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BIPOLAR DISORDERS (R HIRSCHFELD, SECTION EDITOR)

Treatment of Mixed Features in Bipolar Disorder: an Updated View

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Abstract

Purpose of Review Mixed presentations in bipolar disorder have long posed clinical and nosological challenges. The DSM-5 mixed features specifier was developed to provide a more flexible and clinically relevant definition of mixed presentations compared with narrowly defined DSM-IV mixed episodes. However, there is little guidance on treating such presentations. Here, we summarize the evidence for biological treatments of DSM-5 and similarly defined mixed features (MFs).

Recent Findings The literature on treating MFs is almost exclusively based on post hoc analyses. Within this limited evidence base is preliminary positive data for aripiprazole, asenapine, cariprazine, olanzapine, risperidone, and ziprasidone in treating acute mania with MFs, and cariprazine, lurasidone, olanzapine, and ziprasidone for depressive symptoms in depression with MFs. Divalproex may also be efficacious for acute mania with MFs. The few extant maintenance studies suggest that divalproex and olanzapine may have long-term efficacy in those with index MFs or for the prevention of MFs, respectively.

Summary The existing evidence suggests that clinicians consider atypical antipsychotics and divalproex for treating acute mixed presentations. However, adequately powered treatment trials—and studies of maintenance and neurostimulation therapies—are needed. Additionally, data-driven techniques to identify relevant symptom clusters may help improve our conceptualization of mixed presentations.

Keywords Mixed features · Mixed episodes · Bipolar disorder · DSM-5 · Mood stabilizer · Antipsychotic

Introduction

The treatment of mixed symptoms in bipolar disorder has long been a clinical challenge, not least because the definition of mixed symptoms has been under constant debate and revision [1]. Recently, the DSM-5 departed from the rigidly defined DSM-IV mixed episode criteria, taking on a more flexible "mixed categorical-dimensional" approach [1]. Though by no means universally accepted, DSM-5 criteria were seen by many as an improvement in modern understanding and recognition of mixed symptoms [2]. However, such a dramatic shift requires a critical revision of the extant literature on mixed symptoms, much of which is based on DSM-IV definitions. The purpose of this review is to discuss the evolution, clinical features, and evidence for treatment of mixed features in bipolar disorder. Our aim is to orient the clinician to the existing literature on the treatment of DSM-5 and similar conceptualizations of mixed symptoms, while highlighting the gaps in our knowledge.

Historical Context

Over the past century, the conceptualization of mixed states in bipolar disorders has undergone a significant—albeit somewhat circular—evolution [1]. Weygandt, a junior colleague of Kraepelin, formalized the concept in his 1899 monograph *On the Mixed States of Manic-Depressive Insanity* [3]. He described what might be called a dimensional model, wherein mixed states consisted of various combinations of dysfunction in the domains of associative thinking, psychomotor activity, and affect [3]. For example, "agitated depression" was described as a common form of a mixed state consisting of lowered affect and increased psychomotor activity. Importantly, Weygandt and Kraepelin saw mixed states as a frequent manifestation of manic-depressive illness [1, 3]. Thus, at the infancy of modern psychiatric nosology, mixed

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states were dimensionally defined, recognized as common, and understood to be phenotypically varied.

This view of mixed states shifted in the mid to late twentieth century. The DSM-I and DSM-II loosely defined mixed states as combining manifestations of mania and depression [4]. However, the DSM-III codified the separation of bipolar and unipolar affective disorders, and specified symptom and time duration for diagnoses [5]. The DSM-IV would extend this hardening of diagnostic criteria to mixed episodes, defining them as the presence of concurrent, fully syndromal manic and depressive symptoms for at least 1 week [5].

This narrow categorical definition was a clear departure from original conceptualizations of mixed states, and did not accord with clinical observations that mixed presentations commonly manifested as the presence of a few concurrent symptoms of the opposite polarity [2]. Concurrent subsyndromal symptoms also appeared to have therapeutic and prognostic implications. Mild manic symptoms in bipolar depression were associated with treatment-emergent hypo/mania with adjunctive antidepressant therapy [6]; subsyndromal concurrent symptoms were also associated with increased suicidality, increased substance comorbidity, and poorer treatment response [7]. Thus, it was argued that DSM-IV did not reflect what was seen in clinical practice and failed to capture a subset of patients who urgently required identification and more intensive clinical care.

Current Day: DSM-5 Criteria, Prevalence, and Clinical Correlates

To address some of these concerns, the DSM-5 (2013) adopted a more flexible definition, wherein a "mixed features" specifier could be added to a manic, hypomanic, or depressive episode [8]. This specifier required that ≥ 3 non-overlapping symptoms of the opposite pole be present most days, a significant expansion of the DSM-IV definition. These criteria closely reflected an operational definition of "dysphoric mania" proposed over 20 years earlier [9], which suggested that ≥ 3 concurrent depressive symptoms were indicative of "dysphoric mania," and >2 symptoms indicative of "probable" dysphoric mania. These "intermediate" criteria reflected observations that affective states with subsyndromal opposite polarity symptoms appeared to be distinct entities [9, 10].

