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Pharmacological Treatment of Mixed States

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ABSTRACT:

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, COCHRANE LIBRARY, clinicaltrials.gov, current-trials.com (key words: "mixed states/features" AND "bipolar" AND "depressive symptoms/bipolar depression" AND "manic symptoms" AND "treatment" AND "DSM-5") to April 2016. We applied a quality of evidence approach (first-degree evidence: randomised placebo controlled studies of pharmacological interventions used in monotherapy; second-degree evidence comprised a similar design in the absence of a placebo group or of combination therapy; third degree evidence comprised case reports, case series, post-hoc analysis of primary data, non-controlled cohort studies and reviews of published studies).

We found very little primary double-blind, placebo-controlled studies of the treatment of mixed states: the preponderance of available data derives from sub-group analysis performed on studies that originally involved manic patients.

Introduction

Mixed states present particular challenges to the treating clinician and even the prevalence rate changes significantly among studies and in relation to diagnostic criteria used. In DSM-IV, a diagnosis of a mixed episode required simultaneously all criteria for a manic or a major depressive episode. In clinical practice individuals infrequently meet these full criteria. After a 14-year development process including approximately 400 people from different professions and 39 countries, DSM-5 appeared in May 2013. The new DSM-5 "specifier" adopts a broader approach towards 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 and an increase in energy or goal-directed activities), occurring nearly every day during the most recent two weeks of the 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) together with the episode of mania/hypomania, nearly every day throughout the most recent week of a manic episode or during the most recent four days of a hypomanic episode.

Mixed states are generally held to be less responsive to pharmacological treatment and 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 high³. However, the use of an atypical antipsychotic-antimanic agent in some bipolar disorder patients may decrease suicidal ideation⁴. 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 review the pharmacological treatment of "mixed states/episodes" as defined by DSM-IV and DSM-5 manic episodes "with mixed features" .

Methods

Searches

PUBMED, MEDLINE, and the Cochrane library were searched from January 1980 to April 2016 for all publications regarding treatment of mixed features as defined by DSM-IV and DSM-5 manic episodes "with mixed features". Clinical trials registries, 'clinicaltrials.gov' and 'controlled-trials.com', were scrutinised for trials. Search terms included: "Mixed states OR Mixed features" AND "Bipolar disorder" AND "depressive symptoms OR bipolar depression" AND "Manic symptoms" AND "Treatment" AND "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. Articles were screened and selected for full-text review if they met our selection criteria. Once identified titles and abstracts were reviewed independently by two the authors (AC,, AY) and discrepancies were resolved by consensus among all the authors.

Quality assessment

First-degree studies included double blind, placebo controlled randomised controlled trials (RCTs) of pharmacological interventions used in monotherapy. Second-degree referred to a similar design without placebo group +/- combination therapy and third degree referred to any other type of published studies.

Results

The searches identified 913 studies of which 73 met inclusion criteria and investigated mixed states in bipolar disorder. Non-original studies (including editorials, book reviews and letters to the editor) and studies without full-text available were excluded.

These studies evaluated antipsychotics (n=39), mood stabilizers (n=14) and combination therapies (n=20) in patients with DSM-IV mixed episodes or DSM-5 mixed features. Pharmacological evidence for each class of medication is described below and organised according to clinical presentation, length of treatment and degree of evidence (Supplementary Tables with details available upon request).

Antipsychotic medication with mood stabilising properties

1) OLANZAPINE

Acute treatment studies (≤ 8 weeks)

We identified two first degree studies comparing olanzapine with placebo^{6,7}, one second degree evidence study comparing olanzapine with haloperidol⁸ and two with risperidone^{9,10}.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

We identified six second degree studies. One open label post-hoc analysis compared olanzapine with placebo and further five trials compared olanzapine with haloperidol (6-week continuation phase), sodium valproate, lithium and asenapine in two reports (see below for asenapine). A post hoc-analysis open label study of a randomized, placebo-controlled trial¹¹ compared olanzapine with placebo in mixed episode patients for 6-12-week¹². A subsequent 6-week continuation phase of Tohen et al. 12-week comparison trial was also identified (olanzapine vs haloperidol)¹⁰. Tohen and

others¹³ analyzed the efficacy of olanzapine vs. valproate in the treatment of mania and mixed episodes. A further study of 52 weeks¹⁴ compared the efficacy of olanzapine and lithium monotherapy in relapse/recurrence prevention of mood episodes among remitted patients previously treated with a combination therapy of these two compounds (for 6-12 weeks).

