Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials

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Abstract

The purpose of this meta-analysis was to examine the efficacy of maintenance treatments for bipolar disorder. Placebo-controlled or active comparator bipolar maintenance clinical trials of ≥6 months’ duration with at least 15 patients/treatment group were identified using Medline, EMBASE, clinicaltrials.gov, and Cochrane databases (1993 to July 2010). The main outcome measure was relative risk for relapse for patients in remission. Twenty trials (5364 patients) were identified. Overall, lithium and quetiapine were the most studied agents (eight and five trials, respectively). The majority of studies included patients who had previously responded to treatment for an acute episode. All interventions, with the exception of perphenazine + mood stabilizer, showed a relative risk for manic/mixed or depressive relapse below 1.0, although there was variation in the statistical significance of the findings vs. placebo. No monotherapy was associated with a significantly reduced risk for both manic/mixed and depressed relapse. Of the combination treatments, only quetiapine + lithium/divalproex, was associated with a significantly reduced risk vs. comparator (placebo + lithium/valproate) for relapse at both the manic/mixed and depressed poles of bipolar illness. Limitations for the analysis include differences in study durations and definitions of relapse. In conclusion, available maintenance therapies show considerable variation in efficacy. The efficacy of lithium and divalproex has been confirmed, but newer therapies, such as a number of atypical antipsychotics were also shown to be effective in bipolar disorder. Efficacy of all maintenance interventions needs to be balanced against the safety and tolerability profiles of individual agents.

Received 31 January 2011; Reviewed 28 March 2011; Revised 10 May 2011; Accepted 11 May 2011; First published online 22 June 2011

Key words: Bipolar disorder, maintenance therapy, relapse.

Introduction

Bipolar disorder is a major mental health issue associated with considerable morbidity and mortality (Hirschfeld & Vornik, 2005). It is characterized by recurrent episodes of mania or hypomania and depression, separated by periods of relatively normal behaviour (Kasper, 2003; Oswald et al. 2007). In some people, however, symptoms of mania and depression may occur together in what is called a mixed bipolar state. Treatments are available that can stabilize the acute mood swings – mania, hypomania, depression or mixed states – in bipolar disorders. However, because it is a recurrent illness, long-term prophylactic maintenance treatment is usually recommended (Suppes et al. 1991).

The primary therapeutic objective of maintenance therapy is to prevent relapse and recurrence of acute mood events, but as patients are likely to receive maintenance treatment for extensive periods of time,
the tolerability of these agents is also an important consideration. A variety of guidelines exist for bipolar disorders, covering both management of acute mood episodes and long-term prophylaxis (APA, 2002; Goodwin, 2003; Grunze et al. 2010; International Consensus Group, 2008; NICE, 2006; Scottish Intercollegiate Guidelines Network, 2005; Suppes et al. 2005; Yatham et al. 2009). The majority of guidelines include lithium in their recommendations for first-line maintenance therapy (APA, 2002; Goodwin, 2003; NICE, 2006; Scottish Intercollegiate Guidelines Network, 2005; Yatham et al. 2009). Recommendations for other first-line maintenance therapies vary, but usually include divalproex or lamotrigine, and sometimes olanzapine (Fountoulakis et al. 2005). In contrast to most guidelines, those provided by the Texas Implementation of Medication Algorithms recommend different approaches to bipolar maintenance treatment, depending on the nature of the preceding acute episode (Suppes et al. 2005). After an episode of mania or hypomania, lithium or divalproex are recommended, whereas following an acute episode of depression, lamotrigine is recommended, either as monotherapy or in combination with an antimanic agent such as lithium or divalproex (Suppes et al. 2005).

It is likely that there are many reasons underlying the variations in guidelines, including the paucity of controlled head-to-head trials on which to base recommendations, differences in the availability of pharmacological products, and differences in personal experiences and opinions. Furthermore, variation may reflect the rapidly changing armamentarium of agents available for bipolar maintenance, which can result in guidelines becoming outdated (Viesta et al. 2005). Guidelines that are frequently updated, or that have been recently updated, will be based upon different data than those for which an update is due.

In the absence of randomized head-to-head clinical trials of available therapies, physicians, healthcare providers, and organizations involved in drafting guidelines must rely on comparative data obtained from systematic reviews and meta-analyses when making treatment decisions and recommendations. A number of such analyses have been conducted on maintenance therapies for bipolar disorders (Bowden et al. 2000a; Chou & Fazzio, 2006; Derry & Moore, 2007; Grunze et al. 2004; Hellewell, 2006; Muzina & Calabrese, 2005; Rybakowski, 2005; Sachs & Thase, 2000; Smith et al. 2007). In the past, these analyses have provided useful information regarding the appropriate maintenance treatment for bipolar disorder; however, some analyses have included only selected drug classes, which limits interpretation of the findings in the context of available therapies (Bowden et al. 2000a; Derry & Moore, 2007; Grunze et al. 2004; Hellewell, 2006; Muzina & Calabrese, 2005; Rybakowski, 2005; Sachs & Thase, 2000). Moreover, with the introduction of new therapies and publications of new trials of existing therapies, these analyses now need updating.

The most recently published comprehensive analysis on maintenance therapies was conducted by Smith et al. (2007); however, the cut-off date for inclusion was March 2005. Since this time, there have been many developments in the field of bipolar disorder, including new placebo-controlled trials assessing not only traditional maintenance therapies, such as lithium, but also newer options such as aripiprazole, long-acting risperidone, olanzapine, oxcarbazepine, quetiapine and ziprasidone. The introduction of new therapies for bipolar disorder – with different mechanisms of action and indications for both acute and maintenance treatment – raises questions about its optimal management. For example: Is there a rationale for distinguishing between drugs with different mechanisms of action as maintenance treatment options? Do any drugs show efficacy against the recurrence of manic/mixed and depressed mood events (that is to say at both poles of bipolar illness)?

The objective of the current analysis was to determine the relative efficacy of pharmacological therapy in the maintenance treatment of bipolar disorder using evidence from independent clinical trials. In addition, we also consider the findings in the context of the questions outlined above.

Methods

Population

The intended analysis population consisted of adults (aged ≥18 yr) with a diagnosis of bipolar disorder. Both monotherapies and combination therapies, used as bipolar maintenance or relapse/recurrence prevention, were included in the meta-analysis.

Data sources

We searched Medline (1993 to May 2010), EMBASE (1993 to May 2010) and the Cochrane Library. We supplemented this by searching reference lists of identified trials and reviews. The language of publication was restricted to English. In the first instance we used the search term: bipolar AND (maintenance OR prophylaxis OR prevention OR preventive OR recurrence OR relapse) AND randomized AND trial. To capture additional maintenance trials with bipolar mania and
related symptoms as index (initial) episode the following search string was also used: bipolar AND (mania OR manic OR cyclothymic OR hypomania OR rapid cycling) AND randomized AND trial. Different variants and spellings were tested whenever relevant.

A sequential search procedure was used. The first step was a search that combined typical key words for the indication and clinical trials. As a second step, the indication was combined with individual drug names: carbamazepine, valproate/divalproex/valproic acid, clonazepam, phenytoin, oxcarbazepine, licarbazepine, eslicarbazepine, gabapentin, levetiracetam, pregabalin, tiagabine, lamotrigine, topiramate, zonisamide, and retigabine, amisulpride, aripiprazole, clozapine, olanzapine, olanzapine + fluoxetine, quetiapine immediate release (IR) and extended release (XR), risperidone, risperidone injection (long-acting), haloperidol, chlorpromazine, pimozide, perphenazine, flupept(h)ixol, ziprasidone, asemapine, paliperidone, bifeprunox, lurasidone and zotepine. Antidepressants: paroxetine, fluoxetine, sertraline, citalopram, escitalopram, bupropion, venlafaxine, duloxetine, desvenlafaxine, imipramine, moclobemide, mirtazapine, tranylcypromine and agomelatine. Other: pramipexole, modafinil, inositol, tamoxifen and omega-3 fatty acids.

