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REVIEW ARTICLE

Treating mixed mania/hypomania: a review and synthesis of the evidence

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The DSM-5 incorporates a broad concept of mixed states and captured ≥3 nonoverlapping symptoms of the opposite polarity using a "with mixed features" specifier to be applied to manic/hypomanic and major depressive episodes. Pharmacotherapy of mixed states is challenging because of the necessity to treat both manic/hypomanic and depressive symptoms concurrently. High-potency antipsychotics used to treat manic symptoms and antidepressants can potentially deteriorate symptoms of the opposite polarity. This review aimed to provide a synthesis of the current evidence for pharmacotherapy of mixed states with an emphasis on mixed mania/hypomania. A PubMed search was conducted for randomized controlled trials (RCTs) that were at least moderately sized, included a placebo arm, and contained information on acute-phase and maintenance treatments of adult patients with mixed episodes or mania/hypomania with significant depressive symptoms. Most studies were post-hoc subgroup and pooled analyses of the data from RCTs for acute manic and mixed episodes of bipolar I disorder; only two prospectively examined efficacy for mixed mania/hypomania specifically. Aripiprazole, asenapine, carbamazepine, olanzapine, and ziprasidone showed the strongest evidence of efficacy in acute-phase treatment. Quetiapine and divalproex/valproate were also efficacious. Combination therapies with these atypical antipsychotics and mood stabilizers can be considered in severe cases. Olanzapine and quetiapine (alone or in combination with lithium/divalproex) showed the strongest evidence of efficacy in maintenance treatment. Lithium and lamotrigine may be beneficial given their preventive effects on suicide and depressive relapse. Further prospective studies primarily focusing on mixed states are needed.

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Key words: Mania, mixed episodes, mixed mania, mixed hypomania, mixed specifier, mixed features, mixed states, dysphoric mania, bipolar disorder, pharmacotherapy.

Introduction

Kraepelin conceived mixed states as combinations of two opposite polarities–namely, weakness or excitement of mood, thinking, and volition.[1] However, his broad concept of mixed states was long neglected.[1] In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR), mixed states corresponded to "mixed episodes," which were defined quite narrowly as the cooccurrence of full syndromal mania and depression for ≥1 week in the context of bipolar I disorder (BD-I).[2]

Recently, the broad concept of mixed states has reemerged as a spectrum: mixed (or dysphoric) mania/hypomania (mania/hypomania with subsyndromal depression) → full mixed state corresponding with the DSM-IV-defined mixed episode → mixed depression (depression with subsyndromal mania/hypomania).[3] Compared to pure manic or depressive episodes, broadly defined mixed states exhibit several specific features: a longer overall course, higher episode frequency, and increased rates of attempted suicide and comorbid substance abuse.[3,4] Based on the prognostic impacts of these additional features, the DSM-5 removed the narrowly defined "mixed episode," and instead captured ≥3 nonoverlapping symptoms of the opposite polarity using a "with mixed features" specifier to be applied to manic/hypomanic and major depressive episodes (Figure 1).[5] The full mixed state is now included in the category of manic/hypomanic episode with mixed features.[5]

Pharmacotherapy of mixed states is challenging because the physician is required to treat both manic/hypomanic and depressive symptoms concurrently.[4] Monotherapy with high-potency antipsychotics for manic symptoms can potentially promote depressive

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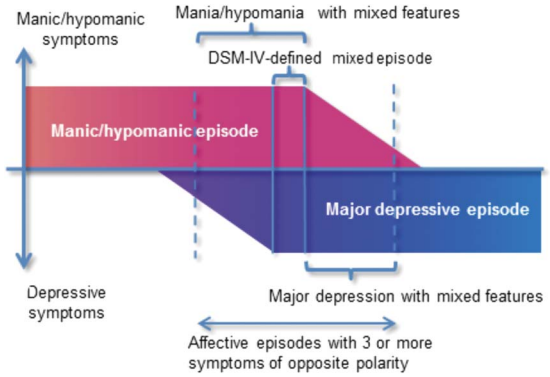

FIGURE 1. Schematic presentation of mixed features according to the DSM–5.

symptoms.[4] Conversely, antidepressants can potentially exacerbate agitation and irritability, leading the task force of the International Society for Bipolar Disorders to recommend avoiding antidepressant treatment in mixed states.[6] Our paper aims to provide a review and synthesis of the available evidence for pharmacotherapy of mixed states, with a focus on mixed mania/hypomania.

