Level of response and safety of pharmacological monotherapy in the treatment of acute bipolar I disorder phases: a systematic review and meta-analysis

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Abstract

In recent years, combinations of pharmacological treatments have become common for the treatment of bipolar disorder type I (BP I); however, this practice is usually not evidence-based and rarely considers monotherapy drug regimen (MDR) as an option in the treatment of acute phases of BP I. Therefore, we evaluated comparative data of commonly prescribed MDRs for both manic and depressive phases of BP I. Medline, PsycINFO, EMBASE, the Cochrane Library, the ClinicalStudyResults.org and other data sources were searched from 1949 to March 2009 for placebo and active controlled randomized clinical trials (RCTs). Risk ratios (RRs) for response, remission, and discontinuation rates due to adverse events (AEs), lack of efficacy, or discontinuation due to any cause, and the number needed to treat or harm (NNT or NNH) were calculated for each medication individually and for all evaluable trials combined. The authors included 31 RCTs in the analyses comparing a MDR with placebo or with active treatment for acute mania, and 9 RCTs comparing a MDR with placebo or with active treatment for bipolar depression. According to the collected evidence, most of the MDRs when compared to placebo showed significant response and remission rates in acute mania. In the case of bipolar depression only quetiapine and, to a lesser extent, olanzapine showed efficacy as MDR. Overall, MDRs were well tolerated with low discontinuation rates due to any cause or AE, although AE profiles differed among treatments. We concluded that most MDRs were efficacious and safe in the treatment of manic episodes, but very few MDRs have demonstrated being efficacious for bipolar depressive episodes.

Received 22 April 2009; Reviewed 9 June 2009; Revised 1 December 2009; Accepted 4 December 2009; First published online 4 February 2010

Key words: Anticonvulsants, antipsychotics, bipolar, bipolar depression, lithium, mania, monotherapy.

Background

A recent systematic review of 913 papers, suggested that lithium, some anticonvulsants and second-generation antipsychotics (SGAs) are valuable in the treatment of acute mania (Fountoulakis & Vieta, 2008). Up until recently, first-generation antipsychotics (FGAs) were often the preferred choice for treatment of acute mania, especially in European countries (Tohen et al. 2001; Vestergaard, 1992); however, some reports suggest that they may induce or worsen depressive symptoms in patients with bipolar disorder (Esparon et al. 1986; Zarate & Tohen, 2004). Furthermore, patients with bipolar disorder compared to patients with schizophrenia appear to be more susceptible to extrapyramidal symptoms (EPS) (Cavazzoni et al.
2006; Mukherjee et al. 1986). For bipolar depressed patients, there is uncertainty about the role of antidepressants as they have been associated with manic relapse (Lewis & Winokur, 1982), lack of efficacy (Post et al. 2006; Sachs et al. 2007), and cycle acceleration (Wehr & Goodwin, 1979).

Although combination drug regimens (CDRs) have become ubiquitous in the treatment of non-refractory BP I around the world (Baldessarini et al. 2007; Blanco et al. 2002; Goldberg et al. 2009; Kupfer et al. 2002; Levine et al. 2000; Wolfsperger et al. 2007), the goal of this review was to examine the efficacy and safety of monotherapy drug regimens (MDRs). Despite treatment guidelines recommending the use of monotherapy as a first-line strategy (Garza et al. 2009), polypharmacy often occurs without evidence-based support or sometimes without clear or adequate optimization. For instance, Perlis et al. (2006) found that differences in acute efficacy in the treatment of mania with SGAs are likely to be small, if any, between monotherapy and add-on therapy. However, the literature suggests that there are patients who do not respond to acute treatment with monotherapy, especially in bipolar depression (Blanco et al. 2002; Goldberg et al. 2009; Kupfer et al. 2002). A recent meta-analysis, however, compared co-therapy (anti-psychotic plus mood stabilizer) with monotherapy (mood stabilizer alone) in the treatment of bipolar mania, and found higher response rates with co-therapy although with decreased tolerability (Smith et al. 2007). Cipriani et al. (2007) have suggested that the small sample sizes and the heterogeneity of the study designs lead to biased results favouring co-therapy.

Material and methods

Search strategy and study selection

We conducted a comprehensive literature search of all the articles published up to March 2009 incorporating results of searches of Medline (from 1950), PsycINFO (from 1949), EMBASE (from 1988), the Cochrane Library (2009 January Issue), LILACS (from 1982), the ClinicalStudyResults.org, and two Internet search engines: PsiTri (www.psitri.stakes.fi) and Google Scholar (scholar.google.com). A limited update literature search using Medline was performed from 15 March 2009 to 13 August 2009.

To capture articles relevant to the scope of our review, we cross-referenced terms like ‘bipolar disorder’, ‘manic depressive’, ‘mania’, ‘mixed’, or ‘bipolar depression’, with trial characteristics search phrases and generic names of medications (approved or non-approved by regulatory agencies for their use in bipolar disorder). The full electronic search strategy is available upon request.

We planned a priori the inclusion of studies meeting the following criteria: randomized controlled trials (RCTs) comparing response and/or remission rates of a MDR with placebo or active treatment in patients with BP I (manic/mixed or depressive episodes). We chose discrete measures (response or remission rates) because they are clinically meaningful outcome measures (Lam & Kennedy, 2005). Exclusion criteria included: use of rating scales not validated in patients with bipolar mania, no clear definition of response or remission criteria, or inclusion of patients who had previously failed to respond to lithium or other mood stabilizers. Sample size was also an eligibility criteria to avoid weighting small studies inappropriately as suggested by Petitti (2000) when using random-effects models. The minimum median sample was 16.5 subjects in each group as suggested by a published empirical model (Richy et al. 2004). Additional information required included trial duration, and medication dosage ranges. In addition, trials had to be peer-reviewed and published.

All RCTs were identified and reviewed by two of the authors (J.T. and G.V.). Any disagreements were discussed in order to reach consensus. Names of authors, institutions, or journals were not kept blind.

Evidence-based data for MDRs

We analysed the evidence supporting a therapeutic advantage for each MDR individually and for all evaluable trials combined vs. placebo or other active medication if they were classified as responders (a reduction of at least 50% in the initial score with any appropriate symptom rating scale) or remitters (a predetermined minimum absolute score as recommended in the literature (Tohen et al. 2009); i.e. Young Mania Rating Scale (YMRS) ≤12 or Mania Rating Scale (MRS) ≤8 for patients with a manic/mixed episode, or Montgomery–Åsberg Depression Rating Scale (MADRS) ≤12 or Hamilton Depression Rating Scale (HAMRS) ≤8 for patients with a depressive episode). Rates of discontinuation due to any cause, lack of efficacy, or adverse events (AEs) were also extracted.

Data synthesis

Studies were first qualitatively summarized. When more than one RCT was available for each MDR-comparator contrast, a meta-analytical calculation was used for each MDR. Efficacy and safety dichotomous
data were statistically combined using a random-effects model. The relative risk (RR), which is defined as the ratio of the risk of an unfavourable outcome (non-response or non-remission) among treatment-allocated participants to the corresponding risk of an unfavourable outcome among those in the control group, was estimated along with their 95% confidence intervals (CIs) using the Review Manager 5.0.21 version software (The Cochrane Collaboration, UK). We also calculated RRs along with their 95% CIs for discontinuation due to any cause or discontinuation due to AEs for each MDR. Effect sizes such as number needed to treat (NNT) and number needed to harm (NNH) were also calculated. For this purpose we calculated risk differences (RDs), so NNT and NNH were estimated from the RD by the formula NNT or NNH = 1/RD, with the 95% CI of NNT or NNH being the inverse of the upper and lower limits of the 95% CI of the RD. Only NNTs or NNHs <10 are considered clinically meaningful (Cook & Sackett, 1995; Kraemer & Kupfer, 2006).