Mixed features as defined by the DSM-5 appear to be relatively common. While prevalence estimates of DSM-III/IV-defined mixed episodes in bipolar disorder range from 6.7 to 28% [11], a 2018 meta-analysis ($n = 17$) found a pooled cross-sectional prevalence of 33.5% (95% CI 31.0–36.1) and 30.0% (95% CI 25.9–34.4) bipolar depressive and hypomanic/manic episodes, respectively, meeting DSM-5 mixed features criteria [12••]. Similar to previous studies examining patients with DSM-IV mixed episodes [13], patients with DSM-5-defined mixed features also display higher rates of comorbid substance use and anxiety disorders [14, 15], earlier age of onset [16], higher rates of suicidal ideation and/or suicidal behaviors [17], increased self-reported physical aggression [18], and more time symptomatic over long-term follow-up [19•].

Treatment of Mixed Features

Thus, DSM-5-defined mixed features (DSM-5 MF) appear to be a common clinical variant requiring swift identification and intensive treatment. However, there has been little synthesis of the evidence regarding treatment of DSM-5 MF. While many reviews have summarized evidence for pharmacological treatment of mixed episodes, few have exclusively examined data from studies using DSM-5 criteria. A 2013 meta-analysis of 9 randomized controlled trials (RCTs) examining the efficacy of atypical antipsychotics (AAPs) in DSM-IV-defined acute mixed episodes found that AAPs, either as monotherapy or adjunctive to mood stabilizers, were more effective than placebo in treating both manic and depressive symptoms [20]. A systematic review of pharmacological treatment of mixed episodes (DSM-IV and DSM-III) and mixed features (DSM-5) found that, of the 18 included studies, only 7 examined pharmacotherapy exclusively in mixed states and the remainder were subgroup analyses [21••]. Given the paucity of data and heterogeneity of results, the authors refrained from drawing any conclusions for clinical practice. The World Federation of Societies of Biological Psychiatry (WFSBP) recently published guidelines on the biological treatment of mixed states in bipolar disorder [22]. The authors found evidence for olanzapine, paliperidone, and aripiprazole in treating manic symptoms in acute mixed states. For maintenance treatment after an index-mixed episode, quetiapine, lithium, and olanzapine (monotherapy or adjunctive) had best evidence for preventing any mood episode. However, this review again collated studies using a variety of mixed episode/mixed state definitions, predominantly DSM-IV. A more recent meta-analysis examined the efficacy of AAPs in the treatment of acute bipolar depression with DSM-5 MF or similar (i.e., 2–3 concurrent manic symptoms) criteria [23]. Seven studies (6 RCTs and 1 open-label placebo-control trial) were included, with results indicating the superior efficacy of AAPs over placebo in treating both depressive and manic symptoms in bipolar depression with mixed features.

The extant reviews on treatment of mixed states in bipolar disorder thus seem to suggest efficacy for AAPs to reduce manic and depressive symptoms. However, the evidence base has a number of problems, including limited number of studies and the majority of data being derived from post hoc analyses of treatment trials. Additionally, most of these reviews have been based largely or solely on studies using DSM-IV-

defined mixed episodes. Optimal treatment approaches for DSM-5 MF thus remain unclear.

The following section summarizes evidence from biological treatment trials (i.e., pharmacotherapy and neurostimulation) in a patient population meeting criteria for DSM-5 MF. To provide a comprehensive overview, we were purposely broad in the type of studies that we reviewed, encompassing double blind randomized controlled trials (DB-RCT), open-label trials, and post hoc analyses. As a broader definition of mixed states had been proposed for many years leading up to the DSM-5, we also here include studies that use operational definitions which approximate this "intermediate" (i.e., mild or subsyndromal symptoms of the opposite polarity) conceptualization of mixed features [9]. Though not identical to the DSM-5 criteria, data from studies using similar "intermediate" formulations may still provide useful guidance for clinicians.

Mania With Mixed Features

Since 2013, 3 analyses have examined the efficacy of medication treatment in acutely manic patients with DSM-5 MF. All 3 applied post hoc proxy criteria (i.e., a score of > 1 on 3 or more Montgomery-Asberg Depression Rating Scale [MADRS] items) to DB-RCTs of AAPs (see Table 1). Four pre-DSM-5 post hoc analyses (3 of AAPs and another of lithium/valproate) examined the efficacy of treatment in participants with at least mild or subsyndromal baseline depressive symptoms.