Methods

The author searched PubMed for English-language articles published since 1990 on the efficacy of pharmacotherapy in adult (≥19 years old) patients with mixed episode or mania/hypomania with significant depressive symptoms. The search was conducted on 19 December 2015 using the following search terms: (mixed episode* OR mixed mania OR mixed hypomania OR mixed specifier OR mixed feature* OR mixed state* OR dysphoric mania OR bipolar mixed) AND (therapy OR treatment OR pharmacotherapy OR trial). Articles were selected for further evaluation by inspecting abstracts. The bibliographies of the selected articles were also included. The eligible articles were randomized controlled trials (RCTs) of acute-phase and maintenance treatments with a placebo arm and ≥25 cases.

The initial PubMed search identified 919 articles, 81 of which were selected for further evaluation. From those, 34 studies were included in our review (summarized in Tables 1 and 2). Only two RCTs prospectively examined the efficacy of pharmacotherapy for mixed mania/hypomania exclusively; the remaining 32 studies were subgroup or pooled analyses of RCTs for manic and mixed episodes of BD-I.

Acute-Phase Treatment

Atypical antipsychotics

Aripiprazole

In a 3-week RCT for acute manic and mixed episodes, aripiprazole demonstrated significantly greater improvements in both manic (by the Young Mania Rating Scale [YMRS]) and depressive (by the Montgomery–Åsberg Depression Rating Scale [MADRS]) symptoms in mixed-episode patients compared to placebo.[7] A pooled analysis of the abovementioned study and another identically designed RCT[8] examined the efficacy of aripiprazole for manic symptoms in patients with baseline MADRS scores >18 (pure mixed) and 9–18 (intermediate mixed).[9] Aripiprazole produced significantly greater endpoint YMRS score improvements than did placebo regardless of baseline MADRS score.

Asenapine

In a 3-week RCT[10] of asenapine and olanzapine (included as a reference intervention) for acute manic and mixed episodes, asenapine demonstrated a YMRS effect significantly greater compared to placebo and similar to that of olanzapine.[10] Further analysis in mixed-episode patients showed that the endpoint YMRS score improvement with asenapine approached statistical significance, while that with olanzapine was highly significant compared to placebo ($p = 0.05$ and 0.006, respectively). However, according to the mixed model for repeated measures analysis, the YMRS effects of asenapine and olanzapine did not reach statistical significance at endpoint compared to placebo.

Using the data from the abovementioned and an identically designed 3-week RCT,[11] three pooled studies examined the efficacies of asenapine and olanzapine for variously defined mixed mania.[12–14] Szegedi *et al.*[12] analyzed the efficacy of asenapine for depressive symptoms (MADRS and Clinical Global Impression for Bipolar Disorder-Depression [CGI-BP-D] scale) in patients with mixed mania as defined by the following criteria: population 1, MADRS scores ≥20; population 2, CGI-BP-D scale severity scores ≥4; population 3, a diagnosis of mixed episode.[14] The baseline severity of depressive symptoms was significantly reduced by asenapine compared with placebo: the MADRS scores were improved at days 7 and 21 in all populations, and the CGI-BP-D scores were improved at day 7 in all populations and at day 21 in population 1. The CGI-BP-D severity score was significantly reduced by olanzapine compared to placebo at day 7 in populations 2 and 3, and at day 21 in population 1. Olanzapine did not affect the MADRS scores significantly. Azorin *et al.*[13,15] extracted the data of the mixed-episode patients.[15] The improvements in YMRS and MADRS baseline scores at 3 weeks were significantly greater with asenapine than placebo; olanzapine had no statistically significant effects. McIntyre *et al.*[14] examined the efficacy of asenapine for both manic and depressive symptoms in patients with ≥2 or ≥3 baseline depressive features defined by DSM-5 criteria for a manic episode with

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TABLE 1. Summary of the efficacy of pharmacotherapy for acute-phase mixed mania/hypomania