Finally, we assessed the quality of the report on every RCT included in this review using a scale designed by Jadad et al. (1996). We performed $\chi^2$ and $I^2$ statistics and the visual inspection of the forest plots derived from the $\chi^2$ values to test the proportion of total variation in study estimates that is due to heterogeneity. This analysis contrasts the RR of the individual trials with the pooled RR or the subgroups of trials. An $I^2$ of at least 50% was taken as indicator of heterogeneity of outcome and considered inconclusive (Egger et al. 1997, 2001; Higgins & Thompson, 2002; Higgins et al. 2003).

**Results**

**Included studies**

We identified 101 non-duplicated RCTs, of which 40 fulfilled search criteria (Fig. 1). Some of the RCTs used a three-arm design thus could be used to make two comparisons each. In some cases, two or more articles/references provide data for the same RCT. The duration of most studies was 3 wk and most of them used the YMRS for the assessment of severity of manic symptoms. For bipolar depression, most studies were at least 7 wk in duration and utilized either the HAMD or the MADRS for the assessment of severity of depressive symptoms.

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**Literature Search**

Databases: Medline, EMBASE, PsycINFO, Cochrane Library, LILACS

No Limits in Language, Journal or Country

**Search results combined (n = 3198)**

First screen of articles on basis of title and/or abstract

Excluded (n = 3097)
- Not related with bipolar disorder, long-term studies, combination or adjunctive therapy studies, sub-analyses, not pharmacological, not clinical, open-label studies, opinion or review papers...

Manuscript review and application of inclusion/exclusion criteria (n = 101)

Excluded (n = 61)
- Sample size: 12
- Absence/inappropriate evaluation of primary objective: 23
- Not homogeneous sample: 20
- Inconclusive results due to early study termination: 1
- Previous no response to a mood stabilizer: 3
- Combination therapy: 2

Included (n = 40)

Manic/mixed episode (n = 31)
Depressive episode (n = 9)

Fig. 1. Flow of information diagram through the different phases of the systematic review.
**MDRs for acute mixed/mania episodes**

Since the first evidence of lithium’s efficacy in mania reported by Cade (1949) a considerable number of RCTs evaluating the efficacy of lithium salts, anti-convulsants, FGAs and SGAs used as MDRs in patients with acute mania have been published. Many studies that were reviewed did not meet our inclusion criteria due to their small sample size. Other studies were excluded because they had used rating scales neither specific nor validated for mania, had not included a clear definition of response or remission criteria, or had included patients that had previously not responded to lithium or other mood stabilizers [Ballenger & Post (1978, 1980), Berk et al. (1999), Bradwejn et al. (1990), Brown et al. (1989), Clark et al. (1997), Cookson et al. (1981), DelBello et al. (2005), Esparon et al. (1986), Findling et al. (2007), Freeman et al. (1992), Garfinkel et al. (1980), Garza-Treviño et al. (1992), Goncalves & Stoll (1985), Goodwin et al. (1969), Harrison & Keating (2005), Ichim et al. (2000), Janicak et al. (1998), Johnson et al. (1968), Kowatch et al. (2000), Kudo et al. (1987), Lerer et al. (1987), Lyseng-Williamson & Perry (2004), McElroy et al. (1991), Mishory et al. (2000), Moreno et al. (2007), Okuma et al. (1979, 1990), Ortega et al. (1993), Platman (1970), Pope et al. (1991), Post et al. (1987), Prien et al. (1972), Segal et al. (1998), Shopsin et al. (1975), Small et al. (1991), Spring et al. (1970), Storosum et al. (2007), Takahashi et al. (1975), Vasudev et al. (2000), Walton et al. (1996), and Zajecka et al. (2002)].

Four RCTs with topiramate (n=433) vs. placebo (n=437) were presented in a combined analysis by Kushner et al. (2006) showing no significant efficacy difference between treatment groups. Two of those RCTs included lithium (n=227) as an active comparator. Unfortunately, separate data for our primary efficacy measures were not available.

In summary, 31 RCTs in acute mania fulfilled our study criteria (Table 1). Patients treated with MDR (n=3798) had a 1.61 (95% CI 1.49–1.75, \( I^2 = 26\% \)) higher chance of response, a 0.86 (95% CI 0.77–0.95, \( I^2 = 40\% \)) lower risk of discontinuation due to any cause, and a 0.55 (95% CI 0.47–0.63, \( I^2 = 30\% \)) lower risk of discontinuation due to lack of efficacy, but a 1.57 (95% CI 1.22–2.03, \( I^2 = 18\% \)) greater risk of discontinuation due to AEs than patients treated with placebo (n=2299). Additional comparisons showed that patients treated with mood stabilizers (n=1112) had a 1.57 (95% CI 1.36–1.81, \( I^2 = 33\% \)) higher chance of response, a 1.42 (95% CI 1.15–1.75) higher chance of remission (\( I^2 = 40\% \)), and a 0.55 (95% CI 0.41–0.74, \( I^2 = 44\% \)) lower risk of discontinuation due to lack of efficacy, but a 2.07 (95% CI 1.46–2.93, \( I^2 = 0\% \)) greater risk of discontinuation due to AEs than those patients treated with placebo (n=975). Furthermore, patients treated with SGAs (n=2107) had a 1.59 (95% CI 1.44–1.75, \( I^2 = 22\% \)) higher chance of response, a 0.55 (95% CI 0.46–0.65, \( I^2 = 16\% \)) lower risk of discontinuation due to lack of efficacy, and a 0.87 (95% CI 0.79–0.95, \( I^2 = 0\% \)) lower risk of discontinuation due to any cause, but a 1.36 (95% CI 1.03–1.79, \( I^2 = 0\% \)) higher risk of discontinuation due to AEs than patients treated with placebo (n=1691).

Included studies were heterogeneous with respect to inclusion of patients with/without a rapid-cycling course, manic/mixed states, presence/absence of psychotic symptoms, severity of mania, rates of study completion, and proportion of mood stabilizer-naive subjects. Almost all the included RCTs were sponsored by the pharmaceutical industry, therefore, there were not enough non-industry-sponsored studies to explore differences related to funding source. Of note, for tamoxifen, an experimental medication for the treatment of acute mania, we found two small RCTs (Yildiz et al. 2008; Zarate et al. 2007) including 40 patients treated with tamoxifen (dose range 40–80 mg/d) with a 7.46 (95% CI 1.90–29.32) higher chance of response and similar risk of discontinuation due to AEs than patients treated with placebo (n=34). Some analyses suggested marginal differences in favour of the MDR or the comparator. In these cases we decided to use the term ‘possibly’ to note that the difference was not conclusive.

We considered each MDR separately:

**Lithium.** We found (Fig. 2; Tables 1 and 2) six RCTs (Bowden et al. 1994, 2005; Keck et al. 2009; Li et al. 2008; Niufan et al. 2008; Singh, 2008). Patients treated with lithium (n=294) had a 1.65 (95% CI 1.23–2.21, \( I^2 = 40\% \)) higher chance of response, but possibly a greater risk of discontinuation due to AEs than patients treated with placebo (n=336). Inclusion of a combined analysis with two RCTs comparing lithium vs. placebo (Kushner et al. 2006) did not significantly change the RR of response (1.61, 95% CI 1.36–1.91, \( I^2 = 12\% \)). In comparison with other MDRs (n=503), patients treated with lithium (n=467) had a 0.90 (95% CI 0.81–1.00, \( I^2 = 0\% \)) lower chance of response.

