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 $\geqslant 6$ 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.

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

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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 Inter-collegiate 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 (Vieta 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, flupent(h)ixol, ziprasidone, asenapine, 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 χ^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 χ^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.* 2000*b*, 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; Quiroz *et al.* 2010; Suppes *et al.* 2009; Tohen *et al.* 2003, 2004, 2005, 2006; Vieta *et al.* 2008*a*, *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.* 2008*a*), perphenazine + mood stabilizer (Zarate & Tohen, 2004), risperidone long-acting injectable monotherapy (Quiroz *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.* 2008*b*) and quetiapine monotherapy (McElroy *et al.* 2008; Young *et al.* 2008); three trials each for divalproex (Bowden *et al.* 2000*a*, *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.* 2000*b*, 2003; Calabrese *et al.* 2003, 2005; Greil *et al.* 1997; Hartong *et al.* 2003; Tohen *et al.* 2005; Vieta *et al.* 2008*a*).

Table 1. Characteristics of included studies[a]

Study	Treatment	Patient population	Duration (wk)	Definition of relapse	Outcomes relating to relapse/recurrence[b]	Discontinuation[b]
Bowden et al. (2000b)	Following stabilization: (1) DVP to give 71–125 μg/ml for divalproex, n=187 (2) lithium to give 0.8–1.2 mmol/l, n=91 (3) placebo, n=94	Bipolar I disorder At randomization: Age: 39±12 yr Male: 49% MRS: 3.4	52	Occurrence of a manic episode (MRS score ⩾16 or requiring hospitalization) or depressive episode (requiring antidepressant use or premature discontinuation from the study due to symptoms)	Any mood episode: (1) 45/187 (24%) (2) 28/91 (31%) (3) 36/94 (38%) Manic relapse: (1) 33/187 (18%) (2) 19/91 (21%) (3) 21/94 (22%) Depressive relapse: (1) 12/187 (6%) (2) 9/91 (10%) (3) 15/94 (16%)	(1) All: 116/187, Relapse: 45/187, Intolerance/ non-compliance: 41/ 187, Other: 30/187 (2) All: 69/91, Relapse: 28/91, Intolerance/ non-compliance: 32/91, Other: 9/91 (3) All: 71/94, Relapse: 36/94, Intolerance/ non-compliance: 11/94, Other: 24/94
Bowden et al. (2003)	Following stabilization: (1) lamotrigine 100–400 mg/d, n=59 (2) lithium to give 0.8–1.1 mEq/l, n=46 (3) placebo, n=70	Bipolar I disorder, manic or hypomanic At randomization: Age: 41±12 yr Male: 47% HAMD 17: 7, CGI-S: 4.3, MRS: 22	76	Requiring intervention – either pharmacotherapy or electroconvulsive therapy	Any mood episode: (1) 28/58 (48%) (2) 18/44 (41%) (3) 49/69 (71%) Manic relapse: (1) 20/58 (34%) (2) 8/44 (18%) (3) 28/69 (41%) Depressive relapse: (1) 8/58 (14%) (2) 10/44 (23%) (3) 21/69 (30%)	(1) All: 56/59, Relapse: 28/59, Adverse event: 3/59 (2) All: 45/46, Relapse: 18/46, Adverse event: 11/46 (3) All: 70/70, Relapse: 49/70, Adverse event: 3/70
Bowden et al. (2010)	Following stabilization: (1) ziprasidone 80–160 mg/d +lithium/divalproex (to give 0.6–1.2 mEq/l and 50–125 μg/ml, respectively), n=127 (2) placebo+lithium/ divalproex (to give 0.6–1.2 mEq/l and 50–125 μg/ml, respectively), n=113	Bipolar I disorder At randomization: Age: 39±12 yr Male: 46%	26	Investigator decision that discontinuation was in best interests of the subject, loss of effect/requirement of treatment change, hospitalization, MRS ⩾18 or MADRS ⩾18 for 2 consecutive visits (<10 days apart)	Any mood episode: (1) 25/127 (20%) (2) 36/111 (32%) Manic relapse: (1) 9/127 (7%) (2) 20/111 (18%) Depressive relapse: (1) 16/127 (13%) (2) 16/111 (14%)	(1) All: 43/127, Lack of efficacy: 9/127, Adverse event: 11/127 (2) All: 58/113, Lack of efficacy: 22/113, Adverse event: 15/113

Calabrese *et al.* (2000)	Following stabilization: (1) lamotrigine 100–500 mg/d, *n*=93 (2) placebo, *n*=89	Rapid cycling bipolar disorder, manic, mixed or depressed At randomization: Age: 38 yr Male: 43% HAMD 17: 6, CGI-S: 2.1, YMRS: 2.7	26	Requiring intervention for a mood episode, or one that was emerging	Any mood relapse (1) 53/90 (59%) (2) 64/87 (74%)	(1) All: 56/93 Requiring therapy: 45/93, Adverse event: 1/93 (2) All: 66/89, Requiring therapy: 49/89, Adverse event: 2/89
Calabrese *et al.* (2003)	Following stabilization: (1) lamotrigine 50, 200 or 400 mg/d, *n*=221 (2) lithium to give 0.8–1.1 mEq/l, *n*=121 (3) placebo, *n*=121	Bipolar I disorder, currently or recently depressed At randomization: Age: 44±12 yr Male: 44% HAMD 17: 6, CGI-S: 2.0, MRS: 1.5	76	Requiring intervention for a mood episode	Any mood episode (1) 115/215 (53%) (2) 56/120 (47%) (3) 66/119 (55%) Manic relapse: (1) 38/215 (18%) (2) 10/120 (8%) (3) 19/119 (16%) Depressive relapse: (1) 77/215 (36%) (2) 46/120 (38%) (3) 47/119 (39%)	(1) All: 183/221, Relapse: 115/221, Adverse event: 20/221 (2) All: 101/121, Relapse: 56/121, Adverse event: 19/121 (3) All: 109/121, Relapse: 66/121, Adverse event: 12/121
Calabrese *et al.* (2005)	Following stabilization: (1) lithium >0.8 mEq/l, *n*=32 (2) divalproex >50 µg/ml, *n*=28	Bipolar I and II disorder At randomization: Age: 37±9 yr Male: 48% Depressed: 60% Hypomanic: 30% Baseline HAMD: 21, YMRS: 12	80	Requiring intervention for a mood episode, or one that was emerging	Median time (wk) to intervention for mood episode: (1) 18 (2) 45 (difference not significant) Median time (wk) to discontinuation for any reason (1) 14 (2) 26 (difference not significant)	(1) All: 27/32, Relapse: 18/32, Adverse event: 5/32 (2) All: 20/28, Relapse: 14/28, Adverse event: 1/28
Greil *et al.* (1997)	Following stabilization: (1) lithium to give 0.6–0.8 mmol/l, *n*=74 (2) carbamazepine to give 4–12 µg/ml, *n*=70	Bipolar I, At randomization: Age: 44±14 yr Males: 48% GAS: 80	130	Research Diagnostic Criteria score of 5 or 6	Symptom recurrence of any mood episode (1) 17/60 (28%) (2) 20/43 (47%)	(1) All: 14/74, Relapse: 17/60, Adverse event: 4/74 (2) All: 27/70, Relapse: 20/43, Adverse event: 9/70
Hartong *et al.* (2003)	From a population of stable patients: (1) lithium to give 0.6–1.0 mmol/l, *n*=44 (2) carbamazepine to give 4–12 µg/ml, *n*=50	Bipolar I and II disorder (BP I: 78%) At randomization: Age: 42±14 yr Males: 46% BPRS: 1.8	104	Fulfilling DSM-III-R criteria for (hypo)mania or major depression	Any mood relapse (1) 12/44 (27%) (2) 21/50 (19%)	(1) All: 16/44, Adverse event: 5/44 (2) All: 13/50, Adverse event: 4/50