Eligibility criteria comprised: double-blind controlled studies (having either a placebo or active comparator), a duration of at least 6 months, and a minimum of 15 patients per treatment arm. These duration and sample sizes are recommended by regulatory agencies or required for conformational statistical testing.

Data extraction and outcomes

Two reviewers decided whether individual studies met the inclusion criteria. A standardized form, which included patient and study characteristics, outcome measures, and study results, was used to independently extract data from the selected studies. Data from intention-to-treat analyses (where available) and outcome data at the longest available follow-up were analysed.

Results are presented for relative risk (RR) of relapse for patients in remission and all-cause discontinuation during the randomized phase.

Data synthesis

The outcomes were combined in a meta-analysis. Binary outcomes (RR) were pooled by risk ratios using the Mantel–Haenszel method (Sutton et al. 2000).

Heterogeneity between studies was measured with the $\chi^2$ test and the $I^2$ score. The $I^2$ score measures the proportion of heterogeneity in individual studies that cannot be explained by chance (Higgins & Thompson, 2002; Higgins et al. 2003). It ranges between 0% and 100%, with lower values representing less heterogeneity. A high value reflects genuine differences between the results of the studies, while a low value reflects differences compatible with chance alone (Higgins et al. 2003). If the $\chi^2$ test indicated heterogeneity, the random-effects analysis was performed using DerSimonian and Laird methods (DerSimonian & Laird, 1986).

Statistical software

All calculations were performed with the general purpose statistical software package Stata version 10.2 (StataCorp LP, USA). The metan package of Stata was used for performing the meta-analyses.

Results

After screening, 226 publications were identified through the combined search strategies, and we identified 21 trials, with a combined total of 5364 participants that fulfilled the inclusion criteria (Bowden et al. 2000b, 2003, 2010; Calabrese et al. 2000, 2003, 2005; Greil et al. 1997; Hartong et al. 2003; Keck et al. 2007; Macfadden et al. 2009; McElroy et al. 2008; Quirroz et al. 2010; Suppes et al. 2009; Tohen et al. 2003, 2004, 2005, 2006; Vieta et al. 2008a, b; Young et al. 2008; Zarate & Tohen, 2004). Table 1 shows details of all trials included in the analysis.

We identified: one trial each for aripiprazole (Keck et al. 2007), olanzapine + mood stabilizer (Tohen et al. 2004), oxcarbazepine + lithium (Vieta et al. 2008a), perphenazine + mood stabilizer (Zarate & Tohen, 2004), risperidone long-acting injectable monotherapy (Quirroz et al. 2010), risperidone long-acting injectable + mood stabilizer (Macfadden et al. 2009) and ziprasidone + mood stabilizer (Bowden et al. 2010); two trials for carbamazepine (Greil et al. 1997; Hartong et al. 2003) and quetiapine + mood stabilizer (Suppes et al. 2009; Vieta et al. 2008b) and quetiapine monotherapy (McElroy et al. 2008; Young et al. 2008); three trials each for divalproex (Bowden et al. 2000a, b; Greil et al. 1997; Tohen et al. 2003), lamotrigine (Bowden et al. 2003; Calabrese et al. 2000, 2003) and olanzapine (Tohen et al. 2003, 2005, 2006); and eight trials for lithium (Bowden et al. 2000b, 2003; Calabrese et al. 2003, 2005; Greil et al. 1997; Hartong et al. 2003; Tohen et al. 2005; Vieta et al. 2008a).
### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patient population</th>
<th>Duration (wk)</th>
<th>Definition of relapse</th>
<th>Outcomes relating to relapse/recurrence</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowden et al.</td>
<td>Following stabilization:</td>
<td>Bipolar I disorder</td>
<td>52</td>
<td>Occurrence of a manic episode (MRS score ( \geq 16 ) or requiring hospitalization) or depressive episode (requiring antidepressant use or premature discontinuation from the study due to symptoms)</td>
<td>Any mood episode:</td>
<td>(1) All: 116/187, Relapse: 45/187, Intolerance/ non-compliance: 41/187, Other: 30/187</td>
</tr>
<tr>
<td>(2000)</td>
<td>(1) DVP to give 71–125 ( \mu )g/ml for divalproex, ( n = 187 )</td>
<td>Age: 39 ± 12 yr, Male: 49%</td>
<td></td>
<td></td>
<td>(2) 28/91 (31%)</td>
<td>(2) All: 69/91, Relapse: 28/91, Intolerance/ non-compliance: 32/91, Other: 9/91</td>
</tr>
<tr>
<td></td>
<td>(2) lithium to give 0.8–1.2 mmol/l, ( n = 91 )</td>
<td>MRS: 3.4</td>
<td></td>
<td></td>
<td>(3) 36/94 (38%)</td>
<td>(3) All: 71/94, Relapse: 36/94, Intolerance/ non-compliance: 11/94, Other: 24/94</td>
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<tr>
<td></td>
<td>(3) placebo, ( n = 94 )</td>
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<tr>
<td>Bowden et al.</td>
<td>Following stabilization:</td>
<td>Bipolar I disorder, manic or hypomanic</td>
<td>76</td>
<td>Requiring intervention – either pharmacotherapy or electroconvulsive therapy</td>
<td>Any mood episode:</td>
<td>(1) All: 56/59, Relapse: 28/59, Adverse event: 3/59</td>
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<tr>
<td>(2003)</td>
<td>(1) lamotrigine 100–400 ( \mu )g/d, ( n = 59 )</td>
<td>Age: 41 ± 12 yr, Male: 47%</td>
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<td></td>
<td>(2) 18/44 (41%)</td>
<td>(2) All: 45/46, Relapse: 18/46, Adverse event: 11/46</td>
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<tr>
<td></td>
<td>(2) lithium to give 0.8–1.1 mEq/l, ( n = 46 )</td>
<td>HAMD 17: 7, CGI-S: 4.3, MRS: 22</td>
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<td></td>
<td>(3) 49/69 (71%)</td>
<td>(3) All: 70/70, Relapse: 49/70, Adverse event: 3/70</td>
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<tr>
<td></td>
<td>(3) placebo, ( n = 70 )</td>
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<tr>
<td>Bowden et al.</td>
<td>Following stabilization:</td>
<td>Bipolar I disorder</td>
<td>26</td>
<td>Investigator decision that discontinuation was in best interests of the subject, loss of effect/requirement of treatment change, hospitalization, MRS ( \geq 18 ) or MADRS ( \geq 18 ) for 2 consecutive visits (&lt;10 days apart)</td>
<td>Any mood episode:</td>
<td>(1) All: 43/127, Lack of efficacy: 9/127, Adverse event: 12/127</td>
</tr>
<tr>
<td>(2010)</td>
<td>(1) ziprasidone 80–160 ( \mu )g/d + lithium/divalproex (to give 0.6–1.2 mEq/l and 50–125 ( \mu )g/ml, respectively), ( n = 127 )</td>
<td>Age: 39 ± 12 yr, Male: 46%</td>
<td></td>
<td></td>
<td>(2) 26/111 (32%)</td>
<td>(2) All: 58/113, Lack of efficacy: 22/113, Adverse event: 15/113</td>
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<td></td>
<td>(2) placebo + lithium/valproex (to give 0.6–1.2 mEq/l and 50–125 ( \mu )g/ml, respectively), ( n = 113 )</td>
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<td></td>
<td>(3) 9/127 (7%)</td>
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<td>(4) 20/111 (18%)</td>
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<td>(5) 16/127 (13%)</td>
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<td>(6) 16/111 (14%)</td>
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<tr>
<td>Study</td>
<td>Treatment</td>
<td>N</td>
<td>Patients Description</td>
<td>Outcome Measures</td>
<td>Results</td>
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<tr>
<td>Calabrese et al. (2000)</td>
<td>Lamotrigine 100-500 mg/d, placebo</td>
<td>182</td>
<td>Rapid cycling bipolar disorder, manic, mixed or depressed</td>
<td>Requiring intervention for a mood episode, or one that was emerging</td>
<td>26 (59%)</td>
<td></td>
</tr>
<tr>
<td>Calabrese et al. (2003)</td>
<td>Lamotrigine 50, 200 or 400 mg/d, lithium to give 0.8-1.1 mEq/l, placebo</td>
<td>372</td>
<td>Bipolar I disorder, currently or recently depressed</td>
<td>Requiring intervention for a mood episode</td>
<td>76 (74%)</td>
<td></td>
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<tr>
<td>Calabrese et al. (2005)</td>
<td>Lithium &gt;0.8 mEq/l, divalproex &gt;50 µg/mL</td>
<td>60</td>
<td>Bipolar I and II disorder</td>
<td>Requiring intervention for a mood episode, or one that was emerging</td>
<td>80 (72%)</td>
<td></td>
</tr>
<tr>
<td>Greil et al. (1997)</td>
<td>Lithium to give 0.6-0.8 mmol/l, carbamazepine to give 4-12 µg/mL</td>
<td>194</td>
<td>Bipolar I, At randomization:</td>
<td>Research Diagnostic Criteria score of 5 or 6</td>
<td>130 (76%)</td>
<td></td>
</tr>
<tr>
<td>Hartong et al. (2003)</td>
<td>Lithium to give 0.6-1.0 mmol/l, carbamazepine to give 4-12 µg/mL</td>
<td>64</td>
<td>Bipolar I and II disorder</td>
<td>Fulfilling DSM-III-R criteria for (hypo)mania or major depression</td>
<td>104 (59%)</td>
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</tbody>
</table>