**Carbamazepine.** Two RCTs with the extended release formulation of carbamazepine (ER-CBZ) (Weisler et al. 2004, 2005) were included. Patients treated with ER-CBZ (n=221) had a 2.02 (95% CI 1.56–2.62, \( I^2 = 0\% \)) higher chance of response and possibly a lower risk of discontinuation due to lack of efficacy, but a greater
<table>
<thead>
<tr>
<th>Trial (in order of appearance in text)</th>
<th>Patient inclusion criteria</th>
<th>Duration (wk)</th>
<th>Number randomized</th>
<th>Start–exit dosage (mg/d) or plasma levels (mean)</th>
<th>RCT quality</th>
<th>Sponsored by industry?</th>
<th>Responders (%)</th>
<th>Remitters (%)</th>
<th>Significant AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowden (1994)</td>
<td>H, 18–65 yr, AM (SADS), MRS ≥ 14</td>
<td>3</td>
<td>36, 74, 69, 74</td>
<td>Li (1950 or 1.2 mmol/l), VAL (2000 or 93.2 µg/ml)</td>
<td>4</td>
<td>Yes Li = 49, VAL = 48, PLA = 25</td>
<td>n.a.</td>
<td>Li – vomiting, twitching, fever VAL – vomiting</td>
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<td>Bowden (2005)</td>
<td>H, ≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>98, 97, 107, 97</td>
<td>Li (900 – 0.73 mEq/l), QUE (400 – 586)</td>
<td>4</td>
<td>Yes Li = 53.1, QUE = 53.3, PLA = 53.3, PLA = 22.1</td>
<td>Li – tremor, headache, ↑ TSH QUE – dry mouth, somnolence, ↑ weight, dizziness</td>
<td></td>
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<tr>
<td>Keck (2009)</td>
<td>H, ≥ 18 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>3</td>
<td>160, 155, 165</td>
<td>Li (900–1500), ARI (15–23.2)</td>
<td>4</td>
<td>Yes Li = 45.8, ARI = 46.8, PLA = 34.4, PLA = 28.2</td>
<td>Li – constipation, nausea, tremor ARI – akathisia, constipation, nausea, sedation</td>
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<td>Niufan (2008)</td>
<td>H, ≥ 18 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>4</td>
<td>71, 69, 78, 69</td>
<td>Li (1110), OLZ (17.8)</td>
<td>4</td>
<td>Yes Li = 73, OLZ = 87, OLZ = 82</td>
<td>Li – nausea, OLZ – ↑ weight, constipation, somnolence</td>
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<tr>
<td>Li (2008)</td>
<td>H, 18–65 yr, AM (CCMD-3), YMRS ≥ 20</td>
<td>4</td>
<td>77, 78, 78, 78</td>
<td>Li (0.8 mmol/l), QUE (648.2)</td>
<td>3</td>
<td>Yes Li = 46, QUE = 60, QUE = 40</td>
<td>Li – nausea, constipation, vomiting, dizziness, diarrhoea QUE – constipation, dizziness, diarrhoea, ↑ ALT, ↑ AST, palpitations, dry mouth</td>
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<tr>
<td>Weisler (2004)</td>
<td>H, ≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>101, 103, 115</td>
<td>ER-CBZ (400–756.44 or 8.9 mg/ml)</td>
<td>4</td>
<td>Yes ER-CBZ = 41.5, n.a. PLA = 22.4</td>
<td>ER-CBZ – dizziness, nausea, somnolence, vomiting, dyspepsia, dry mouth, pruritus, speech disorder</td>
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<tr>
<td>Weisler (2005)</td>
<td>H, ≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>120, 115, 115</td>
<td>ER-CBZ (400–642.6)</td>
<td>4</td>
<td>Yes ER-CBZ = 61, n.a. PLA = 29</td>
<td>ER-CBZ – dizziness, somnolence, nausea, ataxia, vomiting, blurred vision</td>
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<td>Bowden (2006)</td>
<td>H, 18–65 yr, AM (DSM-IV), MRS ≥ 18</td>
<td>3</td>
<td>192, 185, 192</td>
<td>VAL (2057 or 95.9 µg/ml)</td>
<td>4</td>
<td>Yes VAL = 48, PLA = 34, PLA = 35</td>
<td>VAL – somnolence, dizziness, GI complaints</td>
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Table 1 (cont.)

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<thead>
<tr>
<th>Trial (in order of appearance in text)</th>
<th>Patient inclusion criteria</th>
<th>Duration (wk)</th>
<th>Number randomized</th>
<th>Start–exit dosage (mg/d) or plasma levels (mean)</th>
<th>RCT quality*</th>
<th>Sponsored by industry?</th>
<th>Responders (%)</th>
<th>Remitters (%)</th>
<th>Significant AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tohen (2008) O + H, 18–65 yr, AM (DSM-IV-TR), YMRS = 20–30</td>
<td>3</td>
<td>VAL = 201, OLZ = 215, PLA = 105</td>
<td>VAL (848.4), OLZ (11.4)</td>
<td>4 Yes</td>
<td>VAL = 40.3, OLZ = 40.8, PLA = 31.3</td>
<td>VAL – nausea, insomnia, ↓ platelets, ↓ leukocytes, ↓ appetite OLZ – ↑ weight, ↓ TGI, ↑ Glu, ↑ Chol, ↑ prolactin, somnolence</td>
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<td>DelBello (2006) H, 12–18 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>4</td>
<td>VAL = 25, QUE = 25</td>
<td>VAL (20 mg/kg.d – 101 µg/ml), QUE (100–412)</td>
<td>3 No</td>
<td>n.a.</td>
<td>VAL = 60, QUE = 28</td>
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<td>McElroy (1996) H, 18–65 yr, AM (DSM-III-R), psychotic</td>
<td>1</td>
<td>VAL = 21, HAL = 15</td>
<td>VAL (20 mg/kg.d – 1625.8), HAL (0.2 mg/kg.d – 15.5)</td>
<td>3</td>
<td>n.a.</td>
<td>HAL – EPS</td>
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<td>Tohen (2002) H, 18–65 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>VAL = 123, OLZ = 125</td>
<td>VAL (750–1554.1 or 83.9 µg/ml), OLZ (15–16.2)</td>
<td>4 Yes</td>
<td>VAL = 42.3, OLZ = 54.4, PLA = 47.2</td>
<td>VAL – nausea, ↓ platelets, OLZ – somnolence, dry mouth, ↓ appetite, tremor, speech disorder, rigidity, ↑ ALT</td>
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<tr>
<td>Wagner (2009) O, 10–17 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>4</td>
<td>VAL = 76, PLA = 74</td>
<td>VAL (15 mg/kg.d – 1286)</td>
<td>4 Yes</td>
<td>VAL = 24, PLA = 19</td>
<td>VAL – nausea, abdominal pain, ↓ weight, ↓ platelets, ↓ serum ammonia</td>
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<td>McIntyre (2005)</td>
<td>3</td>
<td>HAL = 99, QUE = 101, PLA = 100</td>
<td>HAL (5.2), QUE (400–559)</td>
<td>4 Yes</td>
<td>HAL = 56.1, QUE = 27.7, PLA = 35</td>
<td>HAL – tremor, akathisia, EPS, ↓ prolactin, somnolence</td>
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<tr>
<td>Smulevich (2005)</td>
<td>3</td>
<td>HAL = 144, RIS = 154, PLA = 140</td>
<td>HAL (8.0), RIS (4.2)</td>
<td>4 Yes</td>
<td>HAL = 47, RIS = 48, PLA = 33</td>
<td>HAL – EPS, hyperkinesia, somnolence, hypertonia</td>
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</table>

