Appendix Hoofdstuk 8 Wetenschappelijke onderbouwing farmacotherapie onderhoudsbehandeling

8.2.1 Clinical review protocol

Long-term trials in bipolar disorder include multiple types of studies. Some assign people who are not in an acute episode to receive a new long-term treatment; others randomise participants to discontinue or to continue treatment that was effective in an acute phase (Cipriani et al., 2013a). The GDG considered both types of studies in this review.

The GDG determined that the purpose of long-term management is to prevent new mood episodes and to keep people out of hospital. For this reason, they determined that trials would need to include controlled results at 1 year or more to provide evidence of effects on long-term outcomes. Given the goals of long-term management, the GDG did not consider the use of additional medication to be indicative of treatment failure. They noted that studies may not report the number of people who return to hospital or relapse according to accepted criteria (that is, for a major depressive episode or manic episode), and they considered evidence of effects for other definitions of 'relapse' to be of limited clinical utility, primarily because many studies include in their definition the use of additional medication, which is extremely common in bipolar and may be used to prevent symptoms from escalating into a full episode (a treatment success) rather than treat a full episode (a failure).

The review protocol summary, including the review questions, can be found in Table 1 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 11: Clinical review protocol for the review of pharmacological intervention for long-term management

Topic	Interventions
Review question(s)	RQ3.4: For adults with bipolar disorder, what are the relative benefits and harms of starting a new pharmacological intervention outside of an acute episode? RQ3.5: For adults with bipolar disorder, what are the relative benefits and harms of continuing an acute treatment for 1 year or more? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?

Objectives	To estimate the efficacy of interventions for the long-term management of bipolar disorder.
Criteria for considering studies for the review	
Intervention	All licensed oral medications (and their combinations) delivered for 1 year or more
Comparator	Pill placebo Other pharmacological interventions
Types of participants	Adults (18+) with bipolar disorder. Special consideration will be given to the groups above.
Outcomes	Relapse (all, mania/mixed, depression) (for the purposes of the guideline, relapse was defined as a new episode meeting criteria for MDD or mania) Discontinuation (due to side effect, other) Hospitalisation (rate) Quality of life Mortality (all cause, suicides completed) Weight
Time	Included studies must have included controlled measures of outcomes at 12 months or later.
Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
Include unpublished data?	Unpublished research may be included.
Restriction by date?	No limit.
Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
Minimum sample size	10 participants per group
Study setting	Primary, secondary, tertiary, health and social care

8.2.2 Studies considered

Thirty-five RCTs (N = 8,274) met the eligibility criteria for this review: BERWAERTS2012 (Berwaerts et al., 2012), BOBO2011B (Bobo, 2011; Bobo et

al., 2011), BOWDEN2000 (Bowden et al., 2000; Bowden et al., 2005; Bowden et al., 1997; Gyulai et al., 2003; Keck et al., 2005), BOWDEN2003 (Bowden et al., 2006; Bowden et al., 2003; Sajatovic et al., 2005), CALABRESE2003 (Bowden et al., 2006; Calabrese et al., 2003; Sajatovic et al., 2005), CALABRESE2005C (Calabrese et al., 2005), CARLSON2012 (Carlson et al., 2012; Kemp et al., 2013; Rahman, 2011), COXHEAD1992 (Coxhead et al., 1992), DUNNER1976 (Dunner et al., 1976; Mendlewicz et al., 1973), GEDDES2010 (Geddes et al., 2010), GELENBERG1989 (Gelenberg et al., 1989; Keller et al., 1992; Perlis et al., 2002; Solomon et al., 1996), GHAEMI2010 (Ghaemi et al., 2010), HARTONG2003 (Hartong et al., 2003), JENSEN1995 (Jensen et al., 1996a; Jensen et al., 1995; Jensen et al., 1996b), KLEINDIENST2000 (Greil et al., 1986; Greil et al., 1998; Greil et al., 1997; Greil et al., 1993; Kleindienst & Greil, 2000; Kleindienst & Greil, 2004; Thies-Flechtner et al., 1996), LANGOSCH2008 (Langosch et al., 2008), LICHT2010 (Licht et al., 2010), MACFADDEN2009 (Macfadden et al., 2009), MARCUS2011 (Kemp et al., 2013; Marcus, 2011; Marcus et al., 2011; Yatham et al., 2013a), PRIEN1973 (Prien et al., 1973a; Prien et al., 1974), PRIEN1973B (Prien et al., 1973b), PRIEN1984 (Prien et al., 1984; Shapiro et al., 1989), QUIROZ2010 (Quiroz et al., 2010), QUITKIN1981 (Quitkin et al., 1979; Quitkin et al., 1981), STALLONE1973 (Mendlewicz et al., 1973; Mendlewicz & Stallone, 1975; Stallone et al., 1973), SUPPES2009 (Suppes, 2009; Suppes et al., 2009; Vieta et al., 2012b), TOHEN2004 (Tohen et al., 2004; Tohen et al., 2002), TOHEN2005 (Tohen et al., 2005; Tohen et al., 2012), VIETA2006 (Vieta et al., 2006), VIETA2008 (Vieta et al., 2008a), VIETA2008B (Vieta et al., 2008b; Vieta et al., 2012b), VIETA2012 (Vieta et al., 2012a), WEISLER2011 (Nolen & Weisler, 2013; Weisler, 2009; Weisler et al., 2011), WOLF1997 (Berky et al., 1998; Wolf et al., 1997) and YOUNG2012 (Young et al., 2012).

