CNS Spectrums, (2017), **22**, 186–195.
doi:10.1017/S1092852917000013

REVIEW ARTICLE

Pharmacological treatment of mixed states

*Alessandro Cuomo,[1] Viktoriya L. Nikolova,[2] Nefize Yalin,[2] Danilo Arnone,[2] Andrea Fagiolini,[3] and Allan H. Young[2]**

[1] General Psychiatry Residency Training Program, University of Siena School of Medicine, Siena, Italy
[2] Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College, London
[3] Department of Medical Sciences, Surgery and Neurosciences, University of Siena School of Medicine, Siena, Italy

Mixed states in bipolar disorder have been neglected, and the data concerning treatment of these conditions have been relatively obscure. To address this, we systematically reviewed published pharmacological treatment data for "mixed states/episodes" in mood disorders, including "with mixed features" in DSM-5. We searched PubMed, MEDLINE, The Cochrane Library, clinicaltrials.gov, and controlled-trials.com (with different combinations of the following keywords: "mixed states/features," "bipolar," "depressive symptoms/bipolar depression," "manic symptoms," "treatment," "DSM-5") through to October 2016. We applied a quality-of-evidence approach: first-degree evidence = randomized placebo-controlled studies of pharmacological interventions used as monotherapy; second-degree evidence = a similar design in the absence of a placebo or of a combination therapy as a comparative group; third-degree evidence = case reports, case series, and reviews of published studies. We found very few primary double-blind, placebo-controlled studies on the treatment of mixed states: the preponderance of available data derives from subgroup analysis performed on studies that originally involved manic patients. Future research should study the effects of treatments in mixed states defined using current criteria.

Received 9 August 2016; Accepted 10 November 2016

Key words: Mixed states/episodes, mood disorders, DSM-5, depressive symptoms, manic symptoms, treatment, pharmacological interventions, pharmacotherapies.

Introduction

Mixed states present particular challenges to the treating clinician, and even the prevalence rate changes significantly among studies and in relation to the diagnostic criteria used. In the DSM-IV, a diagnosis of a mixed episode required simultaneously all criteria for a manic or a major depressive episode for a period of one week. Individuals infrequently meet these full criteria in clinical practice. The new DSM-5 "specifier" arguably adopts a broader approach toward mixed states. In the case of depressive episodes, there is a requirement for the presence of at least three manic/hypomanic symptoms (including elevated mood, inflated self-esteem, decreased need for sleep, an increase in energy or goal-directed activities, etc.) occurring nearly every day during a major depressive episode; notably, overlap with symptoms of major depression is restricted. In the case of mania or hypomania, the specifier requires the presence of at least three symptoms of depression (including depressed mood, diminished interest or pleasure, slowed physical and emotional reaction, fatigue or loss of energy, and recurrent thoughts of death, etc.) occurring nearly everyday throughout the manic or hypomanic episode.

Mixed states are generally held to be less responsive to pharmacological treatment, and the response to mood stabilizers and other pharmacotherapies is poor.[1,2] Antidepressants are generally avoided because of exacerbation of manic symptoms and a feared increased risk of suicidality, which is already high.[3] However, the use of an atypical antipsychotic/antimanic agent in some bipolar disorder patients may decrease suicidal ideation.[4] As a result, the choice of medication is usually based on individual factors and short-/long-term harms, safety, and tolerability parameters. The aim of this review is to summarize the pharmacological treatment of "mixed states/episodes" as

* Address for correspondence: Professor Allan H. Young, Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, PO72 De Crespigny Park, London SE5 8AF, United Kingdom. Email: (Allan.Young@kcl.ac.uk)

We thank Ms. Caroline Loveland for her help in preparing this manuscript. Dr. Danilo Arnone is supported by the Academy of Medical Sciences (AMS-SGCL8).

This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London, the Maudsley NHS Foundation Trust, and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

defined by the DSM-III and the DSM-IV, and manic episodes "with mixed features" as defined in the DSM-5.

Methods

Searches

PubMed, MEDLINE, and The Cochrane Library were searched from January of 1980 to October of 2016 for all publications regarding treatment of mixed features as defined by the DSM-III and DSM-IV, and manic or depressive episodes "with mixed features" as defined in the DSM-5. The clinical trials registries in clinicaltrials.gov and controlled-trials.com were scrutinized for trials. The search was done using different combinations of the following keywords: "mixed states/features," "bipolar disorder," "depressive symptoms/bipolar depression," "manic symptoms," "treatment," "DSM-5." Related publications were hand-searched from the reference lists of every identified primary study.

Study selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[5] guidelines (see Figure 1). Articles were selected for inclusion in this review if they met the following criteria: (1) inclusion of a mixed-episode sample (or subgroup) was clearly stated; and (2) research findings for the mixed-episode sample (or subgroup) were presented. Nonoriginal studies (including editorials, book reviews, and letters to the editor) and studies without available full-text versions were excluded.

Quality assessment

First-degree studies included double-blind, placebo-controlled randomized controlled trials (RCTs) of pharmacological interventions used as monotherapy. Second-degree studies had a similar design without a placebo or combination therapy as a comparative group, while third-degree studies referred to any other type of published research.