* RCT quality ranges from 1 (poor) to 5 (excellent)
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<tr>
<th>Study</th>
<th>Age Range</th>
<th>AM (DSM-IV or DSM-IV-TR)</th>
<th>YMRS (or similar)</th>
<th>Haloperidol (HAL)</th>
<th>Aripiprazole (ARI)</th>
<th>Olanzapine (OLZ)</th>
<th>ziprasidone (ZIP)</th>
<th>Pimozide (PLA)</th>
<th>Side Effects</th>
</tr>
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<tbody>
<tr>
<td><strong>Vieta (2008)</strong></td>
<td>18 yr, overweight, AM (DSM-IV-TR), MRS &gt; 14</td>
<td>3</td>
<td>HAL = 171, ZIP = 178, PLA = 88</td>
<td>HAL (8→16), ZIP (80→116.2)</td>
<td>4 Yes</td>
<td>HAL = 54.7, ZIP = 36.9, PLA = 20.5</td>
<td>HAL = 31.9, ZIP = 22.7</td>
<td>4 Yes</td>
<td>ZIP – EPS, akathisia, dyspepsia, ↓ weight, headache</td>
</tr>
<tr>
<td><strong>Young (2009)</strong></td>
<td>≥ 18 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>3</td>
<td>HAL = 165, ARI = 167, PLA = 153</td>
<td>HAL (5→8.5), ARI (15→23.6)</td>
<td>4 Yes</td>
<td>HAL = 49.7, ARI = 47, PLA = 38.2</td>
<td>HAL = 45.3, ARI = 44, PLA = 36.8</td>
<td>4 Yes</td>
<td>HAL – EPS, akathisia, muscle rigidity, ↑ prolactin</td>
</tr>
<tr>
<td><strong>Tohen, 2003</strong></td>
<td>H &amp; OP, ≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>6</td>
<td>HAL = 219, OLZ = 234</td>
<td>HAL (10→7.1), OLZ (15→15)</td>
<td>4 Yes</td>
<td>HAL = 62, OLZ = 55</td>
<td>HAL = 46.1, OLZ = 52.1</td>
<td>4 Yes</td>
<td>OLZ – somnolence, ↑ weight, dizziness, fever</td>
</tr>
<tr>
<td><strong>Vieta (2005)</strong></td>
<td>≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>HAL = 172, ARI = 175, PLA = 120</td>
<td>HAL (10→11.6), ARI (10→22.6)</td>
<td>4 Yes</td>
<td>HAL = 42.6, ARI = 50.9</td>
<td>HAL = 31, ARI = 35</td>
<td>n.a.</td>
<td>ARI – insomnia, HAL – akathisia, ↑ prolactin</td>
</tr>
<tr>
<td><strong>Keck (2003a)</strong></td>
<td>H, ≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>ARI = 123, PLA = 120</td>
<td>ARI (30→27.9)</td>
<td>4 Yes</td>
<td>ARI = 40, PLA = 19</td>
<td>n.a.</td>
<td>ARI – nausea, dyspepsia, vomiting,HAL – EPS, somnolence, EPS, akathisia</td>
<td></td>
</tr>
<tr>
<td><strong>Sachs (2006)</strong></td>
<td>≥ 18 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>3</td>
<td>ARI = 137, PLA = 135</td>
<td>ARI (30→27.7)</td>
<td>4 Yes</td>
<td>ARI = 53, PLA = 32</td>
<td>n.a.</td>
<td>ARI – constipation, dyspepsia, nausea, somnolence, akathisia</td>
<td></td>
</tr>
<tr>
<td><strong>Tohen (1999)</strong></td>
<td>H, 18–65 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>OLZ = 70, PLA = 69</td>
<td>OLZ (10→14.9)</td>
<td>4 Yes</td>
<td>OLZ = 49, PLA = 24</td>
<td>n.a.</td>
<td>OLZ – somnolence, dry mouth, dizziness, ↓ weight</td>
<td></td>
</tr>
<tr>
<td><strong>Tohen (2000)</strong></td>
<td>H, 18–70 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>4</td>
<td>OLZ = 54, PLA = 56</td>
<td>OLZ (15→16.4)</td>
<td>4 Yes</td>
<td>OLZ = 64.8, PLA = 42.9</td>
<td>OLZ = 61.1, PLA = 35.7</td>
<td>4 Yes</td>
<td>OLZ – somnolence</td>
</tr>
<tr>
<td><strong>Tohen (2007)</strong></td>
<td>H, 13–17 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>3</td>
<td>OLZ = 107, PLA = 54</td>
<td>OLZ (2.5→10.7)</td>
<td>4 Yes</td>
<td>OLZ = 48.6, PLA = 22.2</td>
<td>OLZ = 35.2, PLA = 11.1</td>
<td>4 Yes</td>
<td>OLZ – somnolence, ↑ weight, sedation</td>
</tr>
<tr>
<td><strong>Perlis (2006)</strong></td>
<td>H, 18–70 yr, AM (DSM-IV-TR), YMRS ≥ 20</td>
<td>3</td>
<td>OLZ = 165, RIS = 164, PLA = 69</td>
<td>OLZ (14.7), RIS (3.9)</td>
<td>4 Yes</td>
<td>OLZ = 62, RIS = 59.5</td>
<td>OLZ = 38.5, RIS = 28.5</td>
<td>4 Yes</td>
<td>OLZ – dry mouth, ↑ weight</td>
</tr>
<tr>
<td><strong>Hirschfeld (2004)</strong></td>
<td>≥ 18 yr, AM (DSM-IV), YMRS ≥ 20</td>
<td>3</td>
<td>RIS = 125, PLA = 134</td>
<td>RIS (4.1)</td>
<td>5 Yes</td>
<td>RIS = 43, PLA = 24</td>
<td>RIS = 38, PLA = 20</td>
<td>5 Yes</td>
<td>RIS – somnolence, EPS, hyperkinesia, dyspepsia, nausea, ↑ prolactin, ↓ weight</td>
</tr>
<tr>
<td>Trial (in order of appearance in text)</td>
<td>Patient inclusion criteria</td>
<td>Duration (wk)</td>
<td>Number randomized</td>
<td>Start–exit dosage (mg/d) or plasma levels (mean)</td>
<td>RCT quality</td>
<td>Sponsored by industry?</td>
<td>Responders (%)</td>
<td>Remitters (%)</td>
<td>Significant AE</td>
</tr>
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<td>--------------------------------------</td>
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</tr>
<tr>
<td>Khana (2005); Gopal (2005)</td>
<td>≥ 18 yr, AM (DSM-IV), YMRS ≥ 20 (mean score V1 = 37)</td>
<td>3</td>
<td>RIS = 146, PLA = 144</td>
<td>RIS (5.6)</td>
<td>4</td>
<td>Yes</td>
<td>RIS = 73, PLA = 36</td>
<td>RIS = 42, PLA = 13</td>
<td>RIS – EPS, tremor, dystonia, † prolactin</td>
</tr>
<tr>
<td>Keck (2003b)</td>
<td>H, ≥ 18 yr, AM (DSM-IV), MRS ≥ 14</td>
<td>3</td>
<td>ZIP = 131, PLA = 66</td>
<td>ZIP (80→130)</td>
<td>3</td>
<td>Yes</td>
<td>ZIP = 50, PLA = 35</td>
<td>n.a.</td>
<td>ZIP – somnolence, headache, dizziness, hypertonia, akathisia</td>
</tr>
<tr>
<td>Potkin (2005)</td>
<td>H, ≥ 18 yr, AM (DSM-IV), MRS ≥ 14</td>
<td>3</td>
<td>ZIP = 137, PLA = 65</td>
<td>ZIP (80→112)</td>
<td>4</td>
<td>Yes</td>
<td>ZIP = 46, PLA = 29</td>
<td>n.a.</td>
<td>ZIP – somnolence, EPS, dizziness, tremor</td>
</tr>
<tr>
<td>Calabrese (1999)</td>
<td>≥ 18 yr, MDE (DSM-IV), HAMD ≥ 18</td>
<td>7</td>
<td>LAM50 = 64, LAM200 = 63, LAM200 (25→200)</td>
<td>4</td>
<td>Yes</td>
<td>LAM50 = 45, LAM200 = 51, LAM200 (25→200)</td>
<td>n.a.</td>
<td>LAM200 – headache</td>
<td></td>
</tr>
<tr>
<td>Thase (2008) – CN138-096</td>
<td>O, 18–65 yr, MDE (DSM-IV-TR), HAMD ≥ 18</td>
<td>8</td>
<td>ARI = 186, PLA = 188</td>
<td>ARI (10→30)</td>
<td>4</td>
<td>Yes</td>
<td>ARI = 43.2, PLA = 39</td>
<td>ARI = 30.2, PLA = 27.8</td>
<td>ARI – akathisia, insomnia, nausea, fatigue, restlessness, dry mouth, vomiting, † appetite, back pain</td>
</tr>
<tr>
<td>Thase (2008) – CN138-146</td>
<td>O, 18–65 yr, MDE (DSM-IV-TR), HAMD ≥ 18</td>
<td>8</td>
<td>ARI = 187, PLA = 188</td>
<td>ARI (10→30)</td>
<td>4</td>
<td>Yes</td>
<td>ARI = 44.6, PLA = 44.3</td>
<td>ARI = 25.7, PLA = 29</td>
<td>ARI – akathisia, nausea, fatigue, restlessness, anxiety, vomiting, † appetite</td>
</tr>
<tr>
<td>Tohen (2003b) – 3077a S1</td>
<td>≥ 18 yr, MDE (DSM-IV), MADRS ≥ 20</td>
<td>8</td>
<td>OLZ = 181, PLA = 182</td>
<td>OLZ (9.7)</td>
<td>4</td>
<td>Yes</td>
<td>OLZ = 43.6, PLA = 37.6</td>
<td>OLZ = 55, PLA = 46.3</td>
<td>OLZ – †appetite, † weight, † Chol, asthenia, dry mouth, somnolence</td>
</tr>
<tr>
<td>Tohen (2003b) – 3077a S2</td>
<td>≥ 18 yr, MDE (DSM-IV), MADRS ≥ 20</td>
<td>8</td>
<td>OLZ = 169, PLA = 174</td>
<td>OLZ (9.7)</td>
<td>4</td>
<td>Yes</td>
<td>OLZ = 53.3, PLA = 34.7</td>
<td>OLZ = 57, PLA = 44</td>
<td>Combined data on Tohen (2003) above</td>
</tr>
</tbody>
</table>
risk of discontinuation due to AEs than patients treated with placebo \((n = 218)\). The NNH analysis suggested that four patients treated with carbamazepine instead of placebo are needed to observe an additional AE.