**Results**

- All: 56/93 Requiring therapy: 45/93, Adverse event: 1/93
- All: 66/89, Requiring therapy: 49/89, Adverse event: 2/89
- All: 183/221, Relapse: 115/221, Adverse event: 20/221
- All: 101/212, Relapse: 56/121, Adverse event: 19/121
- All: 109/121, Relapse: 66/121, Adverse event: 12/121
- All: 77/215 (36%) (2) 46/120 (38%) (3) 47/119 (39%)
- Median time (wk) to intervention for mood episode:
  - 18
  - 45 (difference not significant)
- Median time (wk) to discontinuation for any reason:
  - 14
  - 26 (difference not significant)
- Symptom recurrence of any mood episode:
  - 17/60 (28%)
  - 20/43 (47%)
- Any mood relapse:
  - 12/44 (27%)
  - 21/50 (19%)
- All: 14/74, Relapse: 17/60, Adverse event: 4/74
- All: 27/70, Relapse: 20/43, Adverse event: 9/70
- All: 16/44, Adverse event: 5/44
- All: 13/50, Adverse event: 4/50
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patient population</th>
<th>Duration (wk)</th>
<th>Definition of relapse</th>
<th>Outcomes relating to relapse/recurrence&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Discontinuation&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Keck et al. (2007) | Following stabilization:  
(1) aripiprazole 15–30 mg/d, n = 78  
(2) placebo, n = 83 (27 at week 26) |
Bipolar I disorder  
At randomization:  
Age: 40 ± 1 yr  
Male: 33%  
Manic: 70%  
Mixed: 30%  
MADRS: 4,  
YMRS: 2.3 |
100 | Hospital admission due to a mood episode and/or addition to or increase in psychotropic medication for manic and/or depressive symptoms | From week 6–100:  
Any mood episode:  
(1) 25/77 (32%)  
(2) 43/83 (52%)  
Manic relapse:  
(1) 9/77 (12%)  
(2) 23/83 (28%)  
Depressive relapse:  
(1) 11/77 (14%)  
(2) 13/83 (16%)  
Mixed relapse:  
(1) 4/77 (5%)  
(2) 5/83 (6%)  
Unknown relapse:  
(1) 1/77 (1%)  
(2) 2/83 (2%) |
(1) All: 32/39, IR: 5/39,  
Adverse event: 1/39  
(2) All: 22/27, IR: 7/27,  
Adverse event: 0/27 |
| McElroy et al. (2008) | Following stabilization:  
(1) quetiapine 300 mg, n = 61  
(2) quetiapine 600 mg, n = 66  
(3) placebo, n = 129 |
Bipolar I and II disorder, following treatment for acute depressive episode  
At randomization:  
Age: 39 yr  
Male: 37%  
Bipolar I: 64%  
DSM-IV-TR criteria for an acute mood episode; requiring additional treatment and YMRS or MADRS >15 and CGI-S ≥4 or CGI-C ≥6 or GAF reduction of >10 points; hospitalization for worsening of symptoms or suicidal ideation |
52 | Requiring medication to treat mood episode, hospitalization for mood episode, YMRS score ≥16 or MADRS score ≥20, or discontinuation due to mood episode | Hazard ratio for the time to recurrence of a mood event of 0.43 (95% CI 0.27 to 0.69)  
Hazard ratio for the time to recurrence of a depressive event of 0.36 (95% CI 0.21 to 0.65) |
(1) All: 32/61  
(2) All: 35/66  
(3) All: 37/60  
(4) All: 27/50 |
| Macfadden et al. (2009) | Following stabilization:  
(1) risperidone long-acting injectable 25–50 mg + mood stabilizer, n = 65  
(2) mood stabilizer, n = 59 |
Bipolar patients with frequently relapsing bipolar disorder  
At randomization:  
Age: 39 ± 12 yr  
Male: 72% |
52 | DSM-IV-TR criteria for an acute mood episode; requiring additional treatment and YMRS or MADRS >15 and CGI-S ≥4 or CGI-C ≥6 or GAF reduction of >10 points; hospitalization for worsening of symptoms or suicidal ideation | Any mood relapse:  
(1) 15/65 (23%)  
(2) 27/59 (46%)  
Manic relapse:  
(1) 5/65 (8%)  
(2) 12/59 (20%)  
Depressive relapse:  
(1) 6/65 (12%)  
(2) 11/59 (19%)  
Mixed:  
(1) 2/65 (3%)  
(2) 4/59 (7%) |
(1) All: 26/65, Relapse: 13/65, Adverse event: 3/65  
(2) All: 34/59, Relapse: 23/59, Adverse event: 1/59 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Details</th>
<th>Baseline Characteristics</th>
<th>Initial Episode</th>
<th>Maintenance</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiroz et al.</td>
<td>Following stabilization: 1) risperidone long-acting injectable 12.5–50 mg, n = 154</td>
<td>Bipolar I disorder</td>
<td>Age: 39 ± 12 yr</td>
<td>Any mood</td>
<td>DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; treatment intervention; hospitalization; YMRS score &gt; 12, MADRS score &gt; 12, or CGI-S score &gt; 4 at any visit; or needing additional risperidone</td>
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<tr>
<td></td>
<td>2) placebo, n = 149</td>
<td></td>
<td>Male: 51%</td>
<td>episode:</td>
<td>(1) 42/135 (31%)</td>
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<td></td>
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<td>Manic: 79%</td>
<td>treatment</td>
<td>(2) 76/133 (57%)</td>
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<td></td>
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<td></td>
<td>Mixed: 21%</td>
<td>intervention; hospitalization; YMRS score &gt; 12, MADRS score &gt; 12, or CGI-S score &gt; 4 at any visit; or needing additional risperidone</td>
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<td></td>
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<td>MADRS: 1.9</td>
<td>(1)</td>
<td>(2) 22/135 (16%)</td>
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<td></td>
<td></td>
<td></td>
<td>YMRS: 2.4</td>
<td>20/135 (15%)</td>
<td>(2) 62/133 (47%)</td>
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<td></td>
<td>CGI-S: 1.6</td>
<td>14/133 (11%)</td>
<td>(2) 14/133 (11%)</td>
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<td></td>
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<td></td>
<td>All: 40/154, Adverse events: 15/154</td>
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<td></td>
<td>All: 37/149, Adverse events: 33/149</td>
</tr>
<tr>
<td>Suppes et al.</td>
<td>Following stabilization: 1) quetiapine 400–800 mg/d + lithium/divalproex (to give 0.5–1.2 mEq/l and 50–125 μg/ml, respectively), n = 310</td>
<td>Bipolar I disorder with &gt; 1 episode of mania, depression, or a mixed episode in last 2 yr</td>
<td>Age: 40 ± 12 yr</td>
<td>Hazard ratio for the time to recurrence</td>
<td>Hazard ratio for the time to recurrence of a mood event of 0.32 (p &lt; 0.0001), corresponding to a risk reduction of 68% for quetiapine + lithium/divalproex compared to placebo + lithium/divalproex</td>
</tr>
<tr>
<td></td>
<td>2) placebo + lithium/divalproex, n = 313</td>
<td></td>
<td>Male: 48%</td>
<td>of a mania event of 0.30 (p &lt; 0.0001), corresponding to a risk reduction of 70%</td>
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<td></td>
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<td></td>
<td>Manic: 24%</td>
<td>Hazard ratio for the time to recurrence of a depressive event of 0.33 (p &lt; 0.0001), corresponding to a risk reduction of 67%</td>
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<td></td>
<td></td>
<td></td>
<td>Depressed: 31%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Mixed: 46%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>MADRS: 4.8, YMRS: 3.6</td>
<td>All: n.a., Relapse: 63/310, Adverse event: 25/310</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) All: n.a., Relapse: 163/313, Adverse event: 8/313</td>
<td></td>
</tr>
<tr>
<td>Tohen et al.</td>
<td>Following stabilization: 1) olanzapine 5–20 mg/d, n = 125</td>
<td>Bipolar disorder, manic or mixed</td>
<td>Age: 41 yr</td>
<td>YMRS &lt; 12</td>
<td>(1) 71/125 (57%)</td>
</tr>
<tr>
<td></td>
<td>2) divalproex 500–2000 mg/d, n = 126</td>
<td></td>
<td>Male: 43%</td>
<td>(2) 57/126 (45%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Manic: 57%</td>
<td>Median time to remission (days)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mixed: 43%</td>
<td>(1) 14</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HAMD:14, YMRS: 28</td>
<td>(2) 62</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>YMRS &lt; 12 and MADRS &lt; 8 at 47 wk</td>
<td>(1) 39/125 (31%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) 39/126 (31%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptomatic relapse into affective episode (YMRS ≥ 15 or HAMD ≥ 15)</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>(1) 14/33 (42%)</td>
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<td></td>
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<td>(2) 13/23 (57%)</td>
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<td></td>
<td></td>
<td>(1) All: 106/125, IR: 24/125, Adverse event: 31/125</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) All: 106/126, IR: 28/126, Adverse event: 25/126</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Patient population</td>
<td>Duration (wk)</td>
<td>Definition of relapse</td>
<td>Outcomes relating to relapse/recurrence$^b$</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
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<td>---------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Tohen et al.     | Following stabilization:  
  (1) olanzapine 5–20 mg/d + lithium (0.6–1.2 mmol/l) or
  divalproex, $n = 51$  
  (2) placebo + lithium  
  (0.6–1.2 mmol/l) or
  divalproex, $n = 48$ | Bipolar I disorder with remission of manic episode after treatment with
  olanzapine +
  lithium or divalproex  
  At randomization:  
  Age: 41 yr  
  Male: 48%  
  Manic: 50%  
  Mixed: 50% | 78            | DSM-IV criteria for a manic mixed or depressive episode, or
  symptomatic according to the YMRS or HAMD            | Symptomatic relapse into affective episode (YMRS +/or HAMD $\geq 15$) without symptoms initially  
  (1) 11/30 (37%)  
  (2) 21/38 (55%)  
  Median time to relapse (days)  
  (1) 163            
  (2) 42  
  Depression alone:  
  (1) 7/30–3% (163 days)  
  (2) 15/38–39% (55 days)  
  Mania alone:  
  (1) 6/30–20% (172 days)  
  (2) 11/38–29% (59 days) | (1) All: 35/51, IR: 13/51,  
  Adverse event: 5/51  
  (2) All: 43/48, IR: 17/48,  
  Adverse event: 8/48 |
| Tohen et al.     | Following stabilization:  
  (1) olanzapine 5–20 mg/d,  
  $n = 217$  
  (2) lithium to give  
  0.6–1.2 mEq/l, $n = 214$ | Bipolar disorder  
  At randomization:  
  Age: 42 ± 13 yr  
  Male: 47%  
  Manic: 93%  
  Psychic: 26%  
  Baseline HAMD: 3.8,  
  YMRS: 1.6 | 52            | YMRS or HAMD $\geq 15$            | Symptomatic recurrence of any mood episode (YMRS +/or HAMD $\geq 15$)  
  (1) 65/217 (30%)  
  (2) 83/214 (39%)  
  Mania:  
  (1) 30/217 (14%)  
  (2) 50/214 (23%)  
  Depression:  
  (1) 34/217 (16%)  
  (2) 23/214 (11%)  
  Time to recurrence not significantly different between groups | (1) All: 116/217, IR: 31/ 
  217, Adverse event: 41/ 
  217  
  (2) All: 144/214, IR: 34/ 
  214, Adverse event: 55/ 
  214 |
**Tohen et al. (2006)**