Results

114 articles were assessed for eligibility, of which 54 investigated mixed states in bipolar disorder. However, while 36 of these studies included some number of patients experiencing a mixed episode at baseline, their focus was on pure mania, and the data from both groups were pooled and analyzed together. Several of these studies briefly reported some exploratory subgroup

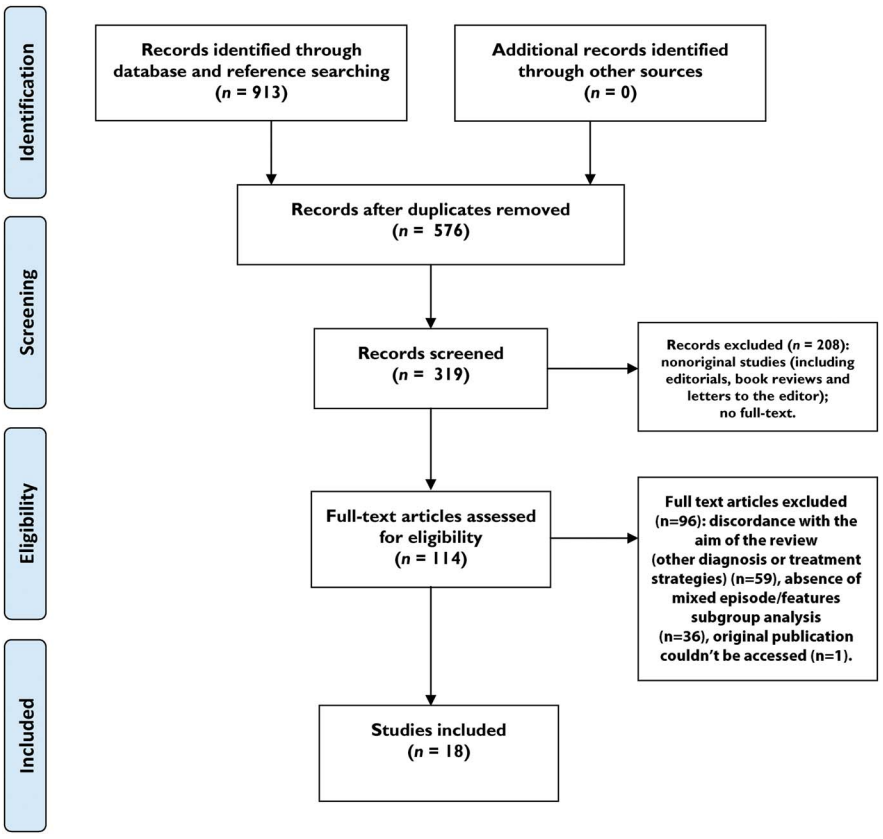

FIGURE 1. PRISMA flow diagram.

https://doi.org/10.1017/S1092852917000013 Published online by Cambridge University Press

analysis or no significant effect of episode on treatment outcome when baseline episode (manic vs. mixed) was added as a covariate. These studies were excluded from the present review as the data reported are not sufficient to provide reliable estimates of treatment efficacy in patients with mixed states. Table 1 presents all the studies that were excluded at this final stage, organized by treatment. In addition, one article examining the effects of gabapentin as adjunctive treatment in mixed states was also excluded from this review as the full text of the publication could not be accessed.[42]

Following the exclusion of these articles, there were 18 studies that met the inclusion criteria and investigated mixed states in bipolar disorder as a separate group. Of these, only 7 studies specifically examined pharmacotherapy for mixed states and the remaining 11 included both manic and mixed episode patients but reported treatment effect separately for each subgroup. These studies evaluated antipsychotics, mood stabilizers, and combination therapies for acute ($n = 12$), maintenance treatment ($n = 5$), or both ($n = 1$) in patients with DSM-III and DSM-IV mixed episodes or DSM-5 mixed features. Pharmacological evidence for each class of medication is presented in Table 2, and the sections below are organized according to aim of treatment (acute vs. maintenance) and drug. The primary findings, degree of evidence, and sample size are also presented in Table 2.

Acute Phase Studies

Antipsychotic medication

We identified six studies that evaluated the efficacy of antipsychotic medication in patients with mixed states.

Two first-degree studies compared aripiprazole with placebo and found that aripiprazole significantly decreased manic symptoms.[43,44] Further, Sachs *et al.*[44] reported a significant reduction in depressive symptoms among patients taking aripiprazole compared to placebo. Suppes *et al.*[43] also reported significantly higher response and remission rates (based on YMRS scores) among those treated with aripiprazole.

We identified two studies that examined the efficacy of ziprasidone.[47,48] One first-degree evidence trial comparing ziprasidone with placebo in major depressive episodes with 2 or 3 concomitant manic symptoms found ziprasidone to be superior to placebo in improving depressive, but not manic symptoms.[47] One study[48] is also available from a pooled analysis of mixed patients with dysphoric mania previously enrolled in two similar placebo-controlled trials.[30,31] This study found ziprasidone to be significantly superior to placebo in improving both manic and depressive symptoms. Response and remission rates were also significantly higher in the ziprasidone group.

In a first-degree placebo-controlled trial, McIntyre *et al.*[45] found that the effect of treatment with sublingual asenapine (compared to placebo) on manic symptoms only approached significance, while the effect was significantly greater in the group treated with olanzapine (compared to placebo).