Oxcarbazepine. One 7-wk RCT with the use of oxcarbazepine in children and adolescents was included (Wagner et al. 2006). Although it was reported that oxcarbazepine did not significantly improve YMRS scores at endpoint compared with placebo, we found that patients treated with oxcarbazepine \((n = 59)\) had a 1.56 (95% CI 1.13–2.16) higher chance of response, although a greater risk of discontinuation due to AEs than patients treated with placebo \((n = 57)\). Nine patients are needed to observe an additional AE if patients are treated with oxcarbazepine instead of placebo.

Valproate/valproic acid. Seven RCTs were included (Bowden et al. 1994, 2006; DelBello et al. 2006; McElroy et al. 1996; Tohen et al. 2002, 2008; Wagner et al. 2009). Patients treated with valproate \((n = 555)\) had a 1.39 (95% CI 1.16–1.65, 3 = 0%) higher chance of response, a 1.27 (95% CI 1.05–1.54) higher chance of remission \((P = 72%)\) and a lower risk of discontinuation due to lack of efficacy, but had a greater risk of discontinuation due to AEs than patients treated with placebo \((n = 457)\). Nine patients are needed to observe an additional AE if patients are treated with valproate instead of placebo. In comparison with other MDRs, patients treated with valproate \((n = 416)\) had a similar chance of response, but a lower risk of discontinuation due to AEs. The exclusion of RCTs in children and adolescents (DelBello et al. 2006; Wagner et al. 2009) does not change the RR for either response vs. placebo or remission vs. other MDRs.

Haloperidol. Seven RCTs with haloperidol were included (McElroy et al. 1996; McIntyre et al. 2005; Smulevich et al. 2005; Tohen et al. 2003a; Vieta et al. 2005, 2008; Young et al. 2009). Patients treated with haloperidol \((n = 579)\) had a 1.31 (95% CI 1.04–1.65, \(P = 0\%\)) higher chance of remission and a 1.63 (95% CI 1.25–2.12) higher chance of response \((P = 64\%)\) than patients treated with placebo \((n = 481)\). Although patients treated with haloperidol showed no increased risk of discontinuation for any cause or AE, a study showed that only two patients treated with haloperidol instead of placebo are needed to observe an additional AE. In comparison with other MDRs \((n = 985)\), patients treated with haloperidol \((n = 1030)\)
showed a similar chance of response \((I^2=62\%)\) or remission \((I^2=51\%)\). The NNT analyses indicated that five patients treated with haloperidol instead of another MDR are needed to observe an additional AE.

**Aripiprazole**. Five RCTs were included (Keck *et al.*, 2003a, 2009; Sachs *et al.*, 2006; Vieta *et al.*, 2005; Young *et al.*, 2009). Patients treated with aripiprazole \((n=582)\) had a 1.50 (95% CI 1.22–1.84, \(I^2=44\%\)) higher chance of response and a 1.28 (95% CI 1.05–1.57, \(I^2=0\%\)) higher chance of remission than patients treated with placebo \((n=573)\). Eight patients treated with aripiprazole instead of placebo are needed to observe an additional AE in comparison with other MDRs \((n=497)\), patients treated with aripiprazole \((n=497)\) had a similar chance of response and remission.
Table 2. Secondary efficacy and safety measures of randomized trials using monotherapeutic drug regimen in patients with a bipolar disorder type I