2) QUETIAPINE

Acute treatment (≤ 8 weeks)

We identified five first degree acute phase studies. Three studies compared quetiapine with placebo¹⁵⁻¹⁷ and two compared quetiapine with lithium or paroxetine and placebo^{18,19}. Another randomized controlled study compared quetiapine with paliperidone extended release to placebo (see paliperidone). A second degree evidence continuation phase of the study which compared quetiapine with paliperidone without placebo is described below (see paliperidone)²⁰.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

One maintenance study compared quetiapine with lithium and placebo as open label extension of a randomised controlled trial in Bipolar I disorder for up to 104 weeks²¹.

3) ARIPIPRAZOLE

Acute treatment (≤ 8 weeks)

We identified five first degree evidence acute phase trials with aripiprazole. Four studies compared aripiprazole with placebo²²⁻²⁵ and one with lithium and placebo²⁶. A one second degree evidence comparison trial analyzed the efficacy of aripiprazole vs. haloperidol²⁷.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

We identified one first degree long term trial which compared aripiprazole with placebo²⁸ and two second degree extension studies^{26,27} comparing aripiprazole with lithium and haloperidol respectively (the treatment received in the first 3 week of treatment are discussed above).

4) ASENAPINE***Acute treatment (≤ 8 weeks)***

There are two first degree evidence trials^{29,30} assessing asenapine in the management of mixed affective symptoms compared with olanzapine and placebo. McIntyre and others combined the above described studies^{29,30} in a post-hoc analysis³¹ based on the DSM-5 mixed specifier for the diagnosis of manic episodes.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

We reported two second degree evidence trials regarding long term treatment of asenapine compared with olanzapine by McIntyre and others. The authors designed these two stepped progressive studies originating from the first 3 week trial by randomising the placebo group into active treatment^{32,33}.

5) LURASIDONE***Acute treatment (≤ 8 weeks)***

We found evidence of efficacy in acute bipolar depression, supported by two monotherapy randomized clinical trials^{34,35} and one second degree adjunctive therapy study (see combination therapy)³⁶.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

No studies were identified.

6) ZIPRASIDONE

Acute treatment (≤ 8 -weeks)

We identified one first degree evidence trial assessing efficacy of ziprasidone compared with placebo in major depressive episodes with 2 or 3 concomitant manic symptoms³⁷. A second degree study is available from a pooled analysis³⁸ of mixed patient with dysphoric mania previously enrolled in two similar placebo controlled trials^{39,40}.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

No studies were identified.

7) RISPERIDONE

Acute treatment (≤ 8 -weeks)

We identified one first degree trial⁴¹ comparing risperidone to placebo in mixed affective conditions.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

No studies were available.

8) PALIPERIDONE

Acute treatment (≤ 8 -weeks)

We identified two first degree trials^{20,42} assessing efficacy of paliperidone in mixed affective conditions.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

Vieta et al. performed a randomized, placebo- active-controlled study of paliperidone extended release for the treatment of acute manic and mixed Bipolar I disorder²⁰..

9) CLOZAPINE

Acute and maintenance treatment

In a case series by Suppes and others 85 consecutive patients were treated with clozapine. 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 sodium valproate. Clozapine effects were often evident within the first few weeks of treatment and sustained over the 3-5 years follow-up period⁴³.

10) CARIPRAZINE

Acute treatment (≤ 8 -weeks)

The three identified first degree randomized controlled trials measured the effect of cariprazine on manic and depressive symptoms in acute mania or mixed episodes⁴⁴⁻⁴⁶.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

Longer-term treatment of subjects with Bipolar I illness was investigated in an open, 16-week study that followed up 402 patients^{47,48}.