The first post hoc analysis of DSM-5 MF pooled results from 2 pivotal olanzapine and placebo controlled RCTs of asenapine for acute mania [24]. Previous analyses of participants with DSM-IV-defined mixed episodes in these trials found that asenapine resulted in significant mania and depression symptom reduction after 3 weeks [25, 26] [27]. Asenapine-treated patients with DSM-5 MF ($n = 117$) similarly experienced significant reductions in mania severity and had a higher rate of remission from depressive symptoms compared with placebo ($n = 76$). These findings held true regardless of the severity of the initial depressive symptoms.

This same analysis also examined efficacy in the olanzapine treatment arm. Olanzapine treatment ($n = 135$) resulted in significantly reduced mania symptom severity compared with placebo in patients with DSM-5 MF, but did not result in higher depression remission rates [24]. Additionally, mania symptom reductions in those treated with olanzapine were only significant in those with mild to moderate, and not severe, baseline depressive symptoms. Another post hoc analysis of 3 DB-RCTs found that olanzapine in acutely manic patients with DSM-5 MF ($n = 66$) resulted in significantly reduced mania severity, as well as increased rates of mania symptom response and remission, compared with placebo ($n = 59$) [28]. There was a numerical reduction in depression symptom severity that did not reach statistical significance (effect size = 0.34).

Lastly, a post hoc analysis of 3 DB-RCTs found that acutely manic patients with DSM-5 MF receiving cariprazine ($n = 79$) experienced significant reductions in mania symptom severity compared with placebo ($n = 62$) [29]. This was true when less stringent mixed features definitions (i.e., ≥ 2 concurrent depressive symptoms or MADRS ≥ 10) were applied. However, only the two more permissive criteria resulted in significant differences in mania response/remission rates and in reductions in depression scores. This lack of statistical significance may have been due to the smaller size of the DSM-5 MF group, as the effect sizes were similar between participants with DSM-5 MF and baseline MADRS ≥ 10.

Pre-DSM-5, 2 post hoc analyses examined the efficacy of AAPs in acutely manic participants with mild concurrent depressive symptoms. Using data from 2 DB-RCTs, aripiprazole treatment in patients with concurrent mild depressive symptoms (MADRS scores of 9–18) resulted in significant reductions in mania symptoms compared with placebo [30]. Another post hoc analysis of a 24-week open-label trial of adjunctive risperidone found that acutely manic BDI patients with a Hamilton Depression Rating Scale (HAM-D) score ≥ 10 at baseline experienced significant and sustained reductions in manic and depressive symptom severity [31]. Another post hoc analysis of 2 DB-RCTs in acute mania found that patients with ≥ 2 depressive symptoms at baseline [32] treated with ziprasidone ($n = 124$) displayed a significant reduction in depressive and manic symptoms compared with the placebo group ($n = 55$), and a higher proportion of participants who concurrently remitted from manic and depression symptoms.

Lastly, a 1997 post hoc analysis of a placebo controlled DB-RCT of lithium versus divalproex found that patients with ≥ 2 depressive symptoms at baseline treated with lithium showed no or slight worsening of manic symptoms compared with placebo, while patients with "classic" mania significantly improved with lithium treatment [33]. However, participants treated with divalproex showed a similar level of response regardless of whether they had "classic" or mixed symptoms. There was a significant treatment × manic type interaction, such that divalproex treated patients with mixed features showed significantly more improvement than those treated with lithium.

Hypomania With Mixed Features

In one of the only DB-RCTs that recruited exclusively participants with mixed symptoms, Suppes et al. (2013) investigated the effect of quetiapine (either monotherapy or adjunctive) in 55 patients with bipolar II disorder, currently hypomanic with mixed symptoms [34]. Mixed symptoms was defined as concurrent scores on the Young Mania Rating Scale (YMRS)

Table 1 Studies examining pharmacological and neurostimulation therapies for acute and maintenance treatment of DSM-5 and similarly defined mixed features in bipolar disorder