In a recent first-degree trial, Suppes *et al.*[46] evaluated the efficacy of lurasidone in major depression with mixed features and found that lurasidone significantly improved both depressive and manic symptoms, and a significantly higher proportion of patients in the lurasidone group met a-priori response and remission criteria (number needed to treat [NNT] of 3 and 4, respectively).

Finally, in a case series by Suppes *et al.*[49] (not included in the table), patients were treated with clozapine in both the acute and maintenance phases. Seven subjects had treatment-resistant bipolar disorder and manic episodes associated with significant depressive symptoms. All patients displayed significant reductions in affective and psychotic symptoms when treated with clozapine alone or in combination with lithium, an antidepressant, or valproate.

Mood stabilizers

We found only one study that satisfied our inclusion criteria. This was a post-hoc analysis by Weisler *et al.*[50] of data from two studies[51,52] that evaluated the efficacy of carbamazepine (extended-release capsules) versus placebo in patients with manic or mixed episodes. Carbamazepine significantly improved both manic and depressive symptoms in the subsample of mixed patients.

Combination therapy

We identified five first-degree trials that met our inclusion criteria. Three trials compared the efficacy of olanzapine in combination with a mood stabilizer (lithium or valproate) versus placebo and presented data for the mixed-patients group.[53–55] Overall, the results from all three studies indicated that adjunctive olanzapine treatment is superior to mood stabilizer monotherapy in improving both depressive and manic symptoms. Conversely, one trial examining the efficacy of a olanzapine/fluoxetine combination for the treatment of mixed depression reported no statistically significant difference in depressive symptoms between patients who received both olanzapine and fluoxetine and those who received olanzapine alone.[56]

Finally, Suppes *et al.*[57] assessed adjunctive quetiapine treatment (to any stable cooccurring treatment) in hypomanic patients experiencing mixed symptoms. Quetiapine adjunctive treatment was significantly more effective in improving depressive, but not hypomanic symptoms.

https://doi.org/10.1017/S1092852917000013 Published online by Cambridge University Press

TABLE 1. List of publications that included mixed patients in the total sample, but did not report results for the mixed-only subgroup

Drug	Reference
Olanzapine	Tohen M, Sanger TM, McElroy SL, *et al.* Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *Am J Psychiatry.* 1999; **156**(5): 702–709.[6]
	Tohen M, Jacobs TG, Grundy SL, *et al.* Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. *Arch Gen Psychiatry.* 2000; **57**(9): 841–849.[7]
Olanzapine vs. risperidone	Novick D, Reed C, Haro JM, *et al.* Comparison of olanzapine and risperidone in the EMBLEM Study: translation of randomized controlled trial findings into clinical practice. *Int Clin Psychopharmacol.* 2010; **25**(5): 257–263.[8]
	Perlis RH, Baker RW, Zarate CA Jr, *et al.* Olanzapine versus risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry.* 2006; **67**(11): 1747–1753.[9]
Olanzapine vs. haloperidol	Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, *et al.* A 12-week, double-blind comparison of olanzapine vs. haloperidol in the treatment of acute mania. *Arch Gen Psychiatry.* 2003; **60**(12): 1218–1226.[10]
Olanzapine vs. lithium	Tohen M, Greil W, Calabrese JR, *et al.* Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry.* 2005; **162**(7), 1281–1290.[11]
Olanzapine vs. asenapine	McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar Disord.* 2009; **11**(8): 815–826.[12]
Olanzapine vs. valproate	Tohen M, Ketter TA, Zarate CA, *et al.* Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry.* 2003; **160**(7): 1263–1271.[13]
Olanzapine + mood stabilizer	Tohen M, Chengappa KN, Suppes T, *et al.* Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry.* 2004; **184**: 337–345.[14]
Quetiapine	Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *J Clin Psychiatry.* 2011; **72**(11): 1452–1464.[15]
Quetiapine + lithium/ valproate	Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord.* 2008; **109**(3): 251–263.[16]
	Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry.* 2009; **166**(4): 476–488.[17]
Aripiprazole	Keck PE Jr, Marcus R, Tourkodimitris S, *et al.* A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry.* 2003; **160**(9): 1651–1658.[18]
	Keck PE, Orsulak PJ, Cutler AJ, *et al.* Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *J Affect Disord.* 2009; **112**(1–3): 36–49.[19]
	Young AH, Oren DA, Lowy A, *et al.* Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. *Br J Psychiatry.* 2008, **194**(1) 40–48.[20]
	Keck PE Jr, Calabrese JR, McIntyre RS, *et al.* Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry.* 2007; **68**(10): 1480–1491.[21]
	Findling RL, Nyilas M, Forbes RA, *et al.* Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2009; **70**(10): 1441–1451.[22]
Aripiprazole vs. haloperidol	Vieta E, Bourin M, Sanchez R, *et al.* Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry.* 2005; **187**: 235–242.[23]
Aripiprazole + valproate/ lithium	Vieta E, T'Joen C, McQuade RD, *et al.* Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry.* 2008; **165**(10): 1316–1325.[24]
	Marcus R, Khan A, Rollin L, *et al.* Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disord.* 2011; **13**(2): 133–144.[25]
	Vieta E, Owen R, Baudelet C, McQuade RD, Sanchez R, Marcus RN. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. *Curr Med Res Opin.* 2010; **26**(6): 1485–1496.[26]
Asenapine	McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *J Affect Disord.* 2010; **126**(3): 358–365.[27]
	McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord.* 2010; **122**(1–2): 27–38.[28]
Ziprasidone	Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry.* 2010; **71**(2): 130–137.[29]
	Keck PE Jr, Versiani M, Potkin S, West SA, Giller E, Ice K. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry.* 2003; **160**(4): 741–748. [30]
	Potkin SG, Keck PE Jr, Segal S, Ice K, English P. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol.* 2005; **25**(4): 301–310.[31]
Paliperidone	Vieta E, Nuamah IF, Lim P, *et al.* A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord.* 2010; **12**(3): 230–243.[32]
	Berwaerts J, Xu H, Nuamah I, Lim P, Hough D. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *J Affect Disord.* 2012; **136**(1–2): e51–e60.[33]
Risperidone	Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry.* 2005; **187**: 229–234.[34]