<table>
<thead>
<tr>
<th>MDR and comparator</th>
<th>NNT response (95% CI)</th>
<th>NNT remission (95% CI)</th>
<th>NNT remission (95% CI)</th>
<th>Relative risk of discontinuation due to any cause (95% CI) [I^2]</th>
<th>Relative risk of discontinuation due to AE (95% CI) [I^2]</th>
<th>Relative risk of discontinuation due to lack of efficacy (95% CI) [I^2]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manic/mixed episode</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Li PL A</td>
<td>5 (3–8)</td>
<td>6 (3–8)</td>
<td>26 (−27 to 79)</td>
<td>0.78 (0.52–1.18) [84%]</td>
<td>1.74 (1.00–3.02) [0%]</td>
<td>0.53 (0.29–0.98) [67%]</td>
</tr>
<tr>
<td>MDR</td>
<td>−23 (−56 to 11)</td>
<td>−23 (−59 to 13)</td>
<td>−11 (−18 to −3)</td>
<td>1.25 (0.91–1.72) [61%]</td>
<td>1.03 (0.65–1.64) [1%]</td>
<td>1.36 (0.69–2.68) [55%]</td>
</tr>
<tr>
<td>EC-CBZ PL A</td>
<td>4 (3–5)</td>
<td>n.a.</td>
<td>4 (3–5)</td>
<td>0.85 (0.69–1.03) [0%]</td>
<td>1.97 (1.04–3.74) [0%]</td>
<td>0.44 (0.20–1.00) [65%]</td>
</tr>
<tr>
<td>OX C</td>
<td>4 (1–7)</td>
<td>n.a.</td>
<td>9 (−2 to 20)</td>
<td>0.84 (0.52–1.35) a</td>
<td>5.31 (1.23–22.93) a</td>
<td>0.41 (0.17–1.00) a</td>
</tr>
<tr>
<td>VA L</td>
<td>9 (4–14)</td>
<td>12 (3–22)</td>
<td>9 (4–14)</td>
<td>0.89 (0.73–1.08) [26%]</td>
<td>2.42 (1.28–4.56) [0%]</td>
<td>0.63 (0.43–0.92) [27%]</td>
</tr>
<tr>
<td>HAL</td>
<td>22 (1–44)</td>
<td>118 (−53 to 767)</td>
<td>5 (4–7)</td>
<td>1.15 (0.95–1.40) [62%]</td>
<td>1.55 (0.96–2.48) [67%]</td>
<td>0.72 (0.42–1.22) [69%]</td>
</tr>
<tr>
<td>ARI</td>
<td>7 (4–9)</td>
<td>10 (2–19)</td>
<td>8 (3–12)</td>
<td>0.98 (0.83–1.17) [0%]</td>
<td>1.21 (0.84–1.75) [7%]</td>
<td>0.67 (0.33–1.38) [72%]</td>
</tr>
<tr>
<td>OL Z</td>
<td>41 (−65 to 148)</td>
<td>124 (−∞ to ∞)</td>
<td>−3 (−4 to −2)</td>
<td>0.86 (0.65–1.14) [76%]</td>
<td>0.86 (0.33–2.24) [0%]</td>
<td>1.46 (0.72–2.95) [68%]</td>
</tr>
<tr>
<td>QUE</td>
<td>6 (3–9)</td>
<td>7 (3–12)</td>
<td>6 (3–10)</td>
<td>0.68 (0.53–0.87) [34%]</td>
<td>1.93 (0.48–7.72) [28%]</td>
<td>0.57 (0.42–0.77) [0%]</td>
</tr>
<tr>
<td>MS</td>
<td>57 (−102 to 215)</td>
<td>13 (5–22)</td>
<td>15 (−3 to 35)</td>
<td>0.86 (0.69–1.07) [62%]</td>
<td>1.01 (0.59–1.72) [44%]</td>
<td>0.93 (0.66–1.31) [30%]</td>
</tr>
<tr>
<td>QUE</td>
<td>6 (3–9)</td>
<td>7 (3–11)</td>
<td>n.a.</td>
<td>0.66 (0.39–1.10) [78%]</td>
<td>1.59 (0.48–5.25) a</td>
<td>0.43 (0.21–0.87) a</td>
</tr>
<tr>
<td>RIS</td>
<td>−88 (−724 to 548)</td>
<td>32 (−49 to 114)</td>
<td>11 (−5 to 26) a</td>
<td>0.76 (0.38–1.50) [59%]</td>
<td>0.62 (0.31–1.25) [0%]</td>
<td>0.88 (0.36–2.17) [37%]</td>
</tr>
<tr>
<td>ZIP</td>
<td>4 (3–5)</td>
<td>4 (3–6)</td>
<td>n.a.</td>
<td>0.66 (0.41–1.08) [67%]</td>
<td>1.18 (0.62–2.27) [0%]</td>
<td>0.44 (0.29–0.65) [0%]</td>
</tr>
<tr>
<td>MDR</td>
<td>−108 (−1013 to 797)</td>
<td>−10 (−20 to 1)</td>
<td>n.a.</td>
<td>1.43 (1.04–1.97) [0%]</td>
<td>1.51 (0.77–2.99) [0%]</td>
<td>1.27 (0.53–3.02) [0%]</td>
</tr>
<tr>
<td>MDR</td>
<td>−6 (−9 to −2) a</td>
<td>−10 (−20 to 1)</td>
<td>−6 (−10 to −3) a</td>
<td>1.07 (0.89–1.29) a</td>
<td>0.45 (0.27–0.78) a</td>
<td>2.24 (1.41–3.57) a</td>
</tr>
<tr>
<td>SGA</td>
<td>6 (3–9)</td>
<td>6 (3–8)</td>
<td>n.a.</td>
<td>0.84 (0.73–0.96) [0%]</td>
<td>2.40 (1.01–5.68) [0%]</td>
<td>0.56 (0.44–0.72) [0%]</td>
</tr>
<tr>
<td>MDR</td>
<td>6 (5–7)</td>
<td>8 (6:10)</td>
<td>7 (5–10)</td>
<td>0.87 (0.79–0.95) [0%]</td>
<td>1.36 (1.03–1.79) [0%]</td>
<td>0.55 (0.46–0.65) [16%]</td>
</tr>
<tr>
<td><strong>Bipolar depressive episode</strong></td>
<td></td>
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</tr>
<tr>
<td>LAM PL A</td>
<td>16 (−4 to 36)</td>
<td>−34 (−159 to 91) a</td>
<td>511 (−∞ to ∞)</td>
<td>1.35 (0.85–2.14) [34%]</td>
<td>0.79 (0.38–1.62) [0%]</td>
<td>1.10 (0.80–1.51) [51%]</td>
</tr>
<tr>
<td>ARI</td>
<td>45 (−100 to 190)</td>
<td>−174 (−∞ to −∞)</td>
<td>14 (−2 to 29) a</td>
<td>2.10 (1.32–3.35) [0%]</td>
<td>0.45 (0.23–0.88) [0%]</td>
<td>1.35 (1.13–1.63) [0%]</td>
</tr>
<tr>
<td>OLZ</td>
<td>8 (3–14)</td>
<td>9 (2–16)</td>
<td>n.a.</td>
<td>0.72 (0.59–0.88) [63%]</td>
<td>1.82 (1.06–3.13) a</td>
<td>0.62 (0.48–0.80) [0%]</td>
</tr>
<tr>
<td>QUE</td>
<td>4 (3–6)</td>
<td>4 (3–6) a</td>
<td>n.a.</td>
<td>1.01 (0.83–1.22) a</td>
<td>1.95 (1.15–3.30) a</td>
<td>0.18 (0.09–0.37) a</td>
</tr>
<tr>
<td>SGA</td>
<td>8 (5–10)</td>
<td>9 (6–13)</td>
<td>n.a.</td>
<td>0.99 (0.73–1.32) [90%]</td>
<td>1.97 (1.47–2.64) [0%]</td>
<td>0.46 (0.29–0.71) [64%]</td>
</tr>
<tr>
<td>MDR</td>
<td>9 (6–12)</td>
<td>10 (6–15)</td>
<td>n.a.</td>
<td>1.02 (0.81–1.28) [86%]</td>
<td>1.77 (1.38–2.26) [0%]</td>
<td>0.51 (0.36–0.73) [46%]</td>
</tr>
</tbody>
</table>