<table>
<thead>
<tr>
<th>Following stabilization:</th>
<th>Bipolar I disorder</th>
<th>YMRS or HAMD $\geq 15$ or hospitalization for a manic, mixed or depressive episode</th>
<th>Symptomatic recurrence of any mood episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) olanzapine 5-20 mg/d, $n = 225$</td>
<td>At randomization: Age: 40 ± 12 yr Male: 39% Manic: 66% Mixed: 34% Psychotic: 18% HAMD: 3.6, YMRS: 4.2</td>
<td>(1) 105/225 (47%) (2) 109/136 (80%)</td>
<td>Mania: (1) 27/225 (12%) (2) 44/136 (32%) Depression: (1) 68/225 (30%) (2) 53/136 (39%) Mixed: (1) 10/225 (4%) (2) 12/136 (9%) Time to any relapse: (1) 174 days (2) 22 days</td>
</tr>
<tr>
<td>(2) placebo, $n = 136$</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Vieta et al. (2008a)**

| (1) oxcarbazepine 1200 mg/d + lithium, $n = 26$ | Bipolar I and II patients currently in remission | DSM-IV-TR criteria for a manic, hypomanic, mixed or depressive episode, YMRS $> 12$ or MADRS $> 20$ | Manic relapse: (1) 4/26 (15%) (2) 8/29 (28%) |
| (2) placebo + lithium, $n = 29$ | Age: 44 yr Male: 35% | | Depressive relapse: (1) 3/26 (12%) (2) 9/29 (31%) Mixed relapse: (1) 1/26 (4%) (2) 1/29 (3%) Any mood episode: (1) 8/26 (31%) (2) 18/29 (62%) |