Table 1 (*cont.*)

Study	Treatment	Patient population	Duration (wk)	Definition of relapse	Outcomes relating to relapse/recurrence[b]	Discontinuation[b]
Keck *et al.* (2007)	Following stabilization: (1) aripiprazole 15–30 mg/d, *n*=78 (39 at week 26) (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%	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 0.63)	(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) 8/65 (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

Quiroz et al. (2010)	Following stabilization: (1) risperidone long-acting injectable 12.5–50 mg, $n=154$ (2) placebo, $n=149$	Bipolar I disorder At randomization: Age: 39 ± 12 yr Male: 51% Manic: 79% Mixed: 21% MADRS: 1.9 YMRS: 2.4 CGI-S: 1.6	104	DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; treatment intervention; hospitalization; YMRS score >12, MADRS score >12, or CGI-S score >4 at any visit; or needing additional risperidone	Any mood episode: (1) 42/135 (31%) (2) 76/133 (57%) Manic relapse: (1) 22/135 (16%) (2) 62/133 (47%) Depressive relapse: (1) 20/135 (15%) (2) 14/133 (11%)	(1) All: 40/154, Adverse events: 15/154 (2) All: 37/149, Adverse events: 33/149
Suppes et al. (2009)	Following stabilization: (1) quetiapine 400–800 mg/d + lithium/divalproex (to give 0.5–1.2 mEq/l and 50–125 μg/ml, respectively), $n=310$ (2) placebo + lithium/divalproex, $n=313$	Bipolar I disorder with $\geqslant 1$ episode of mania, depression, or a mixed episode in last 2 yr At randomization: Age: 40 ± 12 yr Male: 48% Manic: 24% Depressed: 31% Mixed: 46% MADRS: 4.8, YMRS: 3.6	104	Requiring treatment for mixed, manic, or depressive symptoms, hospitalization, YMRS or MADRS total scores $\geqslant 20$ at two consecutive assessments; or discontinuation because of a mood event	Hazard ratio for the time to recurrence of a mood event of 0.32 ($p<0.0001$), corresponding to a risk reduction of 68% for quetiapine + lithium/divalproex compared to placebo + lithium/divalproex Hazard ratio for the time to recurrence of a mania event of 0.30 ($p<0.0001$), corresponding to a risk reduction of 70% Hazard ratio for the time to recurrence of a depressive event of 0.33 ($p<0.0001$), corresponding to a risk reduction of 67%	(1) All: n.a., Relapse: 63/310, Adverse event: 23/310 (2) All: n.a., Relapse: 163/313, Adverse event: 8/313
Tohen et al. (2003)	(1) olanzapine 5–20 mg/d, $n=125$ (2) divalproex 500–2500 mg/d, $n=126$	Bipolar disorder, manic or mixed Age: 41 yr Male: 43% Manic: 57% Mixed: 43% HAMD: 14, YMRS: 28	47	YMRS or HAMD $\geqslant 15$	YMRS $\leqslant 12$ (1) 71/125 (57%) (2) 57/126 (45%) Median time to remission (days) (1) 14 (2) 62 YMRS $\leqslant 12$ and MADRS $\leqslant 8$ at 47 wk (1) 39/125 (31%) (2) 39/126 (31%) Symptomatic relapse into affective episode (YMRS $\geqslant 15$ or HAMD $\geqslant 15$) (1) 14/33 (42%) (2) 13/23 (57%)	(1) All: 106/125, IR: 24/125, Adverse event: 31/125 (2) All: 106/126, IR: 28/126, Adverse event: 25/126

Table 1 (*cont*.)

Study	Treatment	Patient population	Duration (wk)	Definition of relapse	Outcomes relating to relapse/recurrence[b]	Discontinuation[b]
Tohen *et al.* (2004)	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⩾15) without symptoms initially (1) 11/30 (37%) (2) 21/38 (55%) Median time to relapse (days) (1) 163 (2) 42 Depression alone: (1) 7/30–23% (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.* (2005)	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% Psychotic: 26% Baseline HAMD: 3.8, YMRS: 1.6	52	YMRS or HAMD ⩾15	Symptomatic recurrence of any mood episode (YMRS +/or HAMD ⩾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)	Following stabilization: (1) olanzapine 5–20 mg/d, $n=225$ (2) placebo, $n=136$	Bipolar I disorder At randomization: Age: 40±12 yr Male: 39% Manic: 66% Mixed: 34% Psychotic: 18% HAMD: 3.6, YMRS: 4.2	48	YMRS or HAMD ⩾15 or hospitalization for a manic, mixed or depressive episode	Symptomatic recurrence of any mood episode (1) 105/225 (47%) (2) 109/136 (80%) 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	(1) All: 72/225, IR: 4/225, Adverse event: 17/225 (2) All: 18/136, IR: 2/136, Adverse event: 0/136
Vieta et al. (2008a)	(1) oxcarbazepine 1200 mg/d + lithium, $n=26$ (2) placebo + lithium, $n=29$	Bipolar I and II patients currently in remission Age: 44 yr Male: 35%	52	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%) 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%)	(1) All: 10/26, Adverse event: 3/26 (2) All: 10/29, Adverse event: 2/29
Vieta et al. (2008b)	Following stabilization: (1) quetiapine 400–800 mg/d + lithium/divalproex (to give 0.5–1.2 mEq/l and 50–125 μg/ml), $n=336$ (2) placebo + lithium/ divalproex, $n=367$	Bipolar I disorder with current or recent mixed, manic, or depressed episode At randomization: Age: 42±13 yr Male: 45% Manic: 48% Depressed: 29% Mixed: 23% MADRS: 3.5, YMRS: 2.4	104	YMRS or MADRS ⩾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	Hazard ratio for the time to recurrence of a mood event of 0.28 ($p<0.001$), corresponding to a risk reduction of 72% for quetiapine + lithium/ divalproex compared to placebo + lithium/divalproex Hazard ratio for the time to recurrence of a mania event of 0.30 ($p<0.001$), corresponding to a risk reduction of 70% Hazard ratio for the time to recurrence of a depressive event of 0.26 ($p<0.001$), corresponding to a risk reduction of 74%	(1) All: 123/336, Relapse: 62/336, Adverse event: 8/336 (2) All: 233/367, Relapse: 180/367, Adverse event: 9/367