ARI, Aripiprazole; CBZ, carbamazepine; CI, confidence interval; ER-CBZ, extended-release carbamazepine capsules; Li, lithium; LAM, lamotrigine; MDR, monotherapy drug regime; MS, mood stabilizers; n.a., non-available; NNH, number needed to harm; NNT, number needed to treat; OLZ, olanzapine; OX C, oxcarbazepine; PL A, placebo; QUE, quetiapine; RIS, risperidone; SGA, second-generation antipsychotics; VAL, valproate/divalproex; VER, verapamil; ZIP, ziprasidone.

a Based on one RCT.
b Based on combined data from two RCTs.
Olanzapine. Eight RCTs were included (Niufan et al. 2008; Perlis et al. 2005). Patients treated with olanzapine \( (n=446) \) had a 1.62 (95% CI 1.27–2.08, \( I^2=27\% \)) higher chance of response, a 1.68 (95% CI 1.06–2.64) higher chance of remission \( (P=62\%) \), and had a lower risk of discontinuation due to any cause or lack of efficacy than patients treated with placebo \( (n=284) \). Six patients treated with olanzapine instead of placebo are needed to observe an additional AE. In comparison with other MDRs \( (n=778) \), patients treated with olanzapine \( (n=808) \) had a 1.17 (95% CI 1.06–1.30, \( P=0\% \)) higher chance of remission, and a similar chance of response.

Quetiapine. Four RCTs were included (Bowden et al. 2005; DelBello et al. 2006; Li et al. 2008; McIntyre et al. 2005). Patients treated with quetiapine \( (n=208) \) had a similar chance of response \( (1.52, 95\% \text{ CI } 0.97–2.37, \ P=68\%) \) and remission \( (1.59, 95\% \text{ CI } 0.86–2.94, \ P=73\%) \), but a lower risk of discontinuation due to lack of efficacy than patients treated with placebo \( (n=197) \) during the first 3 wk of treatment. However, the NNT was six \( (95\% \text{ CI } 3–9) \) and seven \( (95\% \text{ CI } 3–11) \) for response and remission vs. placebo, respectively. When data for the 12-wk studies were included, patients treated with quetiapine had a higher chance of response and remission vs. placebo. Differences between 3 and 12 wk may be due to the dose titration design in RCTs with quetiapine where the therapeutic dose is reached several days after the first study visit. In comparison with other MDRs \( (n=299) \), patients treated with quetiapine \( (n=310) \) had a similar chance of response \( (P=69\%) \) and remission \( (P=69\%) \).

Risperidone. Data from three RCTs available in four publications were included (Gopal et al. 2005; Hirschfeld et al. 2004; Khanna et al. 2005; Smulevich et al. 2005). Patients treated with risperidone \( (n=425) \) had a 1.77 (95% CI 1.44–2.17, \( P=33\%) \) higher chance of response, a 2.43 (95% CI 1.47–4.00) higher chance of remission \( (P=63\%) \), and a lower risk of discontinuation due to lack of efficacy in comparison with patients treated with placebo \( (n=418) \). In comparison with other MDRs \( (n=309) \), patients treated with risperidone \( (n=318) \) had a similar chance of response and remission, and a similar risk of discontinuation due to AEs, but a higher risk of discontinuation due to any cause.

Ziprasidone. Three RCTs were included (Keck et al. 2003b; Potkin et al. 2005; Vieta et al. 2008). Patients treated with ziprasidone \( (n=446) \) had a 1.58 (95% CI 1.25–2.00, \( P=0\% \)) higher chance of response and a lower risk of discontinuation due to lack of efficacy or any cause, but a greater risk of discontinuation due to AE than those patients treated with placebo \( (n=219) \). Six patients treated with ziprasidone instead of placebo are needed to observe an additional AE. Data from one RCT indicates that patients treated with haloperidol \( (n=171) \) had a 1.48 (95% CI 1.17–1.87) higher chance of response and a 1.43 (95% CI 1.01–2.03) higher chance of remission than patients treated with ziprasidone \( (n=178) \), but a 2.53 (95% CI 1.08–5.94) higher risk of discontinuation due to AEs.

**MDRs for acute depressive episodes**

Many mood stabilizers (Ballenger & Post, 1980; Baron et al. 1975; Davis et al. 2005; Donnelly et al. 1978; Fieve et al. 1968; Geddes et al. 2009 (Trial SCAA2010); Ghaemi et al. 2007; Goodwin et al. 1969, 1972; Mendels, 1976; Noyes et al. 1974; Post et al. 1986; Stokes et al. 1971), antidepressants (Baumhackl et al. 1989; Cohn et al. 1989; Grossman et al. 1999; Himmelhoch et al. 1991; Silverstone et al. 2001; Thase et al. 1992), antipsychotics (DelBello et al. 2009) or other medications (Smeland et al. 1999) have been evaluated as monotherapies in bipolar depression. Not one of those RCTs fulfilled our study criteria therefore they were all excluded from the present analyses.

Nine RCTs fulfilling the study criteria on bipolar depression were included (Table 2). The overall RR for meta-analysis for response in bipolar depressed patients treated with MDR \( (n=1419) \) compared with placebo \( (n=1214) \) was 1.26 (95% CI 1.11–1.44, \( P=54\%) \) (Fig. 3). Further, patients treated with MDR had a 0.51 (95% CI 0.36–0.73, \( P=46\%) \) lower risk of discontinuation due to lack of efficacy, but a 1.77 (95% CI 1.38–2.26, \( P=0\% \)) greater risk of discontinuation due to AEs than those patients treated with placebo. We did not observe a significant difference vs. placebo for the RR for remission, nor for discontinuation due to any cause. Again, analyses including those trials with small sample sizes \( (n=3) \) did not significantly change the final results but increased their heterogeneity. The included studies were all sponsored by the pharmaceutical industry. They were heterogeneous with respect to inclusion of subjects with history of a rapid-cycling course or manic/mixed states, proportion of people with/without psychotic symptoms, severity of depression, rates of study completion, and proportion of mood stabilizer-naive or antidepressant-naive subjects.

Considering each MDR separately, we did not find any trials fulfilling our inclusion criteria to confirm or
had a similar chance of response (I² = 0%) with aripiprazole (2008; Trials CN138-096, CN138-146). Patients treated with lamotrigine (2009; Trials SCA40910, SCA30924). We found that primary efficacy measure after 7–10 wk of treatment. M-H, Mantel–Haenszel.

reject any potential role for valproate as monotherapy in acute bipolar depression, although a small RCT suggested better remission rates for valproate vs. placebo (Davis et al. 2005). For other MDRs we found (Fig. 3; Tables 1 and 2) the following:

Lamotrigine. Data from three RCTs available in five publications/data sources were considered for analysis (Calabrese et al. 1999, 2008; Geddes et al. 2009; Trials SCA40910, SCA30924). We found that patients treated with lamotrigine (≥200 mg/d) (n = 327) had a similar chance of response (I² = 0%) and remission (one study), and a similar risk of discontinuation due to lack of efficacy or AEs than those patients treated with placebo (n = 317). Similar results were observed when we included the BP I and BP II patients, and all the doses evaluated for lamotrigine.