TABLE 1: Continued

Cariprazine	Sachs GS, Greenberg WM, Starace A, *et al.* Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disorders.* 2015; **174**: 296–302.[35]
	Durgam S, Starace A, Li D, *et al.* The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar Disord.* 2015; **17**(1): 63–75.[36]
	Calabrese JR, Keck PE Jr, Starace A, *et al.* Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry.* 2015; **76**(3): 284–292.[37]
Valproate	Bowden CL, Swann AC, Calabrese JR, *et al.* A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry.* 2006; **67**(10): 1501–1510.[38]
Valproate vs. lithium	Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry.* 1992; **149**(1): 108–111.[39]
Lamotrigine + lithium	Bowden CL, Calabrese JR, Sachs G, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry.* 2003; **60**(4): 392–400.[40]
	Calabrese JR, Bowden CL, Sachs G, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry.* 2003; **64**(9): 1013–1024.[41]

Long-Term (≥8 Weeks), Maintenance and Relapse Prevention Studies

Antipsychotic medication

We found one post-hoc analysis of a randomized placebo-controlled trial that compared olanzapine with placebo in mixed-episode patients for 6 to 12 weeks. The results indicated that olanzapine-treated patients had significantly lower rates of symptomatic relapse of any kind compared with placebo, with a reported NNT of 4 to prevent one episode of symptomatic relapse.[58,59]

Mood stabilizers

Two first-degree trials met our inclusion criteria: one of valproate and one of carbamazepine. Bowden *et al.*[60] provided randomized maintenance treatment with valproate, lithium, or placebo to euphoric and dysphoric patients. Among the dysphoric patients, there were no statistically significant treatment-related differences on time to relapse nor on manic and depressive scores.

Ketter *et al.*[61] examined the efficacy of carbamazepine extended-release capsules as maintenance therapy in bipolar patients with manic and mixed episodes in an open-label extension study of two double-blind placebo-controlled trials. Separate data analysis of the mixed subgroup was only reported for depressive symptoms, where carbamazepine treatment maintained the significant decrease of depressive symptoms observed at the end of the double-blind studies.

Combination therapy

One first-degree study of aripiprazole+lamotrigine combination therapy was found.[62] Time to relapse in the mixed-state group was significantly longer in the aripiprazole+lamotrigine group compared to the placebo +lamotrigine group in this study.

Finally, in a 24-week open-label (second-degree) combination trial, Woo *et al.*[63] investigated the efficacy of risperidone in combination with mood stabilizers. A significant improvement from mean baseline was reported for both manic and depressive symptoms among mixed-episode patients.

Discussion

We found that the vast majority of published RCTs initially recruited both pure manic and mixed patients as defined by the DSM-IV classification system and that additional analyses were performed to identify effects in the subgroup of mixed patients only in a small proportion of these studies. This subgroup approach has several shortcomings. First, the resulting sample sizes are usually small, and thus "negative" trials could have been

https://doi.org/10.1017/S1092852917000013 Published online by Cambridge University Press

TABLE 2. Studies evaluating pharmacological treatments for mixed states in bipolar disorder during the acute or long-term/maintenance phase.

A. ACUTE PHASE

Antipsychotic medication (n = 6)

			Primary Findings		
Drug	Study	Sample – mixed state only	Measure	Outcome*	Quality of evidence**
Aripiprazole	Suppes et al., 2008 [43]	Total n = 190 Aripiprazole n = 93 Placebo n = 97	YMRS Response rate (≥50% YMRS reduction) Remission rate (≤12 endpoint YMRS) MADRS	Aripiprazole > placebo, $p < 0.01$ Aripiprazole > placebo, $p = 0.0006$ Aripiprazole > placebo, $p = 0.0107$ Not reported for mixed state group.	1
	Sachs et al., 2006 [44]	Total n = 113 Aripiprazole n = 59 Placebo n = 54	YMRS MADRS	Aripiprazole > placebo, $p = 0.010$ Aripiprazole > placebo, $p = 0.041$	1
Asenapine	McIntyre et al., 2009 [45]	Total n = 146 Asenapine n = 53 Olanzapine n = 58 Placebo n = 35	YMRS MADRS	Asenapine > placebo, $p = 0.05$ Olanzapine > placebo, $p = 0.006$ Not reported for mixed state group.	1
Lurasidone	Suppes et al., 2016 [46]	Total n = 209, Lurasidone n = 109 Placebo n = 100	YMRS MADRS	Lurasidone > placebo, $p < 0.001$ Lurasidone > placebo, $p < 0.001$	1
Ziprasidone	Patkar et al., 2012 [47]	Total n = 73 Ziprasidone n = 35 Placebo n = 38	MRS MADRS	Ziprasidone = placebo Ziprasidone > placebo, $p < 0.0038$	1
	Stahl et al., 2010 [48]	Total n = 179 Ziprasidone n = 124 Placebo n = 55	MRS HAM-D Response rate (≥50% MRS reduction) Remission rate (≤10 endpoint MRS)	Ziprasidone > placebo, $p < 0.01$ Ziprasidone > placebo, $p = 0.027$ Ziprasidone > placebo, $p = 0.02$ Ziprasidone > placebo, $p = 0.01$	1