Table 1 (*cont*.)

Study	Treatment	Patient population	Duration (wk)	Definition of relapse	Outcomes relating to relapse/recurrence[b]	Discontinuation[b]
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

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

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.* 2000*b*; Macfadden *et al.* 2009; McElroy *et al.* 2008; Tohen *et al.* 2003, 2005, 2006; Vieta *et al.* 2008*a*; 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.* 2008*b*). 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 1*a* and 1*b*. 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.* 2008*a*); lithium/divalproex (Bowden *et al.* 2010; Suppes *et al.* 2009; Tohen *et al.* 2004; Vieta *et al.* 2008*b*); 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
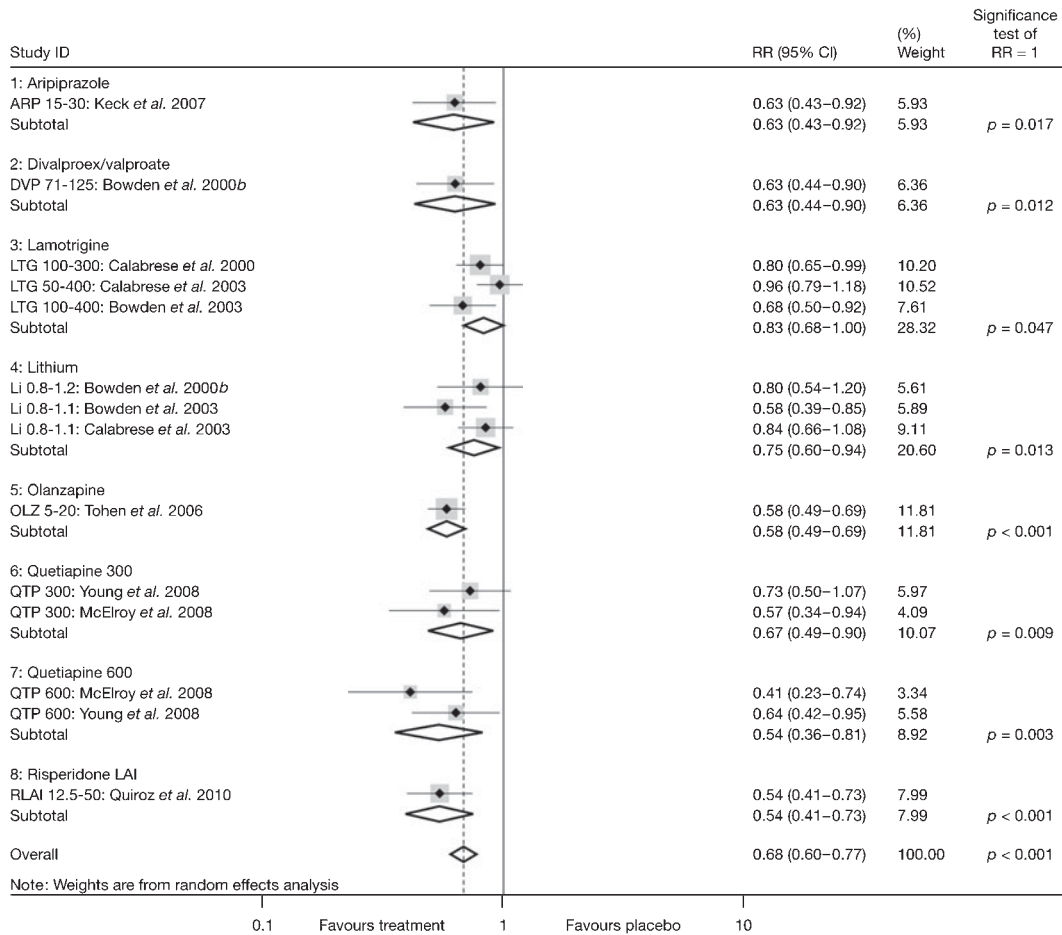
Fig. 1a. Relative risk of any mood episode – monotherapies. Heterogeneity: 3, lamotrigine ($I^2 = 47.4\%$); 4, lithium ($I^2 = 25.7\%$); 6, quetiapine ($I^2 = 0.0\%$); 7, quetiapine ($I^2 = 31.0\%$); overall ($I^2 = 52.3\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; ARP, aripiprazole; DVP, divalproex; Li, lithium; LTG, lamotrigine; OLZ, olanzapine; QTP, quetiapine; RLAI, risperidone long-acting injectable.