Aripiprazole. Data from two RCTs available in three publications/data sources were included (Thase et al. 2008; Trials CN138-096, CN138-146). Patients treated with aripiprazole (n = 373) had a similar chance of response (I² = 0%) and remission (I² = 0%), but greater risk of discontinuation due to lack of efficacy or any cause than those patients treated with placebo (n = 376).

Olanzapine. Data from two RCTs available in three publications/data sources were included (Tohen et al. 2003b; Trial 3077a). Patients treated with olanzapine (n = 350) had a 1.34 (95% CI 1.02–1.76, I² = 51%) higher chance of response, and a 1.24 (95% CI 1.05–1.46, I² = 0%) higher chance of remission, and a lower risk of discontinuation due to lack of efficacy, but a greater risk of discontinuation due to AEs than those patients treated with placebo (n = 356).

Quetiapine. Data from two RCTs available in four publications/data sources were included (Calabrese et al. 2005; MacFadden et al. 2005; Thase et al. 2006; Weisler et al. 2008). Patients treated with quetiapine (n = 435) had a 1.58 (95% CI 1.10–2.26, I² = 74%) higher chance of response, a 1.73 (95% CI 1.40–2.14) (combined data) higher chance of remission, and a lower risk of discontinuation due lack of efficacy, but a greater risk of discontinuation due to AEs than those patients treated with placebo (n = 222). Similar results were observed when we evaluated together the BP I and BP II patients in terms of response, remission or discontinuations due to lack of efficacy or AE.

Discussion

We found in most studies that MDRs are efficacious in the treatment of acute manic episodes. In these studies the entire range of confidence intervals exceeds the cut-off point below which the effect size is defined as no different to placebo (Fig. 2). We also found that it is necessary to treat six (95% CI 5–7) or seven (95% CI 5–8) patients to observe a significant difference in response or remission rates, respectively, with MDR.
over placebo in the treatment of acute manic episodes (Table 2). Finally, a combined analysis with several RCTs suggests that topiramate is not efficacious in the treatment of acute mania (Kushner et al. 2006). In patients with acute manic episodes, study discontinuation due to AEs was significantly more likely to be observed with a MDR than with placebo, but study discontinuation due to lack of efficacy or discontinuation to any cause were significantly lower with SGAs than with placebo. Regarding the comparisons between an active compound against another MDR (usually lithium, valproate or haloperidol), we did not find significant differences in terms of response, remission, or discontinuation due to AEs, lack of efficacy, or discontinuation due to any cause.

Regarding acute bipolar depressive episodes, we found that only olanzapine and quetiapine showed response and/or remission rates superior to those reported with placebo (substantial heterogeneity was observed with both analyses), although the effect size for quetiapine in response was almost double that for olanzapine (Fig. 3). Early RCTs have shown significant therapeutic effects with lithium for bipolar depression (Thase & Sachs, 2000), but small samples and other methodological shortcomings limits the evidence for its use as a MDR for BP I depressed patients.

Although some patients with a bipolar depressive episode may certainly benefit from a MDR, the evidence is still limited and many BP I patients with a depressive episode appear to require the addition of another mood stabilizer (Kramlinger & Post, 1989) or an antidepressant (Tamayo et al. 2003b; Young et al. 2000). Interestingly, some RCTs comparing a CDR with a MDR with no previous lack of response did not report statistical differences favouring the CDR in BP I-depressed patients (Amsterdam & Shults, 2005; Brown et al. 2006; Nolen & Bloemkolk, 2000). On the other hand, although the literature supports the efficacy of lamotrigine in preventing bipolar depressive relapses (Goodwin et al. 2004), it does not provide evidence to support the efficacy of this medication in the acute depressive phase of BP I patients. Recently, a review concluded that lamotrigine monotherapy did not demonstrate efficacy in the acute treatment of bipolar depression in four out of five RCTs (Calabrese et al. 2008). However, a meta-analysis with the same RCT, reported a statistically significant small effect size of depressive symptom benefit only in patients with a HAMD score >24 (Geddes et al. 2009).

The relevance of different therapeutic interventions for BP I and their efficacy must be evaluated based on the best available evidence. Unfortunately, the treatment of patients with BP I is usually complex, and many treatment interventions implemented by clinicians at times may not be evidence-based. A survey in an acute general psychiatric ward indicated that <65% of treatment decisions were based on evidence from RCTs (Goldner et al. 2001). Studies in which pharmacological treatment is allocated by any method other than randomization tend to show larger (and frequently false-positive) treatment effects than do RCTs. Randomization prevents biased assignment of treatment and confounders that are unknown or unmeasured (Chalmers et al. 1983). However, caution is needed in drawing clear-cut generalizations to clinical practice based on our analyses due to the heterogeneity in trial designs, the methodological quality of included trials, and the nature, timing, and dose of mood stabilizers or SGAs. Additionally, the fact that almost all the RCTs in the field of bipolar disorder are aimed at registration approval, there may be a gap between the evidence base of patients who participate in clinical trials and clinical populations (Vieta & Carne, 2005).

We examined the results from available studies to determine the possibility of publication bias or selective reporting bias. We additionally, compared the data published with that reported on the trial registry or at ‘ClinicalStudyResults.org’, and we excluded trials with small sample sizes that would tend to show larger estimates of the effects of the intervention. However, the quality of the studies varied and we were not blinded to their quality when determining their inclusion. Several analyses showed a heterogeneity statistic $I^2 >50\%$ that ‘may represent substantial heterogeneity’ (Deeks et al. 2008) and the funnel plot for each of them showed evidence of considerable asymmetry. As noted by Higgins et al. (2003), regarding heterogeneity, ‘inconsistency of studies’ results in a meta-analysis with reduced confidence of recommendations about treatment’. Additionally, although we examined the ‘ClinicalStudyResults.org’ webpage and several conference proceedings using a combination of hand and electronic searching, we cannot exclude the possibility that there are unpublished negative studies that we were unable to access.

In conclusion, although there are patients who are unresponsive to acute treatment with monotherapy, these results suggest that MDRs should be considered as a first therapeutic option for the treatment of non-refractory manic episodes. This approach may result in the reduction of direct costs of medications, the number and magnitude of AEs and may improve treatment adherence and patient compliance (Grunze et al. 2009). For depressive episodes, the new data with SGAs (quetiapine and olanzapine) suggest that these
MDR, especially quetiapine, are efficacious and well tolerated.

Acknowledgements
The views held by Dr Zarate do not necessarily reflect those of the Federal Government.

Statement of Interest
Dr Tamayo was an employee of Eli Lilly Laboratories during the first analyses for this paper and has received honoraria from Eli Lilly, Janssen, Pfizer, and Wyeth. Dr Zarate is supported by the intramural research program at the NIMH and has not received any industry funding in the past year. Dr Vieta is supported by the Spanish Ministry of Science and Innovation (CIBERSAM), is a consultant to and received honoraria from AstraZeneca, Bristol–Myers, Eli Lilly, Janssen-Cilag, Lundbeck, Sanofi, has received grant or research support from AstraZeneca, Bristol–Myers, Eli Lilly, Janssen-Cilag, Organon, and Pfizer. Dr Vázquez is a consultant to and received honoraria from AstraZeneca, GlaxoSmithKline, Roche and Eli Lilly. Dr Tohen was an employee of Eli Lilly Laboratories during the planning and analyses of this paper and has received honoraria from AstraZeneca, Bristol–Myers Squibb, GlaxoSmithKline, Eli Lilly and Wyeth. His spouse in an employee and stockholder of Eli Lilly.

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