Ongoing trials

An ongoing international 8-week study⁴⁹ of cariprazine vs. placebo in bipolar depression registered on the ClinicalTrials.gov website is currently investigating subjects with Bipolar I depression with a verified previous manic or mixed episode, without psychotic features, aged 18–65, total HAMD score of ≥ 20 , HAMD Item 1 score of ≥ 2 , and CGI-S of ≥ 4 to be randomized to cariprazine 0.75, 1.5, or 3.0 mg/day, or placebo.

Mood stabilizers in management of mixed affective features

1) DIVALPROEX

Acute treatment (≤ 8 weeks)

We found four first degree Divalproex vs. placebo acute treatment trials⁵⁰⁻⁵³.

Maintenance treatment (≥ 8 weeks) No maintenance or relapse prevention trials with divalproex monotherapy were found. Comparison studies are analyzed in the section below (see lithium).

2) LITHIUM

Acute treatment (≤ 16 weeks)

We identified two second degree comparison trials with divalproex (in manic/mixed bipolar patients)⁵⁴ or lamotrigine⁵⁵ in bipolar depression.

Maintenance/relapse prevention treatment (≥ 16 weeks)

Only one trial was identified comparing lithium monotherapy vs. placebo as a prophylactic intervention in major unipolar depression and hypomania in bipolar disorder⁵⁶. Three long-term

phase trials compared lithium with divalproex and placebo⁵⁷ and two lithium with lamotrigine and placebo (described with lamotrigine below).

3) CARBAMAZEPINE

Acute treatment (≤ 8 weeks)

Weisler and others⁵⁸ reported a post hoc analysis of two randomised controlled studies^{59,60}. The first trial showed higher response rates in mixed or manic patients treated with carbamazepine-extended release (CBZ-ER) vs. placebo (42% vs. 22% respectively). The second trial reported response rates in acute manic patient treated with CBZ-ER vs. placebo in the range of 60.8% and 28.7% respectively for mixed patients suggesting that carbamazepine might be effective to treat both manic and depressive symptoms.

Maintenance treatment (≥ 8 weeks)

Ketter and colleagues⁶¹, in an additional secondary analysis confirmed that also long-term monotherapy with extended-release is efficacious against Bipolar I disorder mixed and manic episodes.

4) LAMOTRIGINE

Acute treatment (≤ 16 week)

We found only one first degree study of Bipolar I disorder experiencing a major depressive episode treated with lamotrigine (50 or 200 mg/day) or placebo in monotherapy for a 7-week period.⁶²

Maintenance/ relapse prevention (≥ 16 weeks)

Two first degree trials compared lamotrigine with lithium^{63,64}.

5) GABAPENTIN

Only one open label study investigated gabapentin as adjunctive treatment for treatment resistant Bipolar mixed states presenting at both poles of the illness⁶⁵.

COMBINATION THERAPY

1) ARIPIPIRAZOLE PLUS MOOD STABILIZERS

Acute treatment (≥ 8 weeks)

One trial investigated aripiprazole adjuvant to other mood stabilizers (lithium or valproate) in the treatment of acute phase mixed states⁶⁶.

Longer term maintenance or relapse prevention (≥ 8 weeks)

Two first degree trials^{67,68} compared aripiprazole adjunct to a stabilizers (lithium/valproate and lamotrigine) vs. placebo. A further second degree extension trial compared aripiprazole with lithium or valproate without the placebo arm⁶⁹.

2) OLANZAPINE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Three first degree trials compared olanzapine with a mood stabilizer (lithium or valproate) vs. placebo⁷⁰⁻⁷².

Longer term maintenance/relapse prevention (≥ 8 weeks)

Tohen et al. followed up patients who achieved syndromic remission for 18 months in a double-blind trial⁷³, derived from the 6 weeks trial discussed above⁷¹.

3) OLANZAPINE – FLUOXETINE COMBINATION (OFC)

Acute treatment (≤ 8 weeks)

One first degree study⁷⁴ compared olanzapine monotherapy and in combination (OFC) vs. placebo which included a post-hoc mixed depressed patients analysis. Two second degree trials were also available assessing OFC vs. lamotrigine in bipolar depression with fixed⁷⁵ and flexible doses⁷⁶.