relapse that was below 1.0, although significance *vs.* placebo or comparator varied among treatments (Figs 2*a*, 2*b*). 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 I^2 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. 2*b*). The overall estimate of the RR of manic/mixed relapse compared to comparator [lithium (Vieta *et al.* 2008*a*); lithium/divalproex (Bowden *et al.* 2010; Suppes *et al.* 2009; Tohen *et al.* 2004; Vieta *et al.* 2008*b*); mood stabilizer (Bowden *et al.* 2000*b*; Zarate & Tohen, 2004)] was 0.42 (95% CI 0.33–0.53, $p < 0.001$) for combination
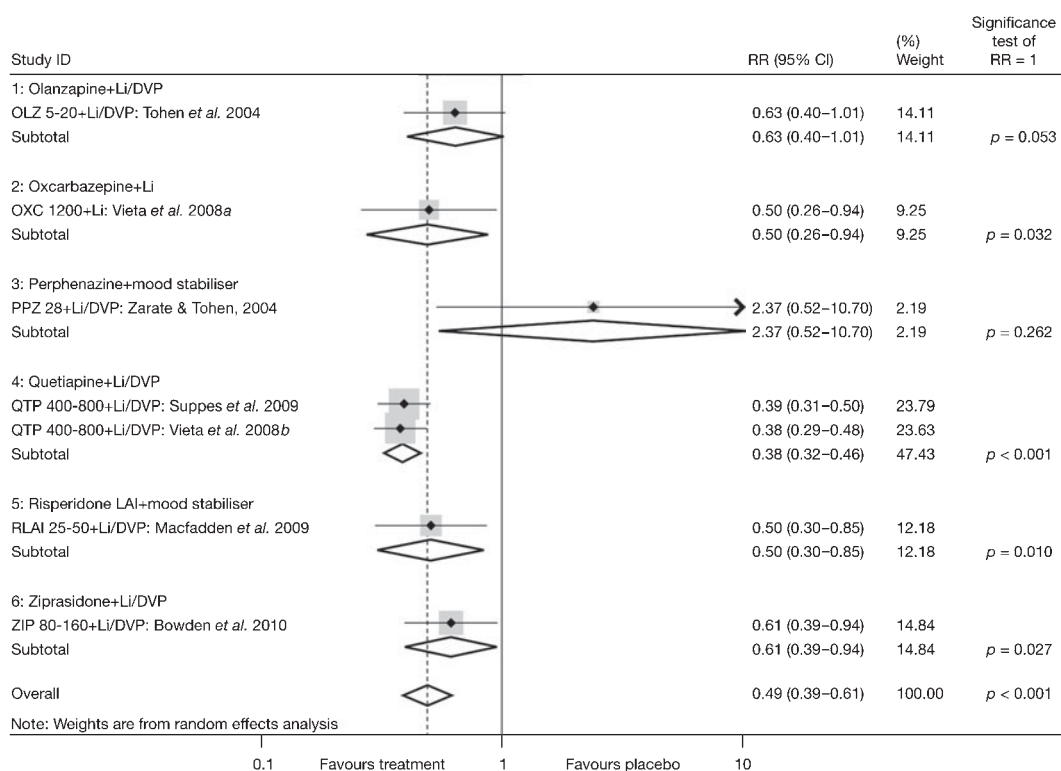
Fig. 1b. Relative risk of any mood episode – combination therapies. Heterogeneity: 4, quetiapine + Li/DVP ($I^2 = 0.0$); overall ($I^2 = 50.3\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; DVP, divalproex; Li, lithium; OLZ, olanzapine; OXC, oxcarbazepine; QTP, quetiapine; PPZ, perphenazine; RLAI, risperidone long-acting injectable; ZIP, ziprasidone.

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 comparator [lithium (Vieta *et al.* 2008a); lithium/divalproex (Suppes *et al.* 2009; Tohen *et al.* 2004; Vieta *et al.* 2008b); mood stabilizer (Macfadden *et al.* 2009; Zarate & Tohen, 2004)] was 0.48 (95% CI 0.35–0.64, $p < 0.001$) (Fig. 3b). 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
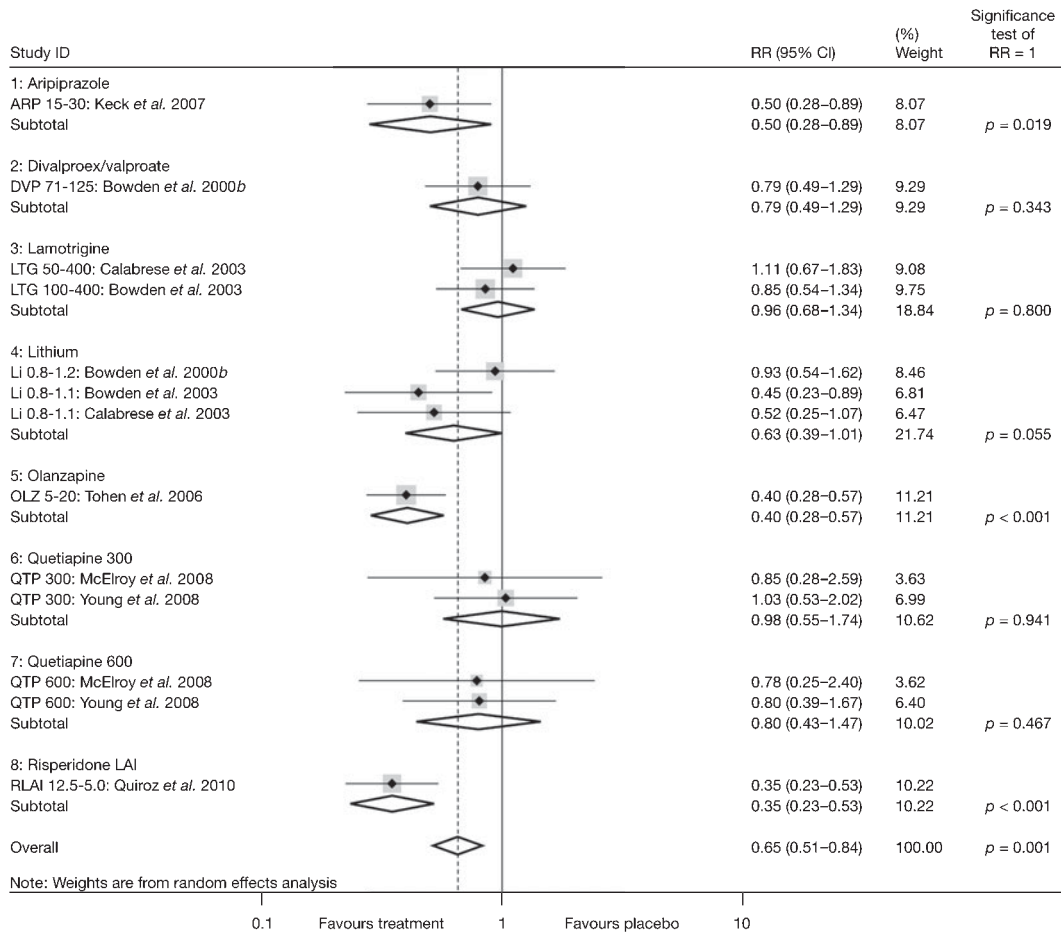
Fig. 2a. Relative risk of manic or mixed relapse – monotherapies. Heterogeneity: 3, lamotrigine ($I^2 = 0.0\%$); 4, lithium ($I^2 = 36.9\%$); 6, quetiapine ($I^2 = 0.0\%$); 7, quetiapine ($I^2 = 31.0\%$); overall ($I^2 = 56.6\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; ARP, aripiprazole; DVP, divalproex; LTG, lamotrigine; Li, lithium; OLZ, olanzapine; QTP, quetiapine; RLAI, risperidone long-acting injectable.