**Vieta et al. (2008b)**

<table>
<thead>
<tr>
<th>Following stabilization:</th>
<th>Bipolar I disorder with current or recent mixed, manic, or depressed episode</th>
<th>YMRS or MADRS $\geq 20$ at two consecutive assessments or discontinuation due to an event (mania, depression or mixed), or hospitalization for mania, depression or a mixed event; or intervention to treat mania, depression or a mixed event</th>
<th>Hazard ratio for the time to recurrence of a mood event of 0.28 ($p &lt; 0.001$), corresponding to a risk reduction of 72% for quetiapine + lithium / divalproex compared to placebo + lithium / divalproex</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) quetiapine 400-800 mg/d + lithium / divalproex (to give 0.5-1.2 mEq/l and 50-125 µg/ml), $n = 336$</td>
<td>At randomization: Age: 42 ± 13 yr Male: 45% Manic: 48% Depressed: 29% Mixed: 23% MADRS: 3.5, YMRS: 2.4</td>
<td></td>
<td>Hazard ratio for the time to recurrence of a mania event of 0.30 ($p &lt; 0.001$), corresponding to a risk reduction of 70%</td>
</tr>
<tr>
<td>(2) placebo + lithium / divalproex, $n = 367$</td>
<td></td>
<td></td>
<td>Hazard ratio for the time to recurrence of a depressive event of 0.26 ($p &lt; 0.001$), corresponding to a risk reduction of 74%</td>
</tr>
</tbody>
</table>

(1) All: 72/225, IR: 4/225, Adverse event: 17/225
(2) All: 18/136, IR: 2/136, Adverse event: 0/136
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patient population</th>
<th>Duration (wk)</th>
<th>Definition of relapse</th>
<th>Outcomes relating to relapse/recurrence $^b$</th>
<th>Discontinuation $^b$</th>
</tr>
</thead>
</table>
| Young et al. (2008)| Following stabilization:  
(1) quetiapine 300 mg, $n = 80$  
(2) quetiapine 600 mg, $n = 83$  
(3) placebo, $n = 165$ | Bipolar I and II disorder, following treatment for acute depressive episode  
At randomization:  
Age: 41 yr  
Male: 41%  
Bipolar I: 62% | 52            | Hazard ratio for the time to recurrence of a mood event of 0.56 (95% CI 0.39–0.82)  
Hazard ratio for the time to recurrence of a depressive event of 0.48 (95% CI 0.29–0.77) | (1) All: 37/80  
(2) All: 36/84  
(3) All: 24/63  
(4) All: 36/74 |
| Zarate & Tohen (2004)| Following stabilization  
(1) perphenazine 4–64 mg/d + mood stabilizer/s, $n = 18$  
(2) placebo + mood stabilizer/s, $n = 19$ | Bipolar I disorder.  
Maintenance after stabilization of manic/mixed episode  
(1) Age: 36 yr, Male: 24%,  
(2) manic: 65%, mixed: 35% | 26            | DSM-IV criteria for a manic or depressive episode | Manic relapse:  
(1) 1/19 (5%)  
(2) 2/18 (11%)  
Depressive relapse:  
(1) 4/19 (21%)  
(2) 0/18 (0%)  
Any mood episode:  
(1) 5/19 (26%)  
(2) 2/18 (11%) | (1) All: 10/19, Adverse event: 4/19  
(2) All: 3/18, Adverse event: 1/18 |

BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression – Severity; CGI-C, Clinical Global Impression – Change; CI, confidence interval; GAF, global assessment of functioning; HAMD, Hamilton Rating Scale for Depression; IR, insufficient response; MADRS, Montgomery–Åsberg Depression Rating Scale; MRS, Mania Rating Scale; TEM, treatment-emergent mania; YMRS, Young Mania Rating Scale.

$^a$ While every effort has been made to provide consistent data, variations in individual publications precluded the ability to provide consistency across all studies.

$^b$ Differences in total patient numbers between the outcomes and discontinuations columns reflects differences in datasets. In general, the intention-to-treat population is used to calculate discontinuations, whereas the efficacy datasets include only patients who received at least one dose of medication.
Table 2. Index episodes for maintenance studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Interventions</th>
<th>Index episode/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese et al.</td>
<td>2003</td>
<td>LTG/Li/Placebo</td>
<td>Depressive episode</td>
</tr>
<tr>
<td>McElroy et al.</td>
<td>2008</td>
<td>QTP 300/QTP 600/Placebo</td>
<td>Depressive episode</td>
</tr>
<tr>
<td>Young et al.</td>
<td>2008</td>
<td>QTP 300/QTP 600/Placebo</td>
<td>Depressive episode</td>
</tr>
<tr>
<td>Calabrese et al.</td>
<td>2000</td>
<td>LTG/Placebo</td>
<td>Manic, mixed, or depressive episode</td>
</tr>
<tr>
<td>Vieta et al.</td>
<td>2008b</td>
<td>QTP+Li or DVP/Placebo</td>
<td>Manic, mixed, or depressive episode</td>
</tr>
<tr>
<td>Suppes et al.</td>
<td>2009</td>
<td>QTP+Li or DVP/Placebo</td>
<td>Manic, mixed, or depressive episode</td>
</tr>
<tr>
<td>Bowden et al.</td>
<td>2000b</td>
<td>DVP/Li/Placebo</td>
<td>Manic/mixed episode</td>
</tr>
<tr>
<td>Zarate et al.</td>
<td>2004</td>
<td>PPZ+Li or DVP/Placebo</td>
<td>Manic/mixed episode</td>
</tr>
<tr>
<td>Tohen et al.</td>
<td>2004</td>
<td>OLZ+Li or DVP/Placebo</td>
<td>Manic/mixed episode</td>
</tr>
<tr>
<td>Tohen et al.</td>
<td>2006</td>
<td>OLZ/Placebo</td>
<td>Manic/mixed episode</td>
</tr>
<tr>
<td>Keck et al.</td>
<td>2007</td>
<td>ARP/Placebo</td>
<td>Manic/mixed episode</td>
</tr>
<tr>
<td>Bowden et al.</td>
<td>2010</td>
<td>ZIP+Li or DVP/Placebo</td>
<td>Manic/mixed episode</td>
</tr>
<tr>
<td>Bowden et al.</td>
<td>2003</td>
<td>LTG/Li/Placebo</td>
<td>Manic/hypomanic episode</td>
</tr>
<tr>
<td>Vieta et al.</td>
<td>2008a</td>
<td>OXC+Li/Placebo</td>
<td>In remission at inclusion</td>
</tr>
</tbody>
</table>

ARP, Aripiprazole; DVP, divalproex; Li, lithium; LTG, lamotrigine; OLZ, olanzapine; OXC, oxcarbazepine; QTP, quetiapine; PPZ, perphenazine; ZIP, ziprasidone.

Studies without placebo comparator were excluded from the analysis (Calabrese et al. 2005; Greil et al. 1997; Hartong et al. 2003; Tohen et al. 2003, 2005).

The length of follow-up was 26 wk in three studies (Bowden et al. 2010; Calabrese et al. 2000; Zarate & Tohen, 2004), between 47 and 52 wk in eight studies (Bowden et al. 2000b; Macfadden et al. 2009; McElroy et al. 2008; Tohen et al. 2003, 2005, 2006; Vieta et al. 2008a; Young et al. 2008), between 72 and 80 wk in four studies (Bowden et al. 2003; Calabrese et al. 2003, 2005; Tohen et al. 2004) and between 100 and 130 wk in six studies (Greil et al. 1997; Hartong et al. 2003; Keck et al. 2007; Quiroz et al. 2010; Suppes et al. 2009; Vieta et al. 2008b). Median follow-up among the 21 studies was 52 wk, and mean follow-up was 68 wk. The majority of studies included a "stabilization phase" during which patients received treatment for an acute episode, and only those patients who responded to treatment were permitted to continue in the maintenance analysis. The index episodes in the acute treatment phases differed for individual studies, which may have influenced the findings (Table 2).

A number of studies were excluded from the meta-analytical calculations because they did not include a placebo group, and used different comparators (Calabrese et al. 2005; Greil et al. 1997; Hartong et al. 2003; Tohen et al. 2003, 2005).