Mood stabilisers (n = 1)

			Primary Findings		
Drug	Study	Sample – mixed state only	Measure	Outcome*	Quality of evidence**
Carbamazepine	Weisler et al., 2006 [50] – post-hoc analysis [51, 52]	Total n = 147 Carbamazepine n = 80 Placebo n = 67	YMRS HAMD	Carbamazepine > placebo, $p < 0.01$ Carbamazepine > placebo, $p < 0.05$	1

Combination therapy (n = 5)

			Primary Findings		
Drug	Study	Sample – mixed state only	Measure	Outcome*	Quality of evidence**
Olanzapine + Valproate	Houston et al., 2009 [53]	Total n = 201, Olanzapine + Valproate n = 100 Placebo + Valproate n = 101	YMRS HAMD	Olanzapine + Valproate > Placebo + Divalproex, $p < 0.004$ Olanzapine + Valproate > Placebo + Divalproex, $p = 0.03$	1
Olanzapine + Valproate/Lithium	Tohen et al., 2002 [54]	Total n = 179 Olanzapine + Valproate/Lithium n = 125 Placebo + Valproate/Lithium n = 54	YMRS HAMD	Olanzapine + Valproate > Placebo + Valproate, $p < 0.001$ Olanzapine + Lithium = Placebo + Lithium Olanzapine + any > Placebo + any, $p < 0.001$	1
	Baker et al., 2004 [55]	Total n = 85 Olanzapine + Valproate/Lithium n = 60 Placebo + Valproate/Lithium n = 25	YMRS HAMD	Olanzapine + any > Placebo + any, $p < 0.001$ Olanzapine + any > Placebo + any, $p < 0.001$	1

https://doi.org/10.1017/S1092852917000013 Published online by Cambridge University Press

TABLE 2: Continued

Olanzapine + Fluoxetine	Benazzi et al., 2009 post hoc analysis [56]	Total n = 376 Olanzapine + Fluoxetine n = 37 Olanzapine n = 173 Placebo n = 166	Response rate (≥50% MADRS reduction & <2 (hypo)manic symptoms)	Olanzapine + Fluoxetine = Olanzapine Olanzapine + Fluoxetine > Placebo, p = 0.0006 Olanzapine > Placebo, p = 0.014	1
Quetiapine + any co-occurring treatment	Suppes et al., 2013 [57]	Total n = 55 Quetiapine + any n = 30 Placebo + any n = 25	YMRS MADRS	Quetiapine = placebo Quetiapine > Placebo , p = 0.0138	1

B. LONGER TERM (≥ 8 WEEKS), MAINTENANCE AND RELAPSE PREVENTION STUDIES

Antipsychotic medication (n = 1)

			Primary Findings		
Drug	Study	Sample – mixed state only	Measure	Outcome*	Quality of evidence**
Olanzapine	Tohen et al., 2009 Post hoc analysis [58,59]	Total n = 121 Olanzapine n = 76 Placebo n = 45	Time to relapse Incidence of relapse	Olanzapine > Placebo, p < 0.001 Olanzapine > Placebo, p < 0.001	1

Mood stabilisers (n = 2)

			Primary Findings		
Drug	Study	Sample – mixed state only	Measure	Outcome*	Quality of evidence**
Valproate	Bowden et al., 2005 [60]	Total n = 247 Valproate n = 104 Lithium n = 89 Placebo n = 54	MRS SADS-DSS Time to relapse	Valproate = placebo Valproate = placebo Valproate = placebo	1
Carbamazepine	Ketter et al, 2004 [61]	Total n = 62 Carbamazepine n = not reported Placebo n = not reported	YMRS HAMD Time to relapse	Not reported for mixed state group. Carbamazepine > placebo, p = 0.0003 Not reported for mixed state group.	1

Combination therapy (n = 2)

			Primary Findings		
Drug	Study	Sample – mixed state only	Measure	Outcome*	Quality of evidence**
Aripiprazole + Lamotrigine	Carlson et al., 2012 [62]	Total n = 173 Aripiprazole + Lamotrigine n = 78 Placebo + Lamotrigine n = 95	Time to relapse	Aripiprazole + Lamotrigine > Placebo + Lamotrigine, p = 0.041	1
Risperidone + Mood stabiliser	Woo et al., 2009 [63]	Total n = 44 No placebo arm.	YMRS HAMD	Significant improvement from baseline, p < 0.0001 Significant improvement from baseline, p < 0.0001	2