Agent(s)	Study		Definitions of mixed mania/hypomania	Efficacy (improvement in)	
	Author, year, reference number	Method		Manic/ hypomanic symptoms	Depressive symptoms
Mixed mania					
Atypical antipsychotics					
ARP	Sachs *et al.*, 2006[7]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	Suppes *et al.*, 2008[9]	Pooled analysis	Manic/mixed episodes (DSM–IV) with MADRS scores >9	>PLA	NR
ASE	McIntyre *et al.*, 2009[10]	Subgroup analysis	Mixed episode (DSM–IV)	=PLA	NR
	Szegedi *et al.*, 2011[12]	Pooled analysis	Population 1, manic/mixed episodes (DSM–IV) with MADRS scores ≥20; population 2, manic/mixed episodes (DSM–IV) with CGI–BP–D scale severity scores ≥4; population 3, mixed episode (DSM–IV)	NR	>PLA
	Azorin *et al.*, 2013[13]	Pooled analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	McIntyre *et al.*, 2013[14]	Pooled analysis	Manic episode with mixed features (DSM–5)	>PLA	>PLA
OLA	Tohen *et al.*, 1999[16]	Subgroup analysis	Manic/mixed episodes (DSM–IV) with HAMD–21 scores ≥20	>PLA	Not worsened
	Tohen *et al.*, 2000[15]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	Baker *et al.*, 2003[17]	Pooled analysis	Manic/mixed episodes (DSM–IV) with HAMD–21 scores ≥20	>PLA	>PLA
	Baldessarini *et al.*, 2003[18]	Pooled analysis	Mixed episode (DSM–IV)	>PLA	NR
	McIntyre *et al.*, 2009[10]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
	Szegedi *et al.*, 2011[12]	Pooled analysis	Population 1, manic/mixed episodes (DSM–IV) with MADRS scores ≥20; population 2, manic/mixed episodes (DSM–IV) with CGI-BP-D scale severity scores ≥4; population 3, mixed episode (DSM–IV)	NR	>PLA
	Azorin *et al.*, 2013[13]	Pooled analysis	Mixed episode (DSM–IV)	=PLA	=PLA
	McIntyre *et al.*, 2013[14]	Pooled analysis	Manic episode with mixed features (DSM–5)	>PLA	>PLA
	Tohen *et al.*, 2014[19]	Pooled analysis	Manic episode with mixed features (DSM–5)	>PLA	=PLA
PAL–ER	Vieta *et al.*, 2010[21]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
	Berwaerts *et al.*, 2012[22]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
QUE–XR	Cutler *et al.*, 2011[23]	Subgroup analysis	Mixed episode (DSM–IV)	=PLA	=PLA
ZIP	Keck *et al.*, 2003[24]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
	Stahl *et al.*, 2010[26]	Pooled analysis	Manic/mixed episodes (DSM–IV) with scores ≥2 on at least 2 of the 8 selected HAMD items	>PLA	>PLA
Mood stabilizers					
CBZ–ERC	Weisler *et al.*, 2004[27]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	Weisler *et al.*, 2005[28]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	=PLA
	Weisler *et al.*, 2006[29]	Pooled analysis	Mixed episode (DSM–IV)	>PLA	>PLA
LI	Swann *et al.*, 1997[31]	Subgroup analysis	Mania (RDC) with significant depressive symptoms defined by SADS–C depression subscale and ADRS	=PLA	NR
DVP	Swann *et al.*, 1997[31]	Subgroup analysis	Mania (RDC) with significant depressive symptoms defined by SADS–C depression subscale and ADRS	>PLA	NR
	Bowden *et al.*, 2006[32]	Subgroup analysis	Mixed episode (DSM–IV–TR)	>PLA	NR
Combination					
OLA + LI/VAL	Tohen *et al.*, 2002[33]	Subgroup analysis	Mixed episode (DSM–IV) with HAMD–21 scores ≥20	>PLA + LI/VAL	>PLA + LI/VAL
	Baker *et al.*, 2004[34]	Subgroup analysis	Manic/mixed episodes (DSM–IV) with HAMD–21 scores ≥20	>PLA + LI/VAL	>PLA + LI/VAL
OLA + VAL	Houston *et al.*, 2009[35]	Prospective	Mixed episode (DSM–IV-TR)	>PLA + VAL	>PLA + VAL
Mixed hypomania					
QUE	Suppes *et al.*, 2013[47]	Prospective	BD–II (DSM–IV–TR) with YMRS scores ≥12 and MADRS scores ≥15	=PLA >PLA, overall severity & functioning*	>PLA