et al. 2004). 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 I^2 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 ($p = 0.056$) com-

pared 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
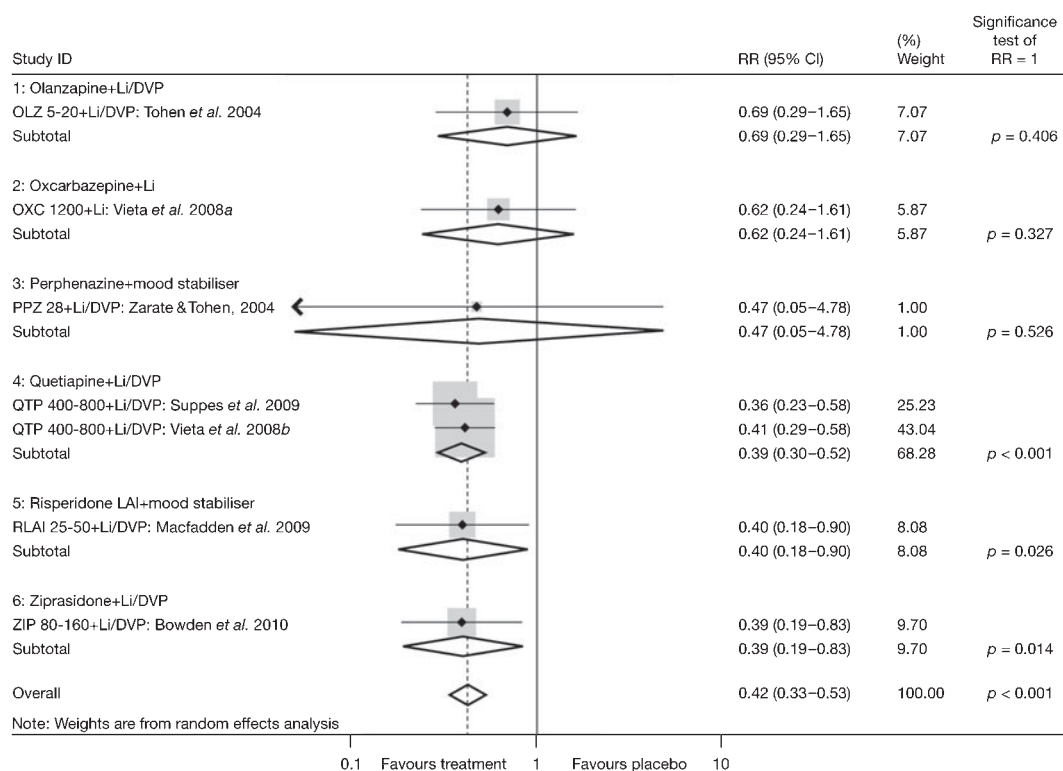
Fig. 2b. Relative risk of manic or mixed relapse – combination therapies. Heterogeneity: 4, quetiapine + Li/DVP ($I^2 = 0.0\%$); overall ($I^2 = 0.0\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; DVP, divalproex; Li, lithium; OLZ, olanzapine; OXC, oxcarbazepine; PPZ, perphenazine; QTP, quetiapine; RLAI, risperidone long-acting injectable; ZIP, ziprasidone.

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 homogenous 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
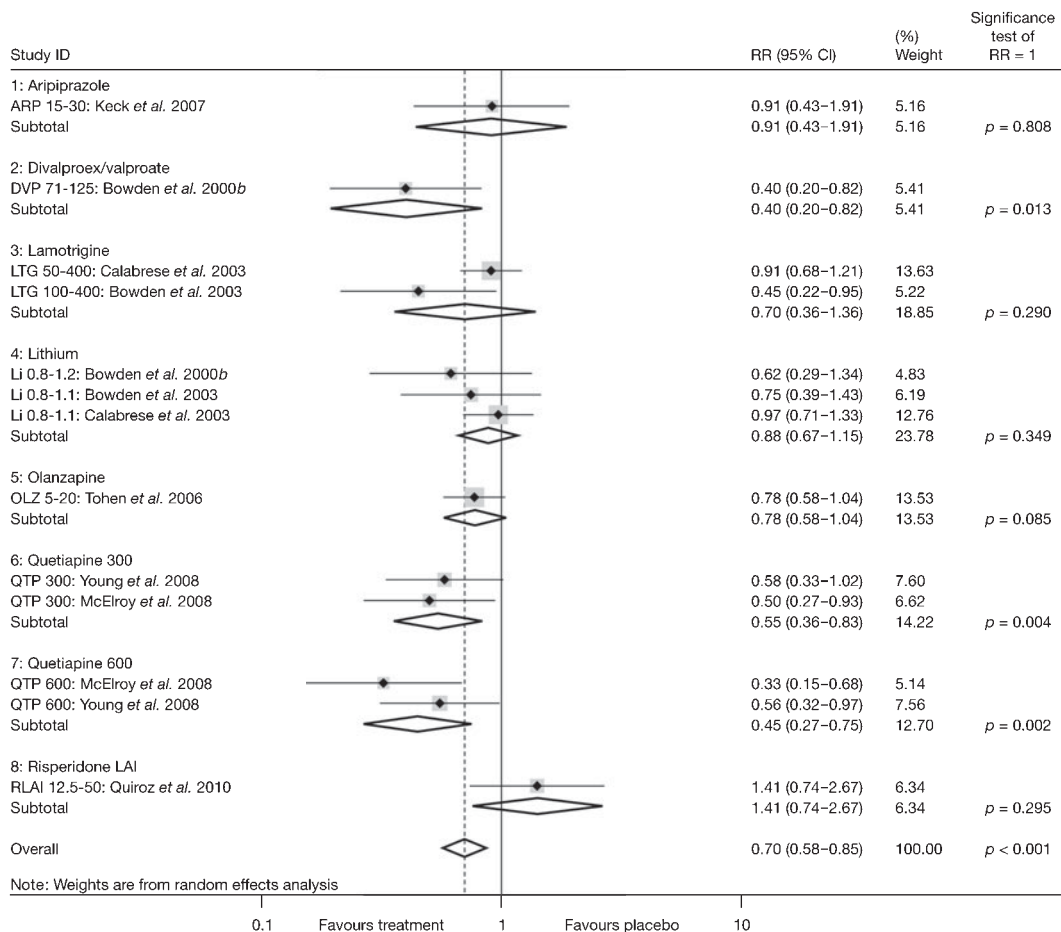
Fig. 3a. Relative risk of depressive relapse – monotherapies. Heterogeniety: 3, lamotrigine ($I^2 = 67.1\%$); 4, lithium ($I^2 = 19.4\%$); 6, quetiapine ($I^2 = 0.0\%$); 7, quetiapine ($I^2 = 21.9\%$); overall ($I^2 = 45.5\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; ARP, aripiprazole; DVP, divalproex; LTG, lamotrigine; Li, lithium; OLZ, olanzapine; QTP, quetiapine; RLAI, risperidone long-acting injectable.

