study participants. In this 8-week RCT, divalproex monotherapy was shown to significantly reduce symptoms of mania/hypomania in subjects with or without mixed features compared to placebo. There was also a trend toward an antidepressant effect; however, this trend was not statistically significant, and the authors commented that the study was likely underpowered to detect an antidepressant effect.

Treatment of bipolar depression with mixed features

Only one prospective RCT was identified that evaluated treatment of bipolar depression with mixed features.[14] Four post-hoc analyses were identified that re-analyzed RCT data through retrospectively identifying subjects that would have met criteria for bipolar depression with mixed features.[13,15–17] All 5 studies assessed the efficacy of second-generation antipsychotics (SGAs), specifically ziprasidone, olanzapine, olanzapine-fluoxetine combination (OFC), and lurasidone. Of interest, 3 of the studies predated the publication of the DSM-5.[13–15] The results of these studies are discussed herein and are summarized in Table 2.

Patkar *et al*[14] conducted a double-blinded, placebo-controlled RCT comparing the efficacy of ziprasidone (40–160 mg/d) compared to placebo in the acute treatment of depression with mixed features after 6 weeks of

https://doi.org/10.1017/S1092852916000547 Published online by Cambridge University Press

TABLE 2. Clinical studies assessing the efficacy of acute treatment specifically for DSM-5–defined bipolar depression with mixed features

Study (PMID)	Study design	Agent	Antidepressant effect	Anti-manic effect
Benazzi *et al*[13]	Post-hoc analysis of an 8-week RCT of BD-I subjects with co-occurrence of a MDE and ≥2 manic symptoms treated with placebo (n = 355), olanzapine (n = 351), or OFC (n = 82)	Olanzapine	Response rates for olanzapine versus placebo had OR = 1.95 (95% CI, 1.14–3.34). Greater number of manic symptoms predicted lower response rates.	No difference in manic switch rate for OFC (6.8%) versus placebo (7.9%).
		OFC (olanzapine/fluoxetine doses: 6/25, 6/50, 12/50 mg/d)	Response rates of OFC versus olanzapine was OR = 2.00 (95% CI, 0.96–4.19) and OFC versus placebo, OR = 3.91 (95% CI, 1.80–8.49). Response rate was stable for OFC regardless of number of baseline manic symptoms.	No difference in manic switch rate for OFC (8.5%) versus placebo (7.9%).
Patkar *et al*[14] and Pae *et al*[15]	RCT of 73 subjects with BD-II or MDD with current MDE with 2 or 3 manic symptoms randomized to ziprasidone (40–160 mg/d) or placebo for 6 weeks Post-hoc analysis by Pae *et al* on same data	Ziprasidone	The primary outcome analysis indicated antidepressant efficacy of ziprasidone versus placebo (p = 0.0038). Efficacy was more pronounced in BD-II compared to MDD (p = 0.036). Post hoc analysis by Pae *et al* did not identify any other factors predictive of response.	Manic symptoms significantly decreased during trial; however, there was no statistically significant difference between the ziprasidone and placebo arm.
Tohen *et al*[16]	Post-hoc analyses of 2 3-week RCTs of BD-I subjects receiving olanzapine monotherapy (n = 690) versus placebo (n = 524) Categorized for mixed features by the number of concurrent manic symptoms at baseline (0, 1 or 2, and ≥3)	Olanzapine	Least-squares mean differences between olanzapine and placebo in the change of MADRS total scores was –3.44 (p = 0.002) for group with MDE with ≥3 manic symptoms with response rates greater for olanzapine (42%) versus placebo (33%). No significant interaction between mixed features and treatment was seen in the MADRS changes or response and remission rates.	The analysis of YMRS total score showed that the olanzapine group experienced a statistically significantly greater mean decrease compared with the placebo group in the total population with no differences in response based on number of manic symptoms.
McIntyre *et al*[17]	Post-hoc analysis of subjects with BD-I with MDE with mixed features in 6-week RCT of lurasidone (n = 186) versus placebo (n = 94) (The presence of mixed features was defined as YMRS score ≥ 4 at study baseline)	Lurasidone	Treatment with lurasidone (vs placebo) was associated with significantly greater reductions in MADRS scores in the mixed features group (–15.7 vs –10.9; P = .001; week 6; mixed model for repeated measures [MMRM]; effect size, 0.48).	There was no difference in manic switch rate from lurasidone (2.2%) versus placebo (3.2%) in group with depression with mixed features.

RCT = randomized controlled trial; MDE = Major Depressive Episode; MDD = Major Depressive Disorder; BD = Bipolar Disorder; OFC = olanzapine-fluoxetine combination; OR = odds ratio; MADRS = Montgomery–Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale; MMRM = mixed model for repeated measures.

treatment. Included in the study were subjects with a diagnosis of major depressive disorder (MDD) or BD-II with a current MDE while also meeting 2 or 3 (but not more nor less) DSM-IV–defined manic criteria. After 3 weeks, the ziprasidone group (n = 38) had a statistically and clinically significant improvement in depression severity (as indicated by change in MADRS scores), which was sustained until the end of the 6-week trial. There was not a statistically significant difference in change in the Mania Rating Scale (MRS) when comparing placebo to ziprasidone. Interestingly, antidepressant efficacy was more pronounced in BD-II subjects compared to MDD subjects (p = 0.036). Of note, Pae *et al*[15] conducted a post-hoc analysis of the same study in an attempt to determine mediating factors that may predict efficacy; however, they were unable to identify any statistically significant factor.