Twenty-six studies were excluded; four because they evaluated medications that are not indicated for mental disorders and not in common use: BERK2008 (Berk et al., 2008), BERK2012 (Berk et al., 2012), ESPARON1986 (Esparon et al., 1986) and NORRIS2013 (Norris et al., 2013); two could not be included in the review because the results were not available: AHLFORS1981 (Ahlfors et al., 1981) and OKUMA1981 (Okuma et al., 1981); one trial, BAASTRUP1970 (Baastrup et al., 1970), of lithium compared with placebo was excluded because the methods were unsound and unethical; the trial continued to enrol participants until results were statistically significant, and participants did not give consent (participants assigned to placebo were not aware that their existing lithium therapy had been switched to placebo); one study, ALTAMURA2003 (Altamura et al., 2003), could not be included because it compared quetiapine with ‘classic mood stabilisers’ and did not describe what these were; one was excluded because it included participants who did not have bipolar disorder: SUPPES1999 (Suppes et al., 1999); and one trial comparing lithium with valproate was excluded because there were only six participants in each group: SOLOMON1997 (Solomon et al., 1997); 16

followed participants for less than 12 months: ALTAMURA2004 (Altamura et al., 2004), AMSTERDAM2005b (Amsterdam & Shults, 2005; Amsterdam et al., 2004), AMSTERDAM2010 (Aigner, 2010; Amsterdam et al., 2013; Amsterdam & Shults, 2010), BOWDEN2010 (Bowden et al., 2010a; Bowden, 2009; Bowden et al., 2010b; Dubovsky & Dubovsky, 2012; Kemp, 2012), BOWDEN2012 (Bowden et al., 2012), BURDICK2012 (Burdick et al., 2012), CALABRESE2000 (Calabrese et al., 2000; Goldberg, 2008), CUNDALL1972 (Cundall et al., 1972), ELMALLAKH2009 (El-Mallakh, 2010; El-Mallakh et al., 2009), GSK2012 (GlaxoSmithKline, 2012a; GlaxoSmithKline, 2012b), KECK2006a (Keck, 2007; Keck et al., 2006), MURPHY2012 (Murphy et al., 2012), STOLL1999 (Stoll et al., 1999), TOHEN2006 (Tohen et al., 2006), WOO2011 (Woo et al., 2011) and ZARATE2004 (Zarate & Tohen, 2004).

Included trials were published in peer-reviewed journals between 1973 and 2012. No unpublished reports were located. The GDG determined that it was not possible to conduct a network meta-analysis because of diversity in study designs, outcome measurement, and participant characteristics across the included trials. Pairwise analyses were conducted for all eligible interventions. Further information about both included and excluded studies can be found in Appendix 34.

Study characteristics

Participants were on average aged 40 years (median of means). Approximately half of the included participants were female (54%). Twenty-nine trials reported the proportion of participants with a diagnosis of bipolar I or bipolar II disorder. Of these, 19 included participants with bipolar I only, and one included participants with bipolar II only; nine trials included some participants with each type of bipolar disorder. Included studies lasted 52 to 129 weeks (79 weeks median of means). Participants and providers were blind to group assignment in most trials, but eight trials were open-label.