* > **indicates 'significantly superior'**; = **indicates 'no significant difference'**; ** 1- first-degree evidence: randomised placebo controlled studies of pharmacological interventions used in monotherapy; 2- second-degree evidence: absence of a placebo group or of combination therapy; 3- third degree evidence: case reports, case series or reviews of published studies; HAMD- Hamilton Depression Rating Scale, MADRAS- Montgomery-Asberg Depression Rating Scale, MRS- Mania Rating Scale, SADS-DSS- Schedule for Affective Disorders and Schizophrenia-Depressive Syndrome Scale, YMRS- Young Mania Rating Scale.

underpowered to detect existing differences between treatment groups. Second, the enrollment criteria in many of these studies were based on manic symptom severity alone, and there was no minimum depressive score cut-off, suggesting that the mixed patients enrolled could be less severely ill than those seen in clinical practice or that they may not be representative of the full spectrum. Third, the categorical definition in the DSM-IV limits the number of patients identified, since it requires the co-occurrence of a full manic and a full depressive

https://doi.org/10.1017/S1092852917000013 Published online by Cambridge University Press

episode. The new DSM-5 specifier, however, has the potential to address this latter issue, as it is likely that it will increase the detection and reporting of mixed states from both ends of the spectrum. A further major shortfall of the literature is that mixed depressive cases are not usually reported in depression RCTs. Additionally, there were only seven studies identified in the literature that exclusively examined pharmacotherapy for the mixed manic or depressive state. Due to the low number of studies, the variety of pharmacological interventions tested, the differences in methodology and in the aim of treatment (acute vs. maintenance), it is not possible to draw informative conclusions for clinical practice at the present point in time.

Some limitations of our work must be acknowledged. Although our search strategy was comprehensive, there is still the chance that relevant papers or studies have been missed. This review did not include books or clinical trials that looked at the effects of other nonpharmacological treatment modalities, such as psychosocial interventions or electroconvulsive therapy. We reported results distinguishing between manic and depressive outcomes when available, which may be more in line with the clinical need to understand to what extent the chosen medication is able to resolve both manic and depressive symptoms in mixed states or, conversely, to independently treat one or the other. Moreover, this is in line with the new "mixed-features" categorization of mood episodes in the DSM-5, as the distinction in efficacy based on the polarity of concomitant symptoms may be more applicable to the clinical setting.

In summary, the currently available evidence does not meet clinicians' demands. Therefore, there is a clear need to conduct well-powered clinical trials specifically designed to enroll the full range of mixed features using current criteria.

Disclosures

Alessandro Cuomo, Viktoriya Nikolova, Nefize Yalin, and Danilo Arnone hereby declare that they do not have anything to disclose.

Andrea Fagiolini reports grants and personal fees from Allergan, Angelini, Astra Zeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Eli Lilly, Janssen, Lundbeck, Novartis, Otsuka, and Roche, outside the submitted work.

Allan Young has the following disclosures. Employed by King's College London. Honorary consultant SLaM (NHS UK). Paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders. No shareholdings in pharmaceutical companies. Lead Investigator for the Embolden Study (AZ), the BCI Neuroplasticity Study, and the Aripiprazole Mania Study. Investigator-initiated studies from AZ, Eli Lilly, Lundbeck, and Wyeth. Grant funding (past and present): NIMH (USA), CIHR (Canada), NARSAD (USA), Stanley Medical Research Institute (USA), MRC (UK), Wellcome Trust (UK). the Royal College of Physicians (Edin), BMA (UK), UBC-VGH Foundation (Canada), WEDC (Canada), CCS Depression Research Fund (Canada), MSFHR (Canada), and NIHR (UK).

REFERENCES:

1. Swann AC, Lafer B, Perugi G, *et al*. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. *Am J Psychiatry*. 2013; **170**(1): 31–42. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.2012.12030301. Accessed January 8, 2017.
2. Vieta E, Valenti M. Mixed states in DSM-5: implications for clinical care, education, and research. *J Affect Disord*. 2013; **148**(1): 28–36. Epub ahead of print Apr 2. http://www.jad-journal.com/article/S0165-0327(13)00232-2/pdf. Accessed January 8, 2017.
3. Castle DJ. Bipolar mixed states: still mixed up? *Curr Opin Psychiatry*. 2014; **27**(1): 38–42.
4. Houston JP, Ahl J, Meyers AL, Kaiser CJ, Tohen M, Baldessarini RJ. Reduced suicidal ideation in bipolar I disorder mixed-episode patients in a placebo-controlled trial of olanzapine combined with lithium or divalproex. *J Clin Psychiatry*. 2006; **67**(8): 1246–1252.
5. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009; **151**(4): W65–W94. Epub ahead of print Jul 20.
6. Tohen M, Sanger TM, McElroy SL, *et al*. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *Am J Psychiatry*. 1999; **156**(5): 702–709. http://ajp.psychiatryonline.org/doi/pdf/10.1176/ajp.156.5.702. Accessed January 8, 2017.
7. Tohen M, Jacobs TG, Grundy SL, *et al*. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. *Arch Gen Psychiatry*. 2000; **57**(9): 841–849. http://jamanetwork.com/journals/jamapsychiatry/fullarticle/205739. Accessed January 8, 2017.
8. Novick D, Reed C, Haro JM, *et al*. Comparison of olanzapine and risperidone in the EMBLEM Study: translation of randomized controlled trial findings into clinical practice. *Int Clin Psychopharmacol*. 2010; **25**(5): 257–263.
9. Perlis RH, Baker RW, Zarate CA Jr, *et al*. Olanzapine versus risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006; **67**(11): 1747–1753.
10. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, *et al*. A 12-week, double-blind comparison of olanzapine vs. haloperidol in the treatment of acute mania. *Arch Gen Psychiatry*. 2003; **60**(12): 1218–1226. http://jamanetwork.com/journals/jamapsychiatry/fullarticle/208076. Accessed January 8, 2017.
11. Tohen M, Greil W, Calabrese JR, *et al*. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry*. 2005; **162**(7): 1281–1290. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.162.7.1281. Accessed January 8, 2017.
12. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar Disord*. 2009; **11**(8): 815–826. Epub ahead of print Oct 14.