ADRS = Affective Disorder Rating Scale; ARP = aripiprazole; ASE = asenapine; BD–II = bipolar II disorder; CBZ–ERC, extended-release carbamazepine capsule; CGI–BP–D = Clinical Global Impression For Bipolar Disorder–Depression; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; DVP = divalproex; HAMD–21 = Hamilton rating scale for depression, 21-item; LI = lithium; MADRS = Montgomery–Åsberg Depression Rating Scale; NR = not reported; OLA = olanzapine; PAL–ER = extended-release paliperidone; PLA = placebo; QUE = quetiapine; QUE–XR = extended-release quetiapine; RDC = research diagnostic criteria; SADS–C = Schedule for Affective Disorders and Schizophrenia–Change Version; VAL = valproate; YMRS = Young Mania Rating Scale; ZIP = ziprasidone; >PLA = the agent demonstrated a significantly higher efficacy compared to placebo. =PLA = the efficacy of the agent was not significantly different from that of placebo. * = overall severity, Clinical Global Impression for Bipolar Disorder Overall Severity Scale; functioning = Global Assessment of Functioning Scale.

mixed features.[16] The change in baseline YMRS scores in patients with ≥3 depressive features was significantly greater with asenapine than placebo at day 2 across all depression levels and continued to decrease to endpoint; olanzapine was significantly more efficacious than placebo only in patients with lower baseline depression

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TABLE 2. Summary of the efficacy of pharmacotherapy for maintenance-phase mixed mania

Agent(s)	Study		Definitions of mixed mania	Efficacy (time to relapse into)	
	Author, year, reference number	Method		Manic episode	Depressive episode
Atypical antipsychotics					
OLA	Tohen *et al.*, 2006[36]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA, any mood episode	
	Tohen *et al.*, 2009[37]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
QUE	Weisler *et al.*, 2011[38]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
Mood stabilizers					
LI	Bowden *et al.*, 2005[39]	Subgroup analysis	Manic episode (DSM–III–R) with significant depressive symptoms defined by SADS-C depression subscale	=PLA	=PLA
	Weisler *et al.*, 2011[38]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	=PLA
DVP	Bowden *et al.*, 2005[39]	Subgroup analysis	Manic episode (DSM–III–R) with significant depressive symptoms defined by the SADS–C depression subscale	=PLA	=PLA
Combination					
ARP + LTG	Carlson *et al.*, 2012[41]	Subgroup analysis	Mixed episode (DSM–IV–TR)	NR	>PLA + LTG
ARP + LI/VAL	Yatham *et al.*, 2013[43]	Subgroup analysis	Mixed episode (DSM–IV–TR)	>PLA*	=PLA
QUE + DVP/LI	Vieta *et al.*, 2008[45]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA + DVP/LI	>PLA + DVP/LI
	Suppes *et al.*, 2009[44]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA + DVP/LI	>PLA + DVP/LI
	Vieta *et al.*, 2012[46]	Pooled analysis	Mixed episode (DSM–IV)	>PLA + DVP/LI	>PLA + DVP/LI

ARP = aripiprazole; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; DVP = divalproex; LI = lithium; LTG = lamotrigine; NR = not reported; OLA = olanzapine; PLA = placebo; QUE = quetiapine; SADS–C = Schedule for Affective Disorders and Schizophrenia–Change Version; VAL = valproate; >PLA = the agent demonstrated a significantly higher efficacy compared to placebo. =PLA = the efficacy of the agent was not significantly different from that of placebo. * = mean change in the baseline Young Mania Rating Scale score.

severities. The differences between the asenapine and placebo groups increased with increasing depression severity. The remission rate of depressive symptoms (MADRS scores ≤12) was significantly higher with asenapine than placebo across most severity levels in patients with ≥3 depressive features. With olanzapine, it was significantly higher only in patients with ≥2 depressive features and mild to moderate depression severity.