**Efficacy relative to comparator**

**RR for relapse of any mood episode**

The combined evidence for both manic and depressive relapses is shown in Figs 1a and 1b. All monotherapies had RRs significantly different from 1.0, favouring treatment. The overall estimate of the RR of any mood episode relapse compared to comparator (placebo) was 0.68 [95% confidence interval (CI) 0.60–0.77, \( p < 0.001 \)], which is of the same order of magnitude as the overall RR for the individual events in maintenance treatment (shown below). The heterogeneity was moderate with an \( I^2 \) score of 52.3%.

Among the combination therapies, oxcarbazepine + lithium, quetiapine + lithium/divalproex, risperidone + mood stabilizer, and ziprasidone + lithium/divalproex had RRs significantly different from 1.0, favouring treatment. The overall estimate of the RR of any mood relapse for combination therapy compared to comparator [lithium (Vieta et al. 2008a); lithium/divalproex (Bowden et al. 2010; Suppes et al. 2009; Tohen et al. 2004; Vieta et al. 2008b); mood stabilizer (Macfadden et al. 2009; Zarate & Tohen, 2004)] was 0.49 (95% CI 0.39–0.61, \( p < 0.001 \)). The heterogeneity was moderate with an \( I^2 \) score of 50.3%. The point estimate for quetiapine + lithium/divalproex was the lowest with a RR of 0.38 (95% CI 0.32–0.46). Quetiapine, however, represented a large part of the evidence for the RR of mood relapse in bipolar maintenance with 47% of the weight in the overall estimate for combination therapy.

**RR for manic/mixed relapse**

All of the therapies – both monotherapy and combination – were found to have a RR for manic/mixed...
relapse that was below 1.0, although significance vs. placebo or comparator varied among treatments (Figs 2a, 2b). The magnitude of the reduction in risk vs. placebo also varied between studies. Divalproex, lamotrigine, lithium and quetiapine monotherapy all had CIs extending beyond 1.0. The point estimate in one of the two studies concerning lamotrigine was below 1.0 (Calabrese et al. 2003), but both studies had quite wide CIs with the upper confidence limit for the RR being above 1.0 (Bowden et al. 2003; Calabrese et al. 2003). A similar finding was observed for 300 mg quetiapine, with one point estimate below 1.0 (McElroy et al. 2008) and the other above 1.0 (Young et al. 2008). As with lamotrigine, both studies had quite wide CIs with the upper confidence limit for the RR being above 1.0 (McElroy et al. 2008; Young et al. 2008). The overall estimate of the RR of manic/mixed relapse compared to placebo was 0.65 (95% CI 0.51–0.84) for monotherapy (p = 0.001). The heterogeneity was moderate with an I² score of 56.6%.

Of the combination treatments, only quetiapine + lithium/divalproex, long-acting risperidone+ mood stabilizer, and ziprasidone+ lithium/divalproex had RRs for manic/mixed relapse vs. their comparator treatments (lithium/divalproex and mood stabilizer, respectively) that were significantly below 1.0 (RR 0.39, 95% CI 0.30–0.52, p < 0.001; RR 0.40, 95% CI 0.18–0.90, p = 0.026; RR 0.39, 95% CI 0.19–0.83, p = 0.014, respectively) (Fig. 2b). The overall estimate of the RR of manic/mixed relapse compared to comparator [lithium (Vita et al. 2008a); lithium/divalproex (Bowden et al. 2010; Suppes et al. 2009; Tohen et al. 2004; Vieta et al. 2008b); mood stabilizer (Bowden et al. 2000b; Zarate & Tohen, 2004)] was 0.42 (95% CI 0.33–0.53, p < 0.001) for combination...
therapy (Fig. 2b). The heterogeneity was low with an $I^2$ score of 0% (scores lower than zero are assigned the value zero).

RR for depressive relapse

The point estimates for all monotherapies except long-acting injectable (LAI) risperidone were below 1.0; however, only divalproex ($p=0.013$), and quetiapine monotherapy ($p=0.004$ for 300 mg/d and $p=0.002$ for 600 mg/d) had RRs for relapse to a depressive episode that were significantly below 1.0 (Fig. 3a). The overall estimate of the RR of depressive relapse for monotherapy compared to placebo was 0.70 (95% CI 0.58–0.85), which is of a similar order of magnitude as the overall RR for manic/mixed relapse in maintenance treatment. The heterogeneity was moderate with an $I^2$ score of 45.5%.

The overall estimate of the RR of depressive relapse for combination therapy compared to placebo was 0.70 (95% CI 0.58–0.85), which is of a similar order of magnitude as the overall RR for manic/mixed relapse in maintenance treatment. The heterogeneity was moderate with an $I^2$ score of 35%. Only for quetiapine in combination with lithium/divalproex was the RR significantly below 1.0 compared to the comparator ($p<0.001$ and $p=0.039$, respectively). Together with oxcarbazepine, which had a mean RR of 0.37, the point estimate was also the lowest with a RR of 0.38 (95% CI 0.29–0.49, $p<0.001$). Quetiapine represented the major part of the evidence for the RR of depressive relapse in bipolar maintenance with 57% of the weight in the overall estimate for combination therapy.

RR for all-cause discontinuation

The RRs of all-cause discontinuation during the randomized phase in bipolar maintenance monotherapies were significantly lower than 1.0 for quetiapine, lamotrigine and divalproex (Fig. 4a). The finding for olanzapine monotherapy appeared to be an outlier, with a RR of 2.42 (95% CI 1.51–3.87, $p<0.001$). However, as this was only based on one study (Tohen et al. 2006), this estimate is of questionable validity given the results for olanzapine in combination with a mood stabilizer, where the RR in the combination therapy arm was 0.77 (95% CI 0.62–0.94, $p=0.013$) compared to mood stabilizer alone (Fig. 4b) (Tohen et al. 2006).
The olanzapine monotherapy finding is primarily explained by the low rate of discontinuation in the placebo arm (18/36 = 13%), rather than a high discontinuation rate in the treatment group (72/225 = 32%).

The overall estimate of the RR of discontinuation for monotherapy compared to placebo was 0.93 (95% CI 0.87–0.99, p = 0.024). The heterogeneity was moderate with an F score of 64.0%. This means that it is very unlikely that observed differences are due to chance alone (Higgins et al. 2003).

The RRs of discontinuation in bipolar maintenance combination therapies were significantly lower than 1.0 for the olanzapine + lithium/divalproex, quetiapine + lithium/divalproex and ziprasidone + lithium/divalproex combinations (Fig. 4b). Long-acting risperidone in combination with a mood stabilizer had a RR that was not significantly below 1.0 (p = 0.056) compared to mood stabilizer alone, but the upper confidence limit was close to 1.0. Compared to mood stabilizer, oxcarbazepine (RR 1.12) and perphenazine (RR 3.16) combination therapies had a RR larger than 1.0 compared to mood stabilizer alone. Both studies were quite small with sample sizes per arm ranging from 18 in the control group of the perphenazine study to 29 patients in the control group of the oxcarbazepine study, but the CI for perphenazine still did not encompass zero (95% CI 1.03–9.66). However, the rate of discontinuation in the perphenazine arm was not exceptionally high (10/19), rather, the discontinuation rate in the control arm (mood stabilizer alone) was unusually low (3/18). Again, this may be due to the small sample size.

The overall estimate of the RR of discontinuation for combination therapy compared to mood stabilizer was 0.75 (95% CI 0.62–0.90, p = 0.003). The
heterogeneity was high with an $I^2$ score of 73.1%. Ziprasidone + lithium/divalproex combination therapy had the lowest discontinuation (RR 0.66, 95% CI 0.49–0.89, $p = 0.007$).