Study	Treatment	Study population	Mixed state definition	Study design	Sample size (mixed features only)	Treatment duration	Outcome measures	Results
Mania with mixed features								
McIntyre et al. [24]	Asenapine (ASE) Olanzapine (OLZ)	BDI, currently manic	≥3 non-overlapping concurrent depressive symptoms (DSM-5)	Post hoc analysis of 2 PBO/OLZ controlled DB-RCTs	$n = 76$ PBO $n = 117$ ASE $n = 135$ OLZ	3 weeks	YMRS reduction MADRS remission (MADRS ≤ 12)	ASE > PBO OLZ > PBO ASE > PBO
McIntyre et al. [29]	Cariprazine (CAR)	BDI, currently manic (participants with MADRS ≥ 18 excluded)	≥3 non-overlapping concurrent depressive symptoms (DSM-5)	Post hoc analysis 3 PBO controlled DB-RCTs	$n = 62$ PBO $n = 79$ CAR	3 weeks	YMRS reduction YMRS response (≥ 50% reduction) YMRS remission (YMRS ≤ 12) MADRS reduction	CAR > PBO CAR = PBO (numerically higher rate in CAR group) CAR = PBO (numerically higher rate in CAR group) CAR = PBO (numerical reduction in CAR group)
Tohen et al. [28]	Olanzapine (OLZ)	BDI, currently manic, or mixed	≥3 non-overlapping concurrent depressive symptoms (DSM-5)	Post hoc analysis of three PBO controlled DB-RCTs	$n = 66$ PBO $n = 59$ OLZ	3 weeks	YMRS reduction HAM-D reduction YMRS response (≥50% reduction) YMRS remission (YMRS ≤12)	OLZ > PBO OLZ = PBO (numerical reduction in OLZ group) OLZ > PBO OLZ > PBO
Stahl et al. [32]	Ziprasidone (ZIP)	BDI, currently manic, or mixed	≥2 concurrent depressive symptoms	Post hoc analysis of 2 PBO controlled DB-RCT	$n = 124$ ZIP $n = 55$ PBO	3 weeks	HAM-D reduction MRS reduction MRS response (≥ 50% reduction MRS) Remission (MRS ≤ 10 and HAM-D ≤ 8) CGI-S PANSS	ZIP > PBO ZIP > PBO ZIP > PBO ZIP > PBO ZIP > PBO ZIP > PBO PANSS total and positive
Suppes et al. [30]	Aripiprazole (ARI)	BDI, currently manic, or mixed	Concurrent MADRS 9–18	Post hoc analysis of 2 PBO controlled DB-RCTs	$n = 112$ PBO $n = 123$ ARI	3 weeks	YMRS reduction YMRS Response (≥ 50% reduction) Remission (YMRS ≤ 12)	ARI > PBO ARI > PBO ARI > PBO
Swann et al. [33]	Lithium (Li) Divalproex (DVP)	BDI, currently manic	≥2 concurrent depressive symptoms	Post hoc analysis of PBO controlled, DB-RCT	$n = 68$ DVP $n = 35$ Li $n = 73$ PBO (sample size of original trial)	3 weeks	MRS reduction MSS reduction	Li = PBO DVP > PBO, DVP > LI Li = PBO DVP> PBO, DVP > LI
Woo et al. [31]					$n = 44$	24 weeks	YMRS reduction	RIS > PBO

Table 1 (continued)

Study	Treatment	Study population	Mixed state definition	Study design	Sample size (mixed features only)	Treatment duration	Outcome measures	Results
	Adjunctive risperidone (RIS)	BDI, currently manic, or mixed	HAM-D at enrollment ≥ 10	Open-label, uncontrolled flexibly dosed RIS adjunctive to mood stabilizer			BPRS reduction HAM-D reduction CGI-BP reduction GAS improvement	RIS > PBO RIS > PBO RIS > PBO RIS > PBO
Hypomania with mixed features								
Suppes et al. [34]	Quetiapine (QUE) monotherapy or adjunctive	BDII, currently hypomanic with mixed symptoms	YMRS ≥ 12 and MADRS ≥ 15	PBO controlled RCT	$n = 30$ QUE $n = 25$ PBO	8 weeks	CGI-BP reduction CGI-BP response (≥ 50% reduction) CGI-BP remission (CGI ≤ 2) MADRS reduction YMRS reduction MADRS/YMRS response (≥ 50% reduction in both) MADRS/YMRS remission (MADRS ≤ 7 and YMRS < 8)	QUE > PBO QUE = PBO (numerically higher rate in QUE group) QUE = PBO (numerically higher rate in QUE group) QUE > PBO QUE = PBO QUE = PBO (numerically higher rate in QUE group) QUE = PBO (numerically higher rate in QUE group)
Depression with mixed features								
Benazzi et al. [36]	Olanzapine (OLZ) Olanzapine-fluoxetine combination (OFC)	BDI, currently depressed	≥ 2 concurrent manic symptoms	Post hoc analysis of PBO controlled DB-RCT	$n = 37$ OFC $n = 173$ OLZ $n = 166$ PBO	8 weeks	Response (≥ 50% reduction in MADRS and < 2 concurrent manic/hypomanic symptoms)	OFC > PBO OLZ > PBO OFC = OLZ (trend towards OFC)
Goldberg et al. [40]	Adjunctive antidepressant (AD)	BDI, BDII or BD-NOS, currently depressed	≥ 2 baseline concurrent manic symptoms	Naturalistic, observational study (STEP-BD)	$n = 145$ AD $n = 190$ no AD	3 months	Clinical monitoring form (CMF, semistructured interview) Recovered (CMF ≤ 2 affective symptoms for ≥ 8 weeks) or recovering (CMF ≤ 2 affective symptoms for ≥ 4 weeks	AD = no AD in time to achieve recovered recovering status
McIntyre et al. [37]	Lurasidone (LUR)	BDI, currently depressed (participants with YMRS > 12 excluded)	YMRS ≥ 4 at baseline	Post hoc analysis of PBO controlled DB-RCT	$n = 182$ LUR $n = 90$ PBO	6 weeks	MADRS reduction MADRS response MADRS remission (MADRS ≤ 12) CGI-BP-S depression reduction YMRS reduction	LUR > PBO LUR > PBO LUR > PBO LUR > PBO LUR = PBO