All other identified studies were post-hoc analyses of previous RCTs in which subjects with bipolar depression with mixed features were retrospectively identified. The first study, by Benazzi *et al*,[13] assessed the efficacy of OFC versus olanzapine versus placebo. They conducted a post-hoc analysis of an 8-week, double-blind RCT of adult bipolar I patients depression treated with placebo (n = 355), olanzapine (5–20 mg/d; n = 351), or OFC (olanzapine/fluoxetine doses: 6/25, 6/50, 12/50 mg/d; n = 82). Bipolar depression with mixed features was defined as the co-occurrence of a MDE and ≥2 manic/hypomanic symptoms. In this analysis, both olanzapine and OFC had greater antidepressant effects compared to placebo by the end of the 8-week trial. Comparing OFC to olanzapine alone, OFC had a non-statistically significant trend of greater response rates [odds ratio (OR) = 2.00 (95% CI, 0.96–4.19)].

Tohen *et al*[16] also conducted a post-hoc analysis by pooling data from 2 placebo-controlled olanzapine studies in patients with bipolar I depression [olanzapine monotherapy (n = 690) and placebo (n = 524)]. Subjects were categorized for mixed features by the number of concurrent manic symptoms at baseline (0, 1 or 2, and ≥3, respectively, as measured by a YMRS item score ≥ 1). As per DSM-5 criteria, subjects with ≥3 manic symptoms would qualify for mixed features. Least-squares mean differences between olanzapine and placebo in the change of MADRS total scores were –3.76 (p = 0.002), –3.20 (p < 0.001), and –3.44 (p = 0.002) for mixed features 0, 1 or 2, and ≥3, respectively, suggesting that olanzapine monotherapy was equally efficacious for bipolar depression with or without mixed features.

McIntyre *et al*[17] conducted another post-hoc analysis evaluating the efficacy of lurasidone versus placebo for subjects with bipolar I depression with mixed features as defined by a MADRS score ≥ 20 and YMRS score between 4 and 12. Subjects were randomly assigned to 6 weeks of double-blind, once-daily treatment with lurasidone 20–120 mg (n = 182) or placebo (n = 90). Treatment with lurasidone compared to placebo was associated with significantly greater reductions in MADRS scores in the mixed features group (–15.7 vs –10.9; p = 0.001; week 6; mixed model for repeated measures [MMRM]; effect size, 0.48). As such, lurasidone was found to be an efficacious antidepressant treatment for bipolar I depression with mixed features and was notably not associated with treatment-emergent mania/hypomania.

Taken together, a limited number of studies has suggested that SGAs may be efficacious treatments of bipolar depression with mixed features, as they lower the severity of both depressive and manic symptoms. Certainly the data discussed have the significant limitation of being secondary analyses, and these finding require further confirmation in RCTs that are designed to assess the efficacy and safety of treatments specifically in bipolar depression with mixed features with this treatment group defined *a priori*.

Conclusion

Mixed features are common in BD, affecting approximately 40% of patients during the course of illness.[6–8] Mixed states are associated with elevated rates of relapse, suicide, comorbidity, and treatment resistance.[9–12] This review article invites the need for adequately powered clinical trials that seek to determine the efficacy, safety, and tolerability of psychotropic agents in mania, hypomania, or depression with mixed features. At the current time, only a limited number of studies has assessed the efficacy of treatments *specifically* for mood disorders with DSM-5–defined mixed features. The current review identified a small number of RCTs and post-hoc analyses evaluating the efficacy of SGAs in the treatment of mood episodes with mixed features. The identified studies suggested that SGAs outperformed placebo in the acute treatment of mania and depression with mixed features. Conventional mood stabilizers (eg, lithium and divalproex) may also be of interest; however, they have not yet been adequately assessed in subjects with DSM-5–defined mixed features.

Post-hoc analyses suggest that olanzapine and asenapine may be efficacious treatments of mania with mixed features.[18,19] One small RCT suggested that adjunctive quetiapine for hypomania with mixed features improved symptoms of depression; however, it did not have a significant improvement in symptoms of hypomania compared to the placebo group.[20] For bipolar depression with mixed features, post-hoc analyses suggested antidepressant efficacy of olanzapine, OFC, and lurasidone compared to placebo.[13,16,17] One RCT showed antidepressant efficacy for ziprasidone in the acute treatment of a MDE with mixed features in subjects with BD-II or MDD, with a greater antidepressant effect in subjects with BD-II.[14]

https://doi.org/10.1017/S1092852916000547 Published online by Cambridge University Press

Taken together, SGAs show great promise for alleviating symptoms of both mania and depression in BD with mixed features. The preliminary efficacy of SGAs in mixed features comports with findings assessing treatments of DSM-IV-TR–defined mixed episodes. However, the low number of studies specific for DSM-5–defined mixed features and the paucity of RCTs limit the generalizability of the current results. Other SGAs and conventional mood stabilizers are also of interest. Prospective studies with *a priori* hypotheses regarding efficacy of treatments specifically for bipolar disorder with DSM-5–defined mixed features are required to assess the efficacy, safety, and tolerability of treatments to adequately inform future treatment guidelines. Studies assessing the pathophysiology of mixed states may also inform future novel treatments that may target etiologic factors specific to mixed states.

Disclosures

Joshua D. Rosenblat has no conflicts of interest to declare. Roger S. McIntyre has received research grant support from Lundbeck, Astra Zeneca, Pfizer, Shire, Otsuka, Bristol Myers Squibb, National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. He has also received speaker/consultant fees from Lundbeck, Pfizer, Astra Zeneca, Elli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol Myers Squibb, and Shire.

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