Longer term maintenance and relapse prevention (≥ 8 weeks)

Brown and others also conducted a 6-month long-term follow-up trial⁷⁷ of the 7-week study above⁷⁶ and reported greater response of OFC flexible doses in comparison with lamotrigine (titrated up to 200 mg/day) for both depressive and manic symptoms in Bipolar depression.

4) QUETIAPINE PLUS MOOD STABILIZERS***Acute treatment (≤ 8 weeks)***

Suppes and others assessed adjunctive quetiapine treatment in Bipolar II patients experiencing hypomania with mixed symptoms in a two-site, randomized, placebo-controlled, double-blind, 8-week investigation⁷⁸.

Longer term maintenance/relapse prevention (≥ 8 weeks)

Two placebo-controlled trials^{79,80} evaluated maintenance treatment with quetiapine (compared to placebo) as an adjunct to lithium or divalproex.

5) RISPERIDONE PLUS MOOD STABILIZERS***Acute treatment (≤ 8 weeks)***

No studies were found.

Longer term manitenzance/relapse prevention (≥ 8 weeks)

Woo and others investigated the efficacy of risperidone in combination with mood stabilizers in a 24-week, open-label third-degree combination trial ⁸¹.

6) LURASIDONE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Loebel and others investigated the efficacy of lurasidone as adjunctive therapy with lithium or valproate for the treatment of Bipolar I depression in a 6-week, randomized, placebo-controlled trial ³⁶.

Longer term maintenance/relapse prevention

No trials available for review.

7) ZIPRASIDONE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

No trials available for review.

Longer term maintenance/relapse prevention (≥ 8 weeks)

Bowden and colleagues assessed the maintenance efficacy of ziprasidone compared to placebo as an adjunct to a mood stabilizer in manic/mixed bipolar I patients for up to 6 months (after ≥ 8 consecutive weeks of stability with open-label ziprasidone and lithium or valproate)⁸².

8) LAMOTRIGINE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Van der Loos and colleagues⁸³ added lamotrigine or placebo to the ongoing lithium treatment of patients with bipolar depression.

Longer term maintenance/relapse prevention (≥ 8 weeks)

Bowden and others trialled lamotrigine alone or in combination with divalproex-extended release in recently depressed patients with bipolar disorder in a maintenance study after 8-week open stabilization phase with lamotrigine or divalproex⁸⁴.

Discussion

We found that the vast majority of published RCTs initially recruited both pure manic and mixed patients as defined in the DSM-IV classification system and that additional sub-analyses were performed to identify effects in a subgroup of mixed patients. A major shortfall in the literature is that mixed depressive cases are not usually reported in depression RCTs. This subgroup approach has several shortcomings: first, the resulting sample sizes are usually small and thus “negative” trials could have been underpowered to detect existing differences between groups or “positive” trials might have an increased probability of being falsely positive; second, mixed patients enrolled in RCTs are probably less severely ill than those seen in clinical practice, and thirdly, the categorical definition of DSM-IV limits the number of patients thus identified, since it requires the co-occurrence of a full manic and a full depressive episode. Additional limitations of our work must be acknowledged. Although our search strategy was comprehensive and included several search terms, there is still the chance that we have missed relevant papers or studies. This review did not include books, or clinical trials that have looked at the effects of other, non-pharmacological, treatment modalities such as psychosocial interventions or ECT. We report results distinguishing between manic and depressive outcomes when available, which may be more in line with the clinical need to know to what extent the chosen medication is able to resolve both manic and depressive symptoms in mixed states and bipolar depression or, conversely, to independently treat one or the other. Moreover, this is in line with the new “with mixed features” categorization of mood episodes in DSM-5, as the distinction in efficacy based on the polarity of concomitant

symptoms may be closer to the real clinical setting. The currently available evidence does not meet clinicians' demands. Therefore, there is a clear need to conduct well-powered trials specifically designed to enrol the full range of mixed features.

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PRISMA Flow Diagram

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