Vieta *et al.* (2008*b*) 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.
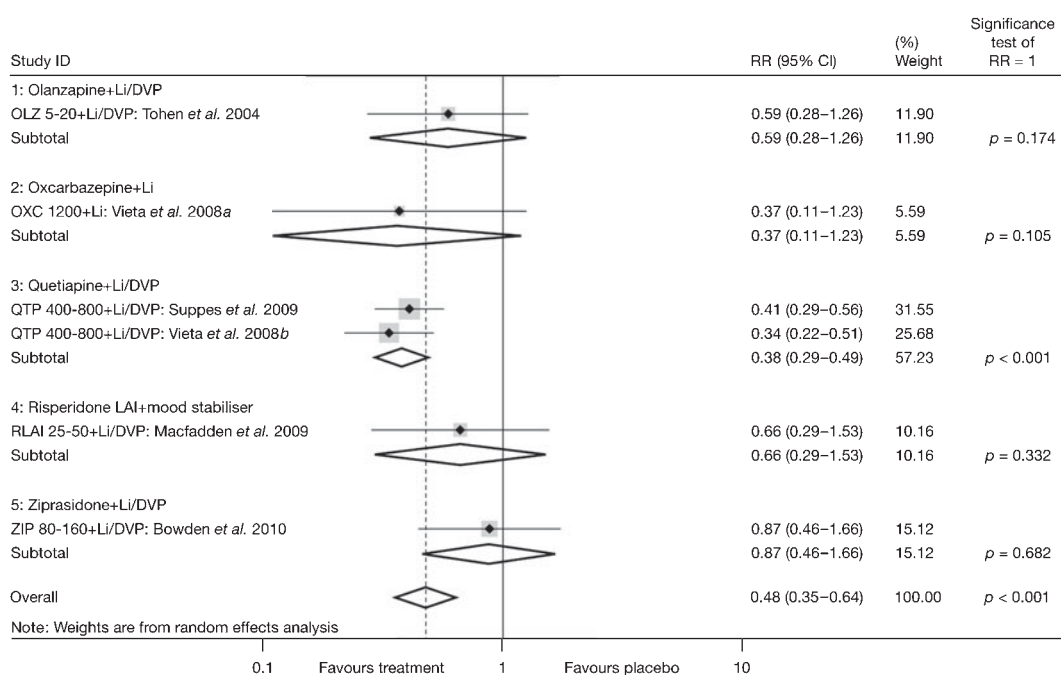
Fig. 3*b.* Relative risk of depressive relapse – combination therapies. Heterogeneity: 4, quetiapine + Li/DVP ($I^2 = 0.0$); overall ($I^2 = 35.1\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; DVP, divalproex; Li, lithium; OLZ, olanzapine; OXC, oxcarbazepine; PPZ, perphenazine; QTP, quetiapine; RLAI, risperidone long-acting injectable; ZIP, Ziprasidone. (Perphenazine was excluded from the analysis, as there were no depressive relapses in the control group.)

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.* 2000*b*; 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.* 2000*b*; Calabrese *et al.* 2005; Tohen *et al.* 2003, 2004, 2005, 2006; Vieta *et al.* 2008*a*). 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.* 2008*a*). 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, diarrhoea, hyperprolactinaemia 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.* 2008*b*). Trial data for risperidone as maintenance treatment indicate that it is associated
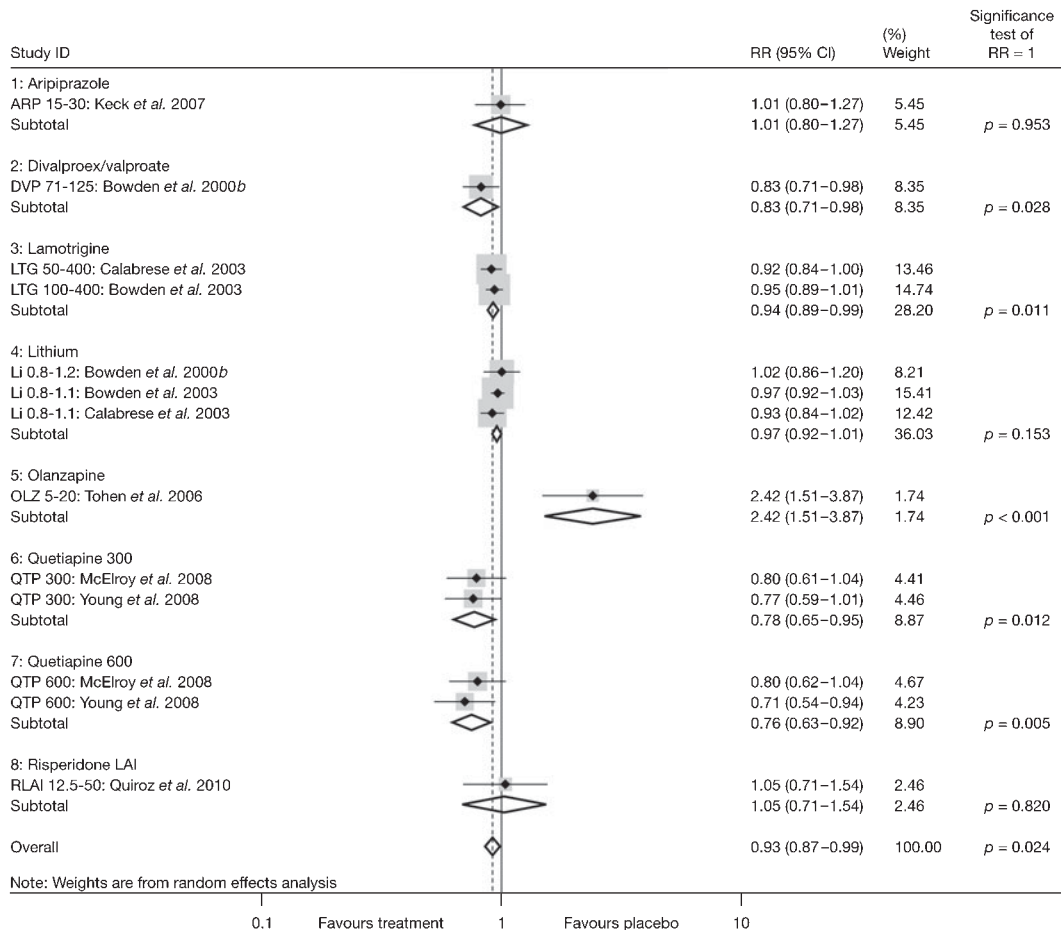
Fig. 4a. Relative risk of discontinuation – monotherapies. Heterogeneity: 3, lamotrigine ($I^2 = 0.0\%$); 4, lithium ($I^2 = 0.0\%$); 6, quetiapine ($I^2 = 0.0\%$); 7, quetiapine ($I^2 = 0.0\%$); overall ($I^2 = 64.0\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; ARP, aripiprazole; DVP, divalproex; LTG, lamotrigine; Li, lithium; OLZ, olanzapine; QTP, quetiapine; RLAI, risperidone long-acting injectable.