Table 1 (continued)

Study	Treatment	Study population	Mixed state definition	Study design	Sample size (mixed features only)	Treatment duration	Outcome measures	Results
McIntyre et al. [38]	Cariprazine (CAR)	BDI, currently depressed (participants with YMRS ≥ 10–12 excluded)	YMRS ≥ 4 at baseline	Post hoc analysis of 3 PBO controlled DB-RCTs	*n* = 262 PBO *n* = 275 CAR 1.5 mg po daily *n* = 271 CAR 3 mg po daily	6 weeks	MADRS reduction	CAR > PBO both dosage groups
							MADRS response (≥ 50% reduction in MADRS)	CAR > PBO both dosage groups
							MADRS remission (MADRS ≤ 10)	CAR > PBO both dosage groups
							CGI-S remission (CGI-S ≤ 2)	CAR > PBO both dosage groups
							CGI-S reduction	CAR > PBO both dosage groups
							YMRS reduction	CAR = PBO both dosage groups
Patkar et al. [39]	Ziprasidone (ZIP)	MDD or BDII, currently depressed	2 or 3 concurrent manic symptoms	PBO controlled DB-RCT	*n* = 35 ZIP (19 with BDII) *n* = 38 PBO (24 with BDII)	6 weeks	MADRS reduction	ZIP > PBO
							MRS reduction	ZIP = PBO
							CGI-BP reduction	ZIP = PBO
							Response (≥ 50% reduction in MADRS and MRS)	ZIP > PBO
							Remission (MADRS < 10 and YMRS < 12)	ZIP > PBO
Tohen et al. [35]	Olanzapine (OLZ)	BDI, currently depressed	≥ 3 concurrent non-overlapping manic symptoms (DSM-5)	Post hoc analysis of two PBO controlled DB-RCTs	*n* = 72 PBO *n* = 73 OLZ	6 weeks	MADRS reduction	OLZ > PBO
							MADRS response (≥ 50% reduction)	OLZ = PBO (numerically higher rate in OLZ group)
							MADRS remission (MADRS ≤ 12)	OLZ > PBO
							YMRS change	OLZ > PBO
Maintenance: index episode with mixed features								
Bowden et al. [41]	Lithium (Li) Divalproex (DVP)	BDI, recovered from index manic episode	Depressed mood and ≥ 1 additional depressive symptom during index episode	Post hoc analysis of PBO controlled maintenance DB-RCT	*n* = 63 PBO *n* = 117 DVP *n* = 69 Li	52 weeks	Time to any mood episode	DVP = LI = PBO
							Time in study	DVP = LI = PBO
							Time to any mood episode or premature discontinuation (joint tolerability/efficacy measure)	DVP > Li
							Premature discontinuation	DVP = LI = PBO DVP = LI > PBO

Table 1 (continued)

Study	Treatment	Study population	Mixed state definition	Study design	Sample size (mixed features only)	Treatment duration	Outcome measures	Results
							Premature discontinuation due to intolerance	
Maintenance: prevention of episodes with mixed features								
Tohen et al. [42]	Lithium (Li) Olanzapine (OLZ)	BDI, recovered from index manic/mixed episode	Subsyndromal mixed: YMRS 6–15 and HAM-D 7–17 Syndromal mixed: HAM-D ≥ 18 and YMRS ≥ 16	Post hoc analysis of maintenance DB-RCT	$n = 214$ Li $n = 217$ OLZ	48 weeks	Days in mood state	Li > OLZ subsyndromal mixed state Li = OLZ syndromal mixed state
Neurostimulation								
Palma et al. [45]	≥ 2 ECT treatments (bifrontal or bitemporal)	Treatment-resistant BD patients (depressed, mixed and manic)	McElroy's (mania/hypomania episode plus ≥ 3 depressive symptoms) & Akiskal's criteria (major depressive episode plus 2–3 manic/hypomanic symptoms)	Retrospective study/chart review	$n = 15$ (mixed) $n = 22$ (depressed) $n = 4$ (manic)	Acute treatment and follow-up (range 10.1–249.9 weeks)	CGI-S	All treatments but one in a mixed state patient showed positive clinical response

BDI, bipolar I disorder; *BDII*, bipolar II disorder; *BD-NOS*, bipolar disorder not otherwise specified; *BPRS*, Brief Psychiatric Rating Scale; *CGI-S*, clinical global impression-severity; *CGI-BP*, clinical global impression for bipolar disorder; *DB-RCT*, double-blind randomized controlled trial; *GAS*, Global Assessment Scale; *HAM-D*, Hamilton Depression Rating Scale; *MADRS*, Montgomery-Asberg Depression Rating Scale; *MRS*, Mania Rating Scale; *MSS*, Manic Syndrome Subscale; *PANSS*, Positive and Negative Syndrome Scale; *PBO*, placebo; *YMRS*, Young Mania Rating Scale

of ≥ 12 and MADRS ≥ 15. Participants treated with quetiapine experienced significant reductions in overall symptom severity and depression symptom severity compared with placebo. The two groups however did not statistically differ in rates of response or remission, or in reductions in mania symptom severity.