Olanzapine

In addition to the aforementioned asenapine trials, other studies support the efficacy of olanzapine for the treatment of mixed mania.[15–19] In 3- and 4-week RCTs for acute manic and mixed episodes, olanzapine demonstrated significantly greater YMRS effects compared to placebo.[15,16] The results were not affected by the baseline diagnosis (i.e., manic vs. mixed). One of these RCTs revealed a significantly greater endpoint improvement in depressive symptoms (Hamilton Rating Scale for Depression, 21-item [HAMD-21]) with olanzapine compared to placebo in patients with baseline HAMD-21 total scores ≥20.[15] Pooling the data from these two RCTs, Baker *et al.*[17,10] examined the efficacy of olanzapine for both manic and depressive symptoms in patients with baseline HAMD-21 total scores ≥20.[19] Olanzapine demonstrated significantly greater improvements in YMRS and HAMD-21 scores than did placebo at 3 weeks. With the same pooled data, Baldessarini *et al.*[18] analyzed the antimanic efficacy of olanzapine in patients with mixed episodes.[20] Olanzapine produced a significantly higher response rate for manic symptoms (≥50% YMRS score reduction) than did placebo.

Tohen *et al.*[19] applied the DSM-5 criteria for manic episodes with mixed features to the pooled sample of three RCTs for acute manic and mixed episodes. The RCTs analyzed included the two olanzapine studies described above[15,16] and a trial of olanzapine and haloperidol.[20] In patients with mixed features, olanzapine demonstrated significantly greater YMRS score improvements compared to placebo at 3 weeks. The decrease in depressive symptoms (17-item Hamilton Rating Scale for Depression [HAMD-17]) was greater with olanzapine compared to placebo. However, the difference did not reach statistical significance, which the authors attributed to low statistical power.

Extended-release paliperidone (paliperidone–ER)

In two RCTs for acute manic and mixed episodes, paliperidone-ER demonstrated significantly greater YMRS score improvements compared to placebo.[21,22] The results were not affected by the baseline diagnosis.

Extended-release quetiapine (quetiapine–XR)

In a 3-week RCT of quetiapine-XR for acute manic and mixed episodes, the YMRS and MADRS changes with

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quetiapine-XR were not significantly different compared to placebo in mixed-episode patients.[23]

Ziprasidone

In a 3-week RCT for acute manic and mixed episodes, ziprasidone improved manic symptoms significantly compared to placebo (MRS).[24] The result was not affected by the baseline diagnosis. In a pooled study[27] using the data from the abovementioned and a similarly designed 3-week RCTs,[25] ziprasidone produced significantly greater HAMD and MRS score improvements than did placebo in patients with dysphoric mania, as defined by a manic episode with a score of ≥2 on at least two of the eight selected HAMD items.[26]

Mood stabilizers

Extended-release carbamazepine capsule (carbamazepine-ERC)

In two identically designed 3-week RCTs for acute manic and mixed episodes, carbamazepine-ERC demonstrated significantly greater YMRS score improvements compared to placebo.[27,28] The results were not affected by the baseline diagnosis. One of these studies also demonstrated significantly greater HAMD score improvements with carbamazepine-ERC compared to placebo in mixed-episode patients continuing treatment.[27] In a pooled analysis of these RCTs, carbamazepine-ERC showed significantly greater YMRS and HAMD changes than did placebo in mixed-episode patients.[29]

Divalproex and lithium

In a 3-week RCT for acute mania as defined by research diagnostic criteria, both divalproex and lithium demonstrated significantly greater improvements in manic symptoms compared to placebo (Manic Syndrome Scale, Behavior-Ideation Scale, and MRS).[30] A post-hoc analysis of this RCT revealed that patients with significant depressive symptoms responded similarly to lithium and placebo, whereas those without depressive symptoms responded significantly better to lithium.[31] The response to divalproex was not significantly different between the two patient groups. Depressive symptoms were associated with a better response to divalproex than lithium. In another 3-week RCT for acute manic and mixed episodes, extended-release divalproex demonstrated significantly greater MRS improvements compared to placebo.[32] The result was not affected by the baseline diagnosis.