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.
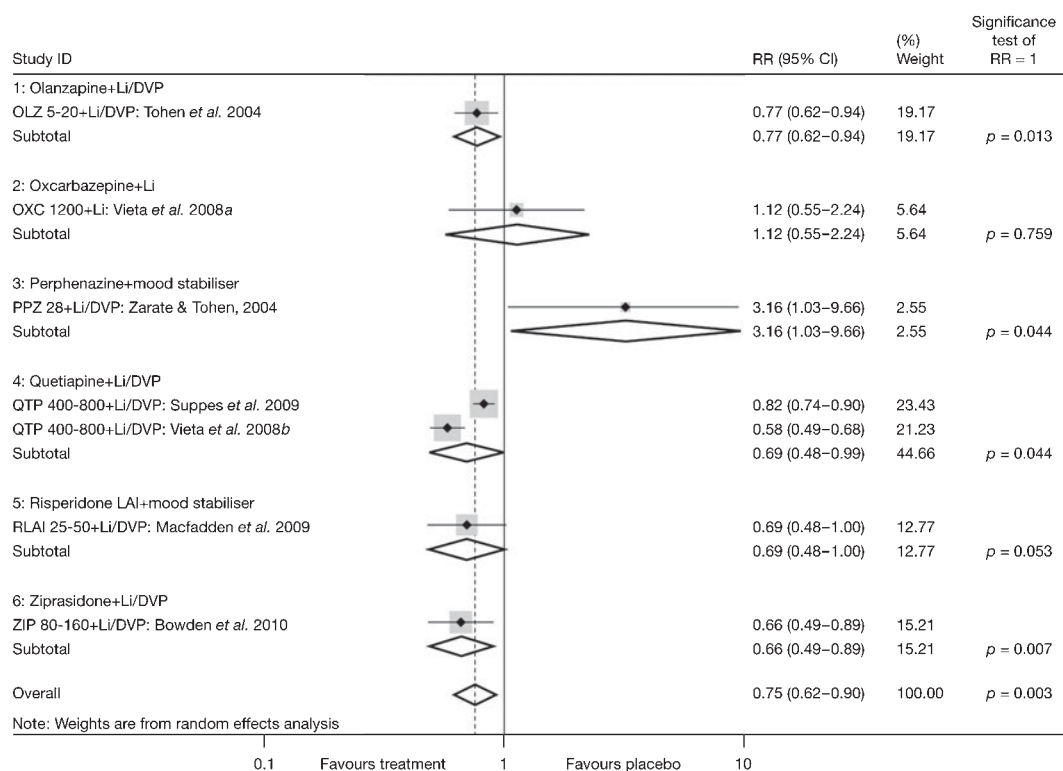
Fig. 4*b***.** Relative risk of discontinuation – combination therapies. Heterogeneity: 4, quetiapine + Li/DVP ($I^2 = 93.1\%$); overall ($I^2 = 73.1\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; DVP, divalproex; Li, lithium; OLZ, olanzapine; OXC, oxcarbazepine; PPZ, perphenazine; QTP, quetiapine.

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.

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,

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References

APA (2002). Practice guideline for the treatment of patients with bipolar disorder (revision). *American Journal of Psychiatry* **159** (Suppl. 4), 1–50.

Baptista T, De Mendoza S, Beaulieu S, Bermúdez A, et al. (2004). The metabolic syndrome during atypical antipsychotic drug treatment: mechanisms and management. *Metabolic Syndrome and Related Disorders* **2**, 290–307.

Bowden CL, Calabrese JR, McElroy SL, Gyulai L, et al. (2000*b*). A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Archives of General Psychiatry* **57**, 481–489.

Bowden CL, Calabrese JR, Sachs G, Yatham LN, et al. (2003). A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Archives of General Psychiatry* **60**, 392–400.

Bowden CL, Lecrubier Y, Bauer M, Goodwin G, et al. (2000*a*). Maintenance therapies for classic and other forms of bipolar disorder. *Journal of Affective Disorders* **59** (Suppl. 1), S57–S67.

Bowden CL, Vieta E, Ice KS, Schwartz JH, et al. (2010). Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *Journal of Clinical Psychiatry* **71**, 130–137.

Calabrese JR, Bowden CL, Sachs G, Yatham LN, et al. (2003). A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *Journal of Clinical Psychiatry* **64**, 1013–1024.

Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, et al. (2005). A 20-month, double-blind, maintenance trial of lithium *vs.* divalproex in rapid-cycling bipolar disorder. *American Journal of Psychiatry* **162**, 2152–2161.

Calabrese JR, Suppes T, Bowden CL, Sachs GS, et al. (2000). A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *Journal of Clinical Psychiatry* **61**, 841–850.

Calabrese JR, Vieta E, El-Mallakh R, Findling RL, et al. (2004). Mood state at study entry as predictor of the polarity of relapse in bipolar disorder. *Biological Psychiatry* **56**, 957–963.

Chou JC, Fazzio L (2006). Maintenance treatment of bipolar disorder: applying research to clinical practice. *Journal of Psychiatric Practice* **12**, 283–299.