Depression With Mixed Features

Only one analysis was identified that specifically examined treatment efficacy in acute depression with DSM-5 MF. This post hoc analysis of 2 DB-RCTs of olanzapine found that acutely depressed BDI patients with 0, 1–2, or ≥ 3 non-overlapping concurrent manic symptoms (DSM-5 criteria; $n = 73$ olanzapine, $n = 72$ placebo) all experienced significant and comparable reductions in depression and manic symptom severity [35]. Olanzapine-treated patients with DSM-5 MF had a significantly higher proportion of participants remitting from depressive symptoms compared with placebo.

Another post hoc analysis of a DB-RCT compared the efficacy of 8 weeks of olanzapine versus olanzapine-fluoxetine combination (OFC) in BDI depression with ≥ 2 concurrent baseline hypo/manic symptoms [36]. Participants with mixed features receiving OFC ($n = 37$) or olanzapine ($n = 173$) both had significantly higher proportion of responders (defined as ≥ 50% reduction in depression symptom scores and < 2 concurrent hypo/manic symptoms) compared with placebo ($n = 166$). There was a trend for superiority in the OFC group compared with the olanzapine group in percentage of responders. A similar percentage of mixed (43.2%) and non-mixed (48.9%) depressed participants responded to OFC treatment, while the proportion of participants with mixed depression receiving olanzapine or placebo had significantly lower response rates compared with those with non-mixed depression (26.5 versus 39.9% for olanzapine; 16.3 versus 27.5% for placebo). Interestingly, there were no differences in the rates of affective switching amongst the three arms (ranging from 6.8 to 8.5% after 8 weeks).

McIntyre et al. (2015) conducted a post hoc analysis of a DB-RCT of 6 weeks of lurasidone treatment for acute bipolar I depression, operationalizing mixed features as a baseline YMRS ≥ 4 [37]. Participants with YMRS > 12 at baseline were excluded in the original study design. Participants with mixed features experienced significant reductions in depression symptom severity compared with placebo, as well as higher response/remission rates. Lurasidone did not differentiate from placebo in improving concurrent manic symptoms. A secondary analysis found that a patient group meeting an alternate definition of mixed features (a score of ≥ 2 on at least 2 YMRS items) also experienced significant reductions in depression symptom severity with lurasidone treatment versus placebo.

Another post hoc analysis of 3 DB-RCTs of acute BDI depression found that cariprazine resulted in significant reductions in depressive symptoms in patients with baseline YMRS ≥ 4 [38]. Cariprazine also resulted in higher depression response/remission rates, as well as significant reductions in overall symptom severity. Reductions in manic symptoms did not significantly differ from placebo; once again, however, the original trials excluded participants with elevated YMRS scores at baseline, potentially limiting ability to detect significant treatment-related changes in this measure.

In the only DB-RCT specifically designed to assess depression with mixed features, Patkar et al. (2012) enrolled 73 currently depressed participants with MDD or BDII and 2–3 concurrent manic symptoms [39]. Participants treated with 6 weeks of ziprasidone showed significant reductions in depression symptom severity and higher response/remission rates from both depression and manic symptoms, compared with placebo. There was a significant diagnosis × treatment interaction, indicating that participants with BDII experienced greater benefit with treatment compared with participants with MDD.

An observational study of the naturalistically treated STEP-BD cohort evaluated the efficacy of antidepressants (including bupropion, SSRIs, venlafaxine, mirtazapine, nefazodone, and nortriptyline) adjunctive to mood stabilizers/atypical antipsychotics in acutely depressed BD patients with ≥ 2 concurrent manic symptoms [40]. There was no difference in time to recovery between patients treated with or without adjunctive antidepressants; furthermore, antidepressant use was associated with higher YMRS scores at 3 months in patients with mixed features.

Maintenance Treatment

Data regarding long-term treatment of patients following recovery from an index episode of DSM-5 MF or similarly defined mixed features, or the long-term prevention of such symptoms, is sparse.