Combination therapy

Olanzapine plus valproate or lithium

A 6-week RCT in patients with acute manic and mixed episodes who were partially nonresponsive to 2-week valproate or lithium monotherapy found adjunctive olanzapine to produce significantly greater YMRS and HAMD-21 score improvements compared to placebo in mixed-episode patients with a baseline HAMD-21 score of ≥20.[33] A post-hoc analysis revealed the efficacy of adjunctive olanzapine in all patients with such HAMD-21 scores.[34] Houston *et al.*[35] conducted a 6-week RCT of adjunctive olanzapine in patients with acute mixed episodes who showed inadequate response to 2-week valproate monotherapy, the only prospective RCT specifically for acute mixed episodes. Adjunctive olanzapine produced significantly greater endpoint YMRS and HAMD-21 score improvements compared to adjunctive placebo.

Maintenance Treatment

Atypical antipsychotics

Olanzapine

A 48-week RCT in patients achieving remission after open-label acute treatment with olanzapine for manic and mixed-index episodes showed that olanzapine significantly increased the time to relapse into any mood event in patients with mixed-index episodes compared to placebo.[36] Moreover, a post-hoc study found a significantly increased time to depressive and manic relapses in patients with mixed-index episodes treated with olanzapine.[37]

Quetiapine

In a 104-week RCT, patients achieving stabilization after open-label treatment with quetiapine for current or recent manic, mixed, or depressive episodes were randomized to continue quetiapine or to switch to placebo or lithium (included as a reference intervention).[38] In patients with mixed-index episodes, quetiapine significantly increased the time to relapse into any mood, manic, or depressive event compared to placebo.

Mood stabilizers

Lithium and divalproex/valproate

In the abovementioned RCT of quetiapine, lithium significantly increased the time to relapse into any mood event compared to placebo in patients with mixed-index episodes.[38] The time to relapse into manic, but not depressive, events was significantly longer with lithium than with placebo. Bowden *et al.*[39] conducted a post-hoc study of the relationship between initial manic symptomatology (euphoric or dysphoric) and the response to maintenance treatment (divalproex, lithium, or placebo) using the data from a 52-week RCT[40] for patients who had recovered from manic-index episodes as defined by

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the DSM-III-R. The time to relapse into any mood, manic, or depressive event was not significantly different between the divalproex, lithium, and placebo groups among initially dysphoric patients.

Combination therapy

Aripiprazole plus lamotrigine

In a 52-week RCT, patients achieving and maintaining stabilization after single-blind treatment with aripiprazole and open-label lamotrigine for recent manic and mixed episodes were randomized to double-blind treatment with lamotrigine plus aripiprazole or placebo.[41] In patients with mixed-index episodes, the aripiprazole combination significantly increased the time to relapse into a depressive event compared to the placebo combination.

Aripiprazole plus lithium or valproate

In a 52-week RCT, patients achieving stabilization after treatment with single-blind aripiprazole plus open-label lithium or valproate for acute manic and mixed episodes were randomized to double-blind lithium/valproate plus aripiprazole or placebo.[42] Yatham *et al.*[43] conducted a post-hoc analysis of this RCT to explore the efficacy of aripiprazole plus lithium/valproate stratified by manic or mixed-index episodes. In patients with mixed-index episodes, the aripiprazole combination demonstrated significantly greater YMRS score improvements than did the placebo combination; however, the time to relapse into any mood episode and the MADRS score change with the aripiprazole combination did not differ significantly compared to the placebo combination.

Quetiapine plus lithium or divalproex

In two identically designed 104-week RCTs, patients achieving stabilization after open-label treatment with quetiapine plus lithium or divalproex for current or most recent manic, mixed, or depressive episodes were randomized to double-blind quetiapine or placebo plus lithium/valproate.[44,45] Each of these studies and their pooled analysis found that the quetiapine combination significantly increased the time to relapse into any mood, manic, or depressive event compared to the placebo combination in patients with mixed-index episodes.[44–46] Moreover, the pooled study revealed that the quetiapine combination significantly increased the time to relapse into a mixed event compared to the placebo combination.[46]

Mixed Hypomania

Suppes *et al.*[47] conducted an RCT of adjunctive quetiapine for patients with hypomania with depressive symptoms (YMRS scores ≥12 and MADRS scores ≥15) of BD-II under a stable medication regimen for ≥2 weeks. Adjunctive quetiapine demonstrated significantly greater improvements in the CGI-BP severity and MADRS scores compared to placebo; the YMRS scores did not change significantly.