https://doi.org/10.1017/S1092852917000013 Published online by Cambridge University Press

13. Tohen M, Ketter TA, Zarate CA, *et al*. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry*. 2003; **160**(7): 1263–1271. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.160.7.1263. Accessed January 8, 2017.
14. Tohen M, Chengappa KN, Suppes T, *et al*. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry*. 2004; **184**: 337–345. http://bjp.rcpsych.org/content/184/4/337.long. Accessed January 8, 2017.
15. Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (trial 144: a randomized controlled study). *J Clin Psychiatry*. 2011; **72**(11): 1452–1464.
16. Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord*. 2008; **109**(3): 251–263. Epub ahead of print Jun 24.
17. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry*. 2009; **166**(4): 476–488. Epub ahead of print Mar 16. http://ajp.psychiatryonline.org/doi/pdfplus/10.1176/appi.ajp.2008.08020189. Accessed January 8, 2017.
18. Keck PE Jr, Marcus R, Tourkodimitris S, *et al*. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003; **160**(9): 1651–1658. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.160.9.1651. Accessed January 8, 2017.
19. Keck PE, Orsulak PJ, Cutler AJ, *et al*. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *J Affect Disord*. 2009; **112**(1–3): 36–49. Epub ahead of print Oct 2, 2008.
20. Young AH, Oren DA, Lowy A, *et al*. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. *Br J Psychiatry*. 2008, **194**(1): 40–48. http://bjp.rcpsych.org/content/194/1/40.long. Accessed January 8, 2017.
21. Keck PE Jr, Calabrese JR, McIntyre RS, *et al*. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry*. 2007; **68**(10): 1480–1491.
22. Findling RL, Nyilas M, Forbes RA, *et al*. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2009; **70**(10): 1441–1451.
23. Vieta E, Bourin M, Sanchez R, *et al*. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005; **187**: 235–242. http://bjp.rcpsych.org/content/187/3/235.long. Accessed January 8, 2017.
24. Vieta E, T'Joen C, McQuade RD, *et al*. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry*. 2008; **165**(10): 1316–1325. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.2008.07101560. Accessed January 8, 2017.
25. Marcus R, Khan A, Rollin L, *et al*. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disord*. 2011; **13**(2): 133–144.
26. Vieta E, Owen R, Baudelet C, McQuade RD, Sanchez R, Marcus RN. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. *Curr Med Res Opin*. 2010; **26**(6): 1485–1496.
27. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *J Affect Disord*. 2010; **126**(3): 358–365.
28. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord*. 2010; **122**(1–2): 27–38.
29. Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry*. 2010; **71**(2): 130–137.
30. Keck PE Jr, Versiani M, Potkin S, West SA, Giller E, Ice K. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003; **160**(4): 741–748. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.160.4.741. Accessed January 8, 2017.
31. Potkin SG, Keck PE Jr, Segal S, Ice K, English P. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol*. 2005; **25**(4): 301–310.
32. Vieta E, Nuamah IF, Lim P, *et al*. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord*. 2010; **12**(3): 230–243.
33. Berwaerts J, Xu H, Nuamah I, Lim P, Hough D. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose–response study. *J Affect Disord*. 2012; **136**(1–2): e51–e60. Epub ahead of print Jul 10, 2010.
34. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry*. 2005; **187**: 229–234. http://bjp.rcpsych.org/content/187/3/229.long. Accessed January 8, 2017.
35. Sachs GS, Greenberg WM, Starace A, *et al*. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disorders*. 2015; **174**: 296–302. Epub ahead of print Nov 24, 2014. http://www.jad-journal.com/article/S0165-0327(14)00728-9/pdf. Accessed January 8, 2017.
36. Durgam S, Starace A, Li D, *et al*. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar Disord*. 2015; **17**(1): 63–75. Epub ahead of print Jul 24, 2014.
37. Calabrese JR, Keck PE Jr, Starace A, *et al*. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015; **76**(3): 284–292.
38. Bowden CL, Swann AC, Calabrese JR, *et al*. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry*. 2006; **67**(10): 1501–1510.
39. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry*. 1992; **149**(1): 108–111.
40. Bowden CL, Calabrese JR, Sachs G, *et al*. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder.