**Discussion**

This analysis identified considerable variation in efficacy among bipolar maintenance therapies. In general, the RR of relapse to any mood event was more homogeneous across the treatments investigated than if manic/mixed or depressive events were considered separately. All medications (mono- and combination therapy) showed a RR for manic/mixed relapse that was below 1.0, although significance vs. placebo varied among treatments. The risk for depressive relapse was below 1.0 for all monotherapy studies identified except for the risperidone LAI study, although only divalproex and quetiapine showed significance vs. placebo. For the combination therapies, only quetiapine + lithium/divalproex had a RR of depressive relapse significantly below 1.0. Interestingly, the combination therapy quetiapine + lithium/divalproex had a RR for both manic/mixed episode and depressive relapse significantly below 1.0, suggesting that this intervention is effective in preventing relapse to either pole of bipolar illness.

Variation was also observed in the RRs for all-cause discontinuations, with RRs significantly lower than 1.0 for quetiapine monotherapy and combination therapy, divalproex monotherapy, lamotrigine monotherapy, olanzapine combination therapy, and ziprasidone combination therapy. The small sample sizes for some of the studies, however, may have contributed to the higher RR of discontinuation for olanzapine monotherapy and the oxcarbazepine and perphenazine combination therapies. Furthermore, as there may be many different reasons for discontinuations – administrative reasons, tolerability problems, lack of efficacy or hidden relapses – caution is advised when comparing discontinuation rates across studies.

Population enrichment may contribute to the variation observed between studies. Some studies, for example, those conducted by Bowden et al. (2003), Calabrese et al. (2000, 2003, 2005), Keck et al. (2007), Suppes et al. (2009), Tohen et al. (2004, 2005, 2006) and
Vieta et al. (2008b) incorporated a stabilization period into the study design after which non-responsive patients or those not considered clinically stable did not participate further. This could be viewed as artificial selection of the most responsive patients, which would limit the comparability between studies. It could also influence the rate of discontinuations as discussed above. However, we did not find any significant differences between the studies in terms of the RR of relapse or discontinuation depending on whether the trials included a stabilization phase or not. The index episode resulting in the initial treatment also differed between studies. In some studies, maintenance treatment was initiated after an acute manic or mixed episode and in other studies after an acute depressive episode. The polarity of the index episode has a relevant impact on the power to prevent further episodes of the same polarity (Calabrese et al. 2004). For instance, the results for quetiapine showed a higher RR favouring treatment for depressive relapse than for manic/mixed relapse, while it was the other way around for olanzapine. Hence, at least a partial explanation for this is that the initial episodes were different in the respective studies, where all patients in the olanzapine study had a manic/mixed index episode, while a substantial proportion of the patients in the quetiapine studies had acute depression as index episode. The index episode may therefore be a potential source of heterogeneity in the studies, and will affect the results concerning the relapse rates. Differences in placebo response is an additional factor that may potentially lead to bias in the results, but no significant correlation between the placebo response and the RR of a mood episode was found (Spearman’s rank correlation coefficient = $-0.051$, $p = 0.836$), indicating that the placebo response and the RR are independent.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>(%) Weight</th>
<th>Significance test of RR = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Aripiprazole</td>
<td>0.91 (0.83–1.91)</td>
<td>5.15</td>
<td>$p = 0.808$</td>
</tr>
<tr>
<td>ARP 15-30: Keck et al. 2007</td>
<td>0.91 (0.83–1.91)</td>
<td>5.15</td>
<td>$p = 0.808$</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.91 (0.83–1.91)</td>
<td>5.15</td>
<td>$p = 0.808$</td>
</tr>
<tr>
<td>2: Divalproex/valproate</td>
<td>0.40 (0.20–0.82)</td>
<td>5.41</td>
<td>$p = 0.013$</td>
</tr>
<tr>
<td>DVP 71–125: Bowden et al. 2000b</td>
<td>0.40 (0.20–0.82)</td>
<td>5.41</td>
<td>$p = 0.013$</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.40 (0.20–0.82)</td>
<td>5.41</td>
<td>$p = 0.013$</td>
</tr>
<tr>
<td>3: Lamotrigine</td>
<td>0.91 (0.68–1.21)</td>
<td>13.63</td>
<td></td>
</tr>
<tr>
<td>LTG 50–400: Calabrese et al. 2003</td>
<td>0.91 (0.68–1.21)</td>
<td>13.63</td>
<td></td>
</tr>
<tr>
<td>LTG 100–400: Bowden et al. 2003</td>
<td>0.45 (0.32–0.99)</td>
<td>5.22</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.70 (0.36–1.36)</td>
<td>18.85</td>
<td>$p = 0.290$</td>
</tr>
<tr>
<td>4: Lithium</td>
<td>0.62 (0.29–1.34)</td>
<td>4.83</td>
<td></td>
</tr>
<tr>
<td>Li 0.8–1.2: Bowden et al. 2000b</td>
<td>0.62 (0.29–1.34)</td>
<td>4.83</td>
<td></td>
</tr>
<tr>
<td>Li 0.8–1.1: Bowden et al. 2003</td>
<td>0.75 (0.39–1.43)</td>
<td>6.19</td>
<td></td>
</tr>
<tr>
<td>Li 0.8–1.1: Calabrese et al. 2003</td>
<td>0.67 (0.71–1.33)</td>
<td>12.76</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.88 (0.67–1.15)</td>
<td>23.78</td>
<td>$p = 0.349$</td>
</tr>
<tr>
<td>5: Olanzapine</td>
<td>0.78 (0.58–1.04)</td>
<td>13.53</td>
<td></td>
</tr>
<tr>
<td>OLZ 5–30: Tosen et al. 2006</td>
<td>0.78 (0.58–1.04)</td>
<td>13.53</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.78 (0.58–1.04)</td>
<td>13.53</td>
<td></td>
</tr>
<tr>
<td>6: Quetiapine 300</td>
<td>0.58 (0.33–1.02)</td>
<td>7.80</td>
<td></td>
</tr>
<tr>
<td>QTP 300: Young et al. 2008</td>
<td>0.58 (0.33–1.02)</td>
<td>7.80</td>
<td></td>
</tr>
<tr>
<td>QTP 300: McElroy et al. 2008</td>
<td>0.50 (0.27–0.93)</td>
<td>6.62</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.55 (0.36–0.83)</td>
<td>14.22</td>
<td>$p = 0.004$</td>
</tr>
<tr>
<td>7: Quetiapine 600</td>
<td>0.33 (0.15–0.68)</td>
<td>5.14</td>
<td></td>
</tr>
<tr>
<td>QTP 600: McElroy et al. 2008</td>
<td>0.33 (0.15–0.68)</td>
<td>5.14</td>
<td></td>
</tr>
<tr>
<td>QTP 600: Young et al. 2008</td>
<td>0.36 (0.22–0.97)</td>
<td>7.35</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.45 (0.27–0.75)</td>
<td>12.70</td>
<td>$p = 0.002$</td>
</tr>
<tr>
<td>8: Risperidone LAI</td>
<td>1.41 (0.74–2.67)</td>
<td>6.34</td>
<td></td>
</tr>
<tr>
<td>RLAI 12.5–50: Guinza et al. 2010</td>
<td>1.41 (0.74–2.67)</td>
<td>6.34</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.41 (0.74–2.67)</td>
<td>6.34</td>
<td>$p = 0.295$</td>
</tr>
<tr>
<td>Overall</td>
<td>0.70 (0.58–0.85)</td>
<td>100.00</td>
<td>$p &lt; 0.001$</td>
</tr>
</tbody>
</table>