A post hoc analysis of a 52-week maintenance DB-RCT of lithium versus divalproex for patients recovered from an index manic episode found that both patients endorsing depressed mood and ≥ 1 additional depressive symptom ("dysphoric mania") treated with divalproex demonstrated a longer time to any mood episode or premature discontinuation (a post hoc-derived joint efficacy and tolerability measure) compared with lithium [41]. Divalproex similarly outperformed lithium in this measure in patients with classic "euphoric" mania. There was no difference between lithium and divalproex in time to any mood episode, depressive relapse, or manic relapse amongst patients with "dysphoric" mania. Patients with mixed features, however, showed a significantly higher rate of study discontinuation in both lithium and divalproex groups,

indicating that these patients might be more susceptible to non-specific treatment-related side effects.

In terms of the long-term prevention of mixed features, Tohen et al. (2016) conducted a post hoc analysis of a 48-week maintenance DB-RCT of lithium versus olanzapine in BDI patients recovered from an index manic or mixed episode [42]. In addition to calculating days in depressive and hypo/manic states, they also calculated total number of days in a "subsyndromal" (YMRS 6–15 and HAM-D 7–17) and "syndromal" (YMRS ≥ 16 and HAM-D ≥ 18) mixed state. While the lithium and olanzapine groups experienced a similar number of days in a syndromal mixed state, participants treated with olanzapine experienced significantly fewer days with subsyndromal mixed symptoms compared with those on lithium.

Neurostimulation

While ECT has shown promise in the treatment of mixed states [43, 44], evidence for treatment of DSM-IV-defined mixed states is plagued by limitations such as small sample sizes and lack of randomized, blinded designs [43].

Data for ECT in the treatment of DSM-5 or similarly defined mixed features is even more sparse. A retrospective chart review on a mixed group of 41 treatment-resistant bipolar patients ($n = 15$ mixed features, $n = 22$ depressed, and $n = 4$ manic) used McElroy's (mania/hypomania plus ≥ 3 depressive symptoms) and Akiskal's criteria (major depressive episodes plus 2–3 manic/hypomanic symptoms) to define mixed features [45]. Response to treatment was defined as retrospective rating of the clinical global impression scale of ≥ 3. All patients except for one with mixed features responded to treatment, with no adverse events reported.

Conclusion

The DSM-5 mixed features specifier signals a shift back to a broader conceptualization of mixed states in bipolar disorder. Recent prevalence data suggests that around one-third of acute manic and depressive episodes in bipolar disorder meet the new DSM-5 criteria for mixed features [12••]. Studies also indicate that patients with DSM-5 MF experience an adverse clinical course, characterized by a younger age of onset, increased time symptomatic, increased comorbidity, and higher suicide risk.

DSM-5 MF are thus a fairly prevalent phenomenon that appears to be a more severe variant of "classic" mood episodes. However, questions remain regarding the validity of the current DSM-5 MF criteria. While DSM-5 requires at least 3 opposite polarity symptoms, recent studies have found that patients who have fewer concurrent symptoms experience a more severe longitudinal course and higher comorbidity rates, arguing for the validity of more permissive criteria [13, 19•, 46]. Similarly, while prevalence rates when overlapping symptoms were included in the mixed features definition did not increase significantly in meta-analysis [12••], there remains evidence that irritability and agitation are important prognostic factors to consider in bipolar depression, arguing for their inclusion in mixed features definitions [47, 48]. Thus, while a significant proportion of acute mood episodes in bipolar disorder may meet DSM-5 criteria for mixed features, there is ongoing debate regarding whether the current criteria remain overly exclusive.

Leaving aside the question of its validity, the evidence base regarding treatment of DSM-5 MF, or similar "intermediate" conceptualizations including mild or subsyndromal concurrent opposite polarity symptoms, is sparse. All analyses explicitly examining DSM-5-defined MF are post hoc analyses of AAP trials. Of all the studies reviewed—including analyses prior to 2013—there were only two trials which exclusively recruited participants meeting DSM-5 MF or similar criteria [34, 39]. Thus, we have no adequately powered, rigorously designed RCTs specifically examining pharmacological therapy for DSM-5 or similarly defined mixed features, such as have been conducted for DSM-IV mixed episodes [49]. In addition to all the challenges inherent to post hoc analyses, they are further limited in this case as many of the original studies excluded participants displaying above a certain severity of opposite polarity symptoms. While these studies can aid in our understanding of patients with mild or subsyndromal concurrent opposite polarity symptoms, they do not address those with more severe mixed presentations that would be included in the current DSM-5 definition. The evidence base for maintenance treatment is even more limited, indicating a need for studies examining both the prevention of mixed features and the long-term efficacy of agents for those who present with index-mixed symptoms. For instance, though aripiprazole was effective in reducing manic symptoms in acutely manic patients with concurrent mild depressive symptoms [30], maintenance treatment with adjunctive aripiprazole has not been found to be effective in preventing manic relapse in patients with an index DSM-IV-defined mixed episode [50]. If these findings are reproduced in patients with index DSM-5 MF, this would reduce the attractiveness of aripiprazole as an option for this group. Similarly, though ECT shows some promise in the treatment of mixed features, there have thus far been no trials assessing its (or other forms of neurostimulation such as rTMS) efficacy in DSM-5 MFs.