Arch Gen Psychiatry. 2003; **60**(4): 392–400. http://jamanetwork.com/journals/jamapsychiatry/fullarticle/207328. Accessed January 8, 2017.

41. Calabrese JR, Bowden CL, Sachs G, *et al*. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003; **64**(9): 1013–1024.
42. Perugi G, Toni C, Ruffolo G, Sartini S, Simonini E, Akiskal H. Clinical experience using adjunctive gabapentin in treatment-resistant bipolar mixed states. *Pharmacopsychiatry*. 1999; **32**(4): 136–141.
43. Suppes T, Eudicone J, McQuade R, Pikalov A 3rd, Carlson B. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. *J Affect Disord*. 2008; **107**(1–3): 145–154. Epub ahead of print Sep 27, 2007.
44. Sachs G, Sanchez R, Marcus R, *et al*. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol*. 2006; **20**(4): 536–546. http://journals.sagepub.com/doi/pdf/10.1177/0269881106059693. Accessed January 8, 2017.
45. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord*. 2009; **11**(7): 673–686.
46. Suppes T, Silva R, Cucchiaro J, *et al*. Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2016; **173**(4): 400–407. Epub ahead of print Nov 10, 2015.
47. Patkar A, Gilmer W, Pae CU, *et al*. A 6-week randomized double-blind placebo-controlled trial of ziprasidone for the acute depressive mixed state. *PloS One*. 2012; **7**(4): e34757. Epub ahead of print Apr 24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335844/. Accessed January 8, 2017.
48. Stahl S, Lombardo I, Loebel A, Mandel FS. Efficacy of ziprasidone in dysphoric mania: pooled analysis of two double-blind studies. *J Affect Disord*. 2010; **122**(1–2): 39–45. Epub ahead of print Jul 17, 2009.
49. Suppes T, McElroy SL, Gilbert J, Dessain EC, Cole JO. Clozapine in the treatment of dysphoric mania. *Biol Psychiatry*. 1992; **32**(3): 270–280.
50. Weisler RH, Hirschfeld R, Cutler AJ, *et al*. Extended-release carbamazepine capsules as monotherapy in bipolar disorder: pooled results from two randomised, double-blind, placebo-controlled trials. *CNS Drugs*. 2006; **20**(3): 219–231.
51. Weisler RH, Kalali AH, Ketter TA. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry*. 2004; **65**(4): 478–484.
52. Weisler RH, Keck PE Jr, Swann AC, Cutler AJ, Ketter TA, Kalali AH. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2005; **66**(3): 323–330.
53. Houston JP, Tohen M, Degenhardt EK, Jamal HH, Liu LL, Ketter TA. Olanzapine-divalproex combination versus divalproex monotherapy in the treatment of bipolar mixed episodes: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2009; **70**(11): 1540–1547. Epub ahead of print Sep 22.
54. Tohen M, Chengappa KN, Suppes T, *et al*. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry*. 2002; **59**(1): 62–69.
55. Baker RW, Brown E, Akiskal HS, *et al*. Efficacy of olanzapine combined with valproate or lithium in the treatment of dysphoric mania. *Br J Psychiatry*. 2004; **185**: 472–478. http://bjp.rcpsych.org/content/185/6/472.long. Accessed January 8, 2017.
56. Benazzi F, Berk M, Frye MA, Wang W, Barraco A, Tohen M. Olanzapine/fluoxetine combination for the treatment of mixed depression in bipolar I disorder: a post hoc analysis. *J Clin Psychiatry*. 2009; **70**(10): 1424–1431.
57. Suppes T, Ketter TA, Gwizdowski IS, *et al*. First controlled treatment trial of bipolar II hypomania with mixed symptoms: quetiapine versus placebo. *J Affect Disord*. 2013; **150**(1): 37–43. Epub ahead of print Mar 19.
58. Tohen M, Calabrese JR, Sachs GS, *et al*. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry*. 2006; **163**(2): 247–256. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.163.2.247. Accessed January 8, 2017.
59. Tohen M, Sutton VK, Calabrese JR, Sachs GS, Bowden CL. Maintenance of response following stabilization of mixed index episodes with olanzapine monotherapy in a randomized, double-blind, placebo-controlled study of bipolar 1 disorder. *J Affect Disord*. 2009; **116**(1–2): 43–50. Epub ahead of print Dec 2, 2008.
60. Bowden CL, Collins MA, McElroy SL, *et al*. Relationship of mania symptomatology to maintenance treatment response with divalproex, lithium, or placebo. *Neuropsychopharmacology*. 2005; **30**(10): 1932–1939. http://www.nature.com/npp/journal/v30/n10/pdf/1300788a.pdf. Accessed January 8, 2017.
61. Ketter TA, Kalali AH, Weisler RH. A 6-month, multicenter, open-label evaluation of beaded, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry*. 2004; **65**(5): 668–673.
62. Carlson BX, Ketter TA, Sun W, *et al*. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). *Bipolar Disord*. 2012; **14**(1): 41–53.
63. Woo YS, Bahk WM, Jon DI, *et al*. Risperidone in the treatment of mixed state bipolar patients: results from a 24-week, multicenter, open-label study in Korea. *Psychiatry Clin Neurosci*. 2010; **64**(1): 28–37. Epub ahead of print Nov 4, 2009.