Fig. 3a. Relative risk of depressive relapse – monotherapies. Heterogeneity: 3, lamotrigine ($I^2 = 67.1\%$); 4, lithium ($I^2 = 19.4\%$); 6, quetiapine ($I^2 = 0.0\%$); 7, quetiapine ($I^2 = 21.9\%$); overall ($I^2 = 45.5\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; ARP, aripiprazole; DVP, divalproex; LTG, lamotrigine; Li, lithium; OLZ, olanzapine; QTP, quetiapine; RLAI, risperidone long-acting injectable.
The meta-analysis presented here was intended to have a broader scope than some of the previously published meta-analyses, including many studies that had not been published when previous analyses were carried out. However, despite this the number of studies for some medications, e.g. aripiprazole, was not large. In contrast, lithium was well represented in these studies, reflecting its established position as a maintenance therapy for bipolar disorder. Another limitation of this analysis relates to the comparability of the data from these studies. Differences exist in the definition of a relapse, potentially making some studies more sensitive than others to demonstrations of efficacy. For example, some studies defined relapse as initiation of treatment at the discretion of the treating physician (e.g. Bowden et al. 2003; Calabrese et al. 2000, 2003), some studies included hospitalization in their criteria for relapse (e.g. Bowden et al. 2000b; Greil et al. 1997; Keck et al. 2007), and others defined relapse according to changes in scales such as the Hamilton Rating Scale for Depression (HAMD), Young Mania Rating Scale (YMRS), Mania Rating Scale (MRS), and Montgomery–Åsberg Depression Rating Scale (MADRS) (e.g. Bowden et al. 2000b; Calabrese et al. 2005; Tohen et al. 2003, 2004, 2005, 2006; Vieta et al. 2008a). Even where the same scales were used, the cut-off values were not necessarily the same. For example, Tohen et al. (2003, 2004, 2005, 2006) defined relapse to mania as YMRS ≥ 15, whereas, Vieta and colleagues defined patients with YMRS > 12 as having a recurrence (Vieta et al. 2008a). A further consideration is that there was no adjustment for study duration and thus exposure to treatment.

The efficacy seen with the atypical antipsychotics – aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone – as maintenance therapies must be balanced against their side-effect profiles. While it was beyond the scope of this particular meta-analysis to analyse all the safety and tolerability issues involved in bipolar disorder maintenance trials, the data indicate that aripiprazole is associated with tremor, akathisia, dry mouth, and weight gain (Keck et al. 2007). Trial data for olanzapine show that treatment is associated with somnolence, increased appetite, dry mouth, sedation, weight gain, tremor, asthenia, diarrhea, hyperprolactinemia and nausea (Tohen et al. 2005, 2006). Quetiapine, as a maintenance treatment, is associated with dry mouth, sedation, somnolence, dizziness, constipation, extrapyramidal side-effects, and increases in weight compared to placebo (Suppes et al. 2009; Vieta et al. 2008b). Trial data for risperidone as maintenance treatment indicate that it is associated

### Table

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Significance test of RR = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Olanzapine+Li/DVP</td>
<td>0.59 (0.28–1.26)</td>
<td>0.174</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.56 (0.28–1.26)</td>
<td>0.174</td>
</tr>
<tr>
<td>2: Oxcarbazepine+Li</td>
<td>0.37 (0.11–1.23)</td>
<td>0.105</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.37 (0.11–1.23)</td>
<td>0.105</td>
</tr>
<tr>
<td>3: Quetiapine+Li/DVP</td>
<td>0.41 (0.29–0.58)</td>
<td>0.001</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.38 (0.29–0.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>4: Risperidone LAI/mood stabiliser</td>
<td>0.66 (0.29–1.53)</td>
<td>0.332</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.66 (0.29–1.53)</td>
<td>0.332</td>
</tr>
<tr>
<td>5: Ziprasidone+Li/DVP</td>
<td>0.87 (0.46–1.66)</td>
<td>0.682</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.87 (0.46–1.66)</td>
<td>0.682</td>
</tr>
</tbody>
</table>

Fig. 3b. Relative risk of depressive relapse – combination therapies. Heterogeneity: 4, quetiapine + Li/DVP (I² = 0.0); overall (I² = 35.1%). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; DVP, divalproex; Li, lithium; OLZ, olanzapine; OXC, oxcarbazepine; PPZ, perphenazine; QTP, quetiapine; RLA, risperidone long-acting injectable; ZIP, Ziprasidone. (Perphenazine was excluded from the analysis, as there were no depressive relapses in the control group.)
with weight gain and hyperprolactinaemia (Quiroz et al. 2010). Long-term ziprasidone treatment is associated with weight gain (Bowden et al. 2010). There are also concerns of increased risk of metabolic syndrome – characterized by obesity, insulin resistance, hypertension, and dyslipidaemia – with atypical antipsychotics (Baptista et al. 2004). It is important to be aware, however, that adverse events occurring during maintenance treatment may differ from those observed in patients treated with agents for the first time.

In regard to the question as to whether there is a rationale for distinguishing between drugs with different mechanisms of action as maintenance treatment options, the findings from this meta-analysis suggest a blurring of the lines between drugs with different mechanisms of action and their potential uses for this indication. The findings have confirmed the efficacy of lithium, widely viewed as a ‘mood stabilizer’ as effective in the maintenance phase of bipolar disorder. Aripiprazole, olanzapine and quetiapine, which are classed as ‘antipsychotics’ also show ‘mood stabilizing’ efficacy in patients who have responded to them during an acute episode. These findings suggest that the original drug classification of ‘antipsychotic’ may be misleading, and that treatment decisions should be made regarding each individual agent rather than viewing them as particular drug classes.

As for the question of whether any drugs show efficacy against the recurrence of manic/mixed and depressed mood events (i.e. at both poles of bipolar illness), the findings from this analysis show that only combination therapy with quetiapine + lithium/divalproex was associated with reduced risk for relapse at both the manic/mixed and depressed poles of bipolar illness.
Conclusions

This meta-analysis indicates that there are several options available for the long-term treatment of bipolar disorder, although considerable variation in the efficacy profile exists among bipolar maintenance therapies. The long-term efficacy of lithium and divalproex has been confirmed, and some atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine, and risperidone are also effective in preventing depressive or manic/mixed relapses. Neither lamotrigine nor oxcarbazepine showed a RR below 1.0 for either manic/mixed or depressive relapse, providing little support for these agents used as monotherapies. For the combination therapies, ziprasidone + lithium/divalproex and risperidone + lithium/divalproex significantly reduced the risk of a manic relapse, but only quetiapine + lithium/divalproex significantly reduced risk for relapse at both the manic/mixed and depressed poles of bipolar illness. Interventions with proven efficacy could be considered appropriate options as first-line maintenance treatment but their efficacy will need to be balanced against safety and tolerability issues.

Acknowledgements

This study was supported by AstraZeneca Pharmaceuticals LP. The authors acknowledge the editorial assistance of Lucy Kanan, Ph.D. (PAREXEL), with manuscript review and revisions. Financial support for this assistance was provided by AstraZeneca Pharmaceuticals LP.

Statement of Interest

All authors have completed the Unified Competing Interest form (www.icmje.org/coi_disclosure.pdf, available on request from the corresponding author) and declare that: M.E. is an employee of i3 Innovus, which received support from AstraZeneca for the submitted work; O.G. and C.M. were employees of i3 Innovus at the time the work was performed; E.V. has received grants and served as consultant, advisor or speaker for the following entities: Almirall, AstraZeneca, Bristol–Myers Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, GlaxoSmithKline, Janssen-Cilag, Jazz, Johnson and Johnson, Lundbeck, Merck, Novartis, Organon, and others.
Otsuka, Pfizer, Sanofi-Aventis, Servier, Schering-Plough, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, Takeda, United Biosource Corporation, and Wyeth; J.L., M.A. and B.P., are full-time employees of AstraZeneca Pharmaceuticals LP; J.L. and B.P. hold stock/stock options in AstraZeneca; M.L.C. is a consultant to AstraZeneca Pharmaceuticals LP.

References