Synthesis of Evidence

Most evidence for the treatment of mixed mania comes from post-hoc subgroup and pooled analyses of RCTs for patients with manic and mixed episodes of BD-I. Because such analyses often produce false positive and false negative results, they should be interpreted with caution.

Acute-phase treatment

Regarding treatment of manic symptoms, there is evidence of efficacy of aripiprazole, asenapine, carbamazepine-ERC, divalproex/valproate, olanzapine (as monotherapy and co-therapy with lithium or divalproex/valproate), paliperidone-ER, and ziprasidone. Generally, the efficacy for manic symptoms did not differ between mixed and pure mania, which was also shown in a meta-analysis of the efficacies of atypical antipsychotics for acute mixed episodes.[48] However, agents also efficacious for concurrent depressive symptoms are required for the treatment of mixed mania. In this regard, aripiprazole, asenapine, carbamazepine-ERC, olanzapine (as monotherapy and in combination with lithium or valproate), and ziprasidone produced the strongest evidence of efficacy. These results are in line with the three extant reviews of the pharmacotherapy of mixed states.[49–51] Despite having failed to show efficacy in one study, quetiapine is worth considering because of its established efficacy for acute manic and depressive episodes of BD.[52,53] The efficacy of divalproex/valproate for depressive symptoms was not obvious in the articles included in the present review; however, this agent is also worth considering because of its probable efficacy in bipolar depression.[54,55] Because there is no evidence of differential effectiveness in mixed states among these agents so far, selection should be made based on the profiles of possible adverse effects for individual cases.

For severe cases, combination therapy with these atypical antipsychotics and mood stabilizers, such as olanzapine plus lithium or valproate, is recommended. The poor efficacy of lithium for mixed or dysphoric mania derived from an earlier case series has been widely taken for granted.[31] Surprisingly, only one subgroup analysis has compared the efficacy of lithium with placebo so far. Given the well-known efficacy of lithium for suicide prevention and the high rate of attempted suicide reported in dysphoric mania, lithium may be a

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valid treatment option.[4,56] Further studies are needed to determine its value in the treatment of mixed states.

Maintenance treatment

Compared to acute phase, the evidence for maintenance treatment of mixed mania is scarce. Evidence of efficacy in preventing manic relapse was found for aripiprazole plus lithium/divalproex, lithium, olanzapine, and quetiapine (as monotherapy and in combination with lithium/divalproex), whereas evidence of efficacy in preventing depressive relapse was found for aripiprazole plus lamotrigine, olanzapine, and quetiapine (as monotherapy or in combination with lithium/divalproex). Considering the necessity to prevent both manic and depressive relapses, olanzapine and quetiapine (as monotherapy or in combination with lithium/divalproex) have shown the strongest evidence. Although our review did not find any evidence for the efficacy of lithium monotherapy in depressive relapse prevention in addition to its antimanic effects, it may still be worth considering as a maintenance treatment in light of its proven effectiveness in suicide prevention. Patients whose first episode is mixed tend to experience subsequent depressive relapses.[57] Therefore, lamotrigine may also be worth considering given its established efficacy in preventing depressive relapses in the entire BD population[58] and despite its having hardly been studied in the context of mixed states.

Mixed hypomania

In the author's experience, this state places a substantial burden on outpatients. One prospective RCT suggests that quetiapine and, by analogy, other agents that show efficacy in the treatment of mixed mania could be effective. However, the evidence is too poor to venture any recommendation.

Conclusions

Most evidence for the treatment of mixed mania comes from post-hoc subgroup and pooled analyses. With this limitation, aripiprazole, asenapine, carbamazepine-ERC, olanzapine, and ziprasidone show the strongest evidence of efficacy in acute-phase treatment. Quetiapine and divalproex/valproate are also worth considering. Combination therapies with these atypical antipsychotics and mood stabilizers can be considered in severe cases. Olanzapine and quetiapine (as monotherapy and in combination with lithium/divalproex) show the strongest evidence of efficacy as maintenance treatments. Lithium and lamotrigine may be beneficial given their preventive effects on suicide and depressive relapse. To verify this synthesis, further prospective studies focusing on mixed states are encouraged.

Disclosures

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