However, the existing literature on acute mood episodes with mixed features does provide some general—albeit quite preliminary—guidance in terms of clinical practice and future research (Table 2). Broadly, AAPs, either adjunctive or in monotherapy, appear to have efficacy in the treatment of mixed features. Olanzapine (monotherapy) was the most studied agent in acute mania and acute depression with mixed

Table 2 Summary of pharmacological studies of the treatment of acute mood episodes with mixed features

	Acute mania/hypomania with mixed features		Acute depression with mixed features	
	Manic symptoms	Depressive symptoms	Manic symptoms	Depressive symptoms
Atypical antipsychotics (AAP)				
Aripiprazole (monotherapy)	+ [30]			
Asenapine (monotherapy)	+ [24]	+ [24]		
Cariprazine (monotherapy)	+ [29]	- [29]^{t}	- [38]^{t}	+ [38]
Lurasidone (monotherapy)			- [37]^{t}	+ [37]
Olanzapine (monotherapy)	+ [24]	- [24]	+ [35]	+ [35]
	+ [28]	- [28]	+ [36]	+ [36]
Quetiapine (adjunctive/monotherapy)	- [34]	+ [34]		
Risperidone (adjunctive)	+ [31]	+ [31]		
Ziprasidone (monotherapy/adjunctive)	+ [32]	+ [32]	+ [39]	+ [39]
Mood stabilizers (MS)				
Lithium	- [33]			
DVP	+ [33]			
Combination AAP/MS + antidepressant				
Olanzapine + fluoxetine			+ [36]	+ [36]
AAP/MS + antidepressant (multiple agents)				- [40]

+ indicates significant improvement compared with placebo or significant post-treatment improvement in symptoms. - indicates lack of significant difference compared with placebo or significant post-treatment improvement. Contributing study is referenced in brackets

^{t} Contributory studies excluded participants with elevated concurrent YMRS (≥ 10/12) or MADRS (≥ 18) scores at baseline

features. While it did not statistically differentiate from placebo in treating depressive symptoms in acute mania with mixed features, this may have been due to underpowered analyses. Olanzapine however did reach statistical significance compared with placebo in treating manic symptoms in acute mania with mixed features, and manic and depressive symptoms in acute depression with mixed features. The use of olanzapine is however limited in clinical practice by its adverse metabolic profile. Asenapine and ziprasidone monotherapy, and adjunctive risperidone, showed some effect on both manic and depressive symptoms in acute mania with mixed features, while cariprazine and lurasidone appeared to improve depressive symptoms in acute depression with mixed features. We found only one analysis of mood stabilizers in acute treatment of mixed features which found that patients with acute mania and concurrent depressive symptoms do not benefit with lithium treatment [33]. There is also a preliminary evidence that lithium may not be as efficacious as divalproex or olanzapine in the prevention of mixed symptoms or in the long-term treatment of those with index-mixed features [41, 42]. While acknowledging the severe limitations in the literature, this review suggests that clinicians may consider AAPs, and be less inclined to use lithium, in the acute and maintenance treatment of patients with mixed features. The use of adjunctive antidepressants remains an area of contention; while one study found that olanzapine-fluoxetine combination was efficacious and safe, a larger observational study found that adjunctive antidepressants did not result in swifter recovery from acute depression with mixed features and resulted in worsening manic symptoms after 3 months. Thus, further analyses are required to clarify the role of adjunctive antidepressants in mixed presentations. Additionally, though this review is focused on biological treatments, there is evidence that psychosocial interventions such as psychoeducation may prevent mixed symptoms and deserve further attention [51].

More broadly speaking, future studies examining mixed presentations may benefit from looking to the past. While DSM-5 criteria represent a shift back towards the conceptualization of mixed states as set out by Kraeplin and Weygandt, it is in reality a broader categorical formulation rather than truly dimensional. Using data-driven analytical techniques to identify symptom dimensions may be a more fruitful approach than grouping patients based on symptom number cut offs. For example, a factor analysis of bipolar mixed states found that interpretable factors included disorientation/disorganization, anxiety, psychotic symptoms, and depressive symptoms [52]. One can see an overlap between the results derived from such sophisticated statistical methods and the dimensions of associative thinking, psychomotor activity, and affect generated from clinical observation over a century ago. There also

continues to be evidence that symptom dimensions outside of the current DSM-5 definition, such as anxiety/irritability/agitation, have an impact on treatment response [48]. Thus, future efforts may focus on the empirical identification of symptom dimensions and targeting interventions towards such specific symptom clusters.

Compliance With Ethics Standards

Conflict of Interest Trisha Chakrabarty and Kamyar Keramatian each declare no potential conflicts of interest.

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- • Of importance
- •• Of major importance

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