Derry S, Moore RA (2007). Atypical antipsychotics in bipolar disorder: systematic review of randomised trials. *BMC Psychiatry* **7**, 40.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**, 177–188.

Fountoulakis KN, Vieta E, Sanchez-Moreno J, Kaprinis SG, et al. (2005). Treatment guidelines for bipolar disorder: a critical review. *Journal of Affective Disorders* **86**, 1–10.

Goodwin GM; Consensus Group of the British Association for Psychopharmacology (2003). Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* **17**, 149–173.

Greil W, Ludwig-Mayerhofer W, Erazo N, Schöchlin C, et al. (1997). Lithium *vs.* carbamazepine in the maintenance treatment of bipolar disorders – a randomised study. *Journal of Affective Disorders* **43**, 151–161.

Grunze H, Kasper S, Goodwin G, Bowden C, et al. (2004). The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. *World Journal of Biological Psychiatry* **5**, 120–135.

Grunze H, Vieta E, Goodwin GM, Bowden C, et al. (2010). The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: update 2010 on the treatment of acute bipolar depression. *World Journal of Biological Psychiatry* **11**, 81–109.

Hartong EG, Moleman P, Hoogduin CA, Broekman TG, et al. (2003). Prophylactic efficacy of lithium *vs.* carbamazepine in treatment-naive bipolar patients. *Journal of Clinical Psychiatry* **64**, 144–151.

Hellewell JS (2006). A review of the evidence for the use of antipsychotics in the maintenance treatment of bipolar disorders. *Journal of Psychopharmacology* **20** (Suppl. 2), 39–45.

Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta–analysis. *Statistics in Medicine* **21**, 1539–1558.

Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003). Measuring inconsistency in meta-analyses. *British Medical Journal* **327**, 557–560.

Hirschfeld RM, Vornik LA (2005). Bipolar disorder – costs and comorbidity. *American Journal of Managed Care* **11** (Suppl. 3), S85–S90.

International Consensus Group (2008). International Consensus Group on the evidence-based pharmacologic treatment of bipolar I and II depression. *Journal of Clinical Psychiatry* **69**, 1632–1646.

Kasper S (2003). Issues in the treatment of bipolar disorder. *European Neuropsychopharmacology* **13** (Suppl. 2), S37–S42.

Keck PE, Calabrese JR, McIntyre RS, McQuade RD, et al. (2007). Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-wk, double-blind study *vs.* placebo. *Journal of Clinical Psychiatry* **68**, 1480–1491.

Macfadden W, Alphs L, Haskins JT, Turner N, *et al.* (2009). A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders* **11**, 827–839.

McElroy S, Olausson B, Chang W, Olausson B, *et al.* (2008). A double-blind, placebo-controlled study with acute and continuation phase of quetiapine in adults with bipolar depression (EMBOLDEN II). Presented at the 3rd Biennial Conference of the International Society for Bipolar Disorders. January 27–28, Dehli, India.

Muzina DJ, Calabrese JR (2005). Maintenance therapies in bipolar disorder: focus on randomized controlled trials. *Australian and New Zealand Journal of Psychiatry* **39**, 652–661.

NICE (2006). The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Clinical guideline 38, July 2006. National Institute for Health and Clinical Excellence (http://www.nice.org.uk/Guidance/CG38). Accessed 19 January 2011.

Oswald P, Souery D, Kasper S, Lecrubier Y, *et al.* (2007). Current issues in bipolar disorder: a critical review. *European Neuropsychopharmacology* **17**, 687–695.

Quiroz JA, Yatham LN, Palumbo JM, Karcher K, *et al.* (2010). Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biological Psychiatry* **68**, 156–162.

Rybakowski J (2005). Maintenance treatment of bipolar disorders. *Neuroendocrinology Letters* **26** (Suppl. 1), 49–65.

Sachs GS, Thase ME (2000). Bipolar disorder therapeutics: maintenance treatment. *Biological Psychiatry* **48**, 573–581.

Scottish Intercollegiate Guidelines Network (2005). http://www.sign.ac.uk/guidelines/published/index.html#Mental). Accessed 19 January 2011.

Smith LA, Cornelius V, Warnock A, Bell A, *et al.* (2007). Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disorders* **9**, 394–412.

Suppes T, Baldessarini RJ, Faedda GL, Tohen M (1991). Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Archives of General Psychiatry* **48**, 1082–1088.

Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, *et al.* (2005). The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *Journal of Clinical Psychiatry* **66**, 870–886.

Suppes T, Vieta E, Liu S, Brecher M, *et al.* (2009). Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *American Journal of Psychiatry* **166**, 476–488.

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, *et al.* (2000). *Methods for Meta-Analysis in Medical Research.* Chichester, UK: John Wiley & Sons Ltd.

Tohen M, Calabrese JR, Sachs GS, Banov MD, *et al.* (2006). Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *American Journal of Psychiatry* **163**, 247–256.

Tohen M, Chengappa KN, Suppes T, Baker RW, *et al.* (2004). Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *British Journal of Psychiatry* **184**, 337–345.

Tohen M, Greil W, Calabrese JR, Sachs GS, *et al.* (2005). Olanzapine *vs.* lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *American Journal of Psychiatry* **162**, 1281–1290.

Tohen M, Ketter TA, Zarate CA, Suppes T, *et al.* (2003). Olanzapine *vs.* divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *American Journal of Psychiatry* **160**, 1263–1271.

Vieta E, Cruz N, Garcia-Campayo J, de Arce R, *et al.* (2008*a*). A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. *International Journal of Neuropsychopharmacology* **11**, 445–452.

Vieta E, Nolen WA, Grunze H, Licht RW, *et al.* (2005). A European perspective on the Canadian guidelines for bipolar disorder. *Bipolar Disorders* **7** (Suppl. 3), 73–76.

Vieta E, Suppes T, Eggens I, Persson I, *et al.* (2008*b*). Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *Journal of Affectve Disorders* **109**, 251–263.

Yatham LN, Kennedy SH, Schaffer A, Parikh S, *et al.* (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disorders* **11**, 225–255.

Young AH, McElroy S, Chang W, Olausson B, *et al.* (2008). A double-blind, placebo-controlled study with acute and continuation phase of quetiapine in adults with bipolar depression (EMBOLDEN I). Presented at the 3rd Biennial Conference of the International Society for Bipolar Disorders. 27–28 January, Delhi, India.

Zarate CA, Tohen M (2004). Double-blind comparison of the continued use of antipsychotic treatment *vs.* its discontinuation in remitted manic patients. *American Journal of Psychiatry* **161**, 169–171.