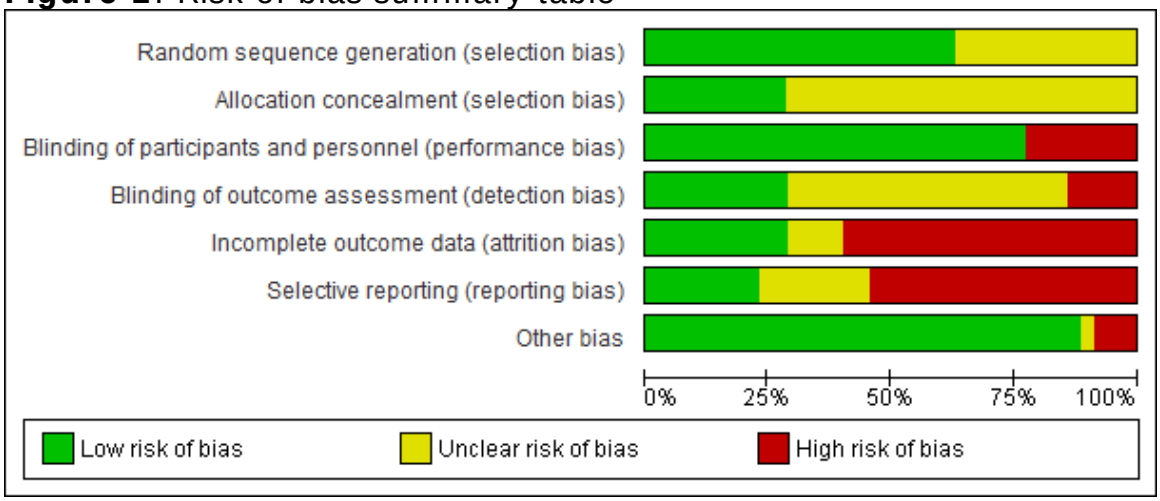
Risk of bias

All included trials were assessed for risk of bias (see Appendix 15). For sequence generation, 22 trials were at low risk of bias and ten of these were at low risk of bias for allocation concealment. Allocation concealment was unclear in 25 trials. For blinding of participants and providers, 27 trials were at low risk of bias and eight were at high risk. Assessor blinding was considered separately for all trials, and nine had a low risk of bias. Four trials had a high risk of bias for assessor blinding and 22 were unclear. For incomplete outcome data, 10 trials were at low risk of bias and 23 trials were at high risk of bias, mostly because of the large amount of missing data.

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. All authors were contacted to request trial registrations and unpublished outcomes, and all authors of included studies, all stakeholders, and all pharmaceutical manufacturers were asked to provide unpublished trials. Only sixteen of the included studies were known to be registered and eight were at low risk of selective outcome reporting bias; 18 were at high risk of bias and nine were unclear. Comparing published reports and unpublished documents for two trials, we found that published reports misrepresent the number of people randomised; we used the unpublished data for our analyses (VIETA2006; VIETA2012).

Figure 1: Risk of bias summary table



8.2.3 Clinical evidence for the long-term pharmacological management of bipolar disorder

Evidence from primary outcomes is presented in Table 2. Additional forest plots and details about the quality of evidence can be found in Appendices 14 to 17.

Lithium

Lithium compared with placebo

Seven trials (N = 1,434) included a comparison of lithium with placebo (STALLONE1973, DUNNER1976, CALABRESE2003, BOWDEN2003, BOWDEN2000, PRIEN1973B, WEISLER2011). Because of differences in study design, data for relapse and discontinuation could not be combined for all trials. Results are summarised for several comparisons.

Two trials (N = 90) compared lithium with placebo for participants who were euthymic (normal non-depressed, reasonably positive mood) at study entry (STALLONE1973, DUNNER1976). The length of follow-up was 121 weeks in

STALLONE1973 and 69 weeks in DUNNER1976. There was very low quality evidence that lithium reduced the risk of relapse (RR = 0.41, 95% CI = 0.07 to 2.43), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that lithium might be associated with an increase in the risk of discontinuation for any reason (RR = 1.39, 95% CI = 0.58 to 3.34).

Two trials (N = 358) compared lithium with placebo (CALABRESE2003, BOWDEN2003); both included a third arm that received lamotrigine (comparisons involving lamotrigine are described below). In both trials, which were conducted by the same investigators, participants were euthymic at randomisation following 8 to 16 weeks of active treatment with lamotrigine alone or in addition to another psychotropic medication. Lithium was titrated to serum levels of 0.8-1.1 mEq per litre and participants were followed for approximately 74 weeks. There was very low quality evidence that lithium reduced the risk relapse (RR = 0.71, 95% CI = 0.47 to 1.06), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. Very low quality evidence suggested that lithium may increase the risk of participants discontinuing for any reason (RR = 1.38, 95% CI = 0.78 to 2.45).

One trial (N = 185) compared lithium with placebo for participants who were not experiencing an acute episode at randomisation, but had experienced the onset of a manic episode within 3 months (BOWDEN2000). The trial included a third arm that received valproate (comparisons involving valproate are described below). Lithium was titrated to serum levels of 0.8 to 1.2 mmol per litre and participants were followed for 1 year. There was very low quality evidence that lithium reduced the risk relapse (RR = 0.80, 95% CI = 0.54 to 1.20), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. Very low quality evidence suggested that lithium may increase the risk of participants discontinuing for any reason (RR = 1.21, 95% CI = 0.86 to 1.71).

One trial (N = 205) compared lithium (1000 mg) with placebo for participants who had remitted from a manic episode and were receiving stable doses of lithium (PRIEN1973). There was very low quality evidence that continued lithium reduced the risk relapse (RR = 0.53, 95% CI = 0.41 to 0.67), but the definition of relapse did not meet the criteria set by the GDG. Very low quality evidence suggested that lithium reduced the risk of participants discontinuing for any reason (RR = 0.42, 95% CI = 0.28 to 0.62).

One trial (N = 31) compared lithium (1250 mg) with placebo for participants who at randomisation had remitted from a manic episode and were receiving stable doses of lithium (PRIEN1973B). The trial included a third arm that received imipramine (comparisons involving imipramine are described below). Relapse was reported separately for manic and depressive episodes,

and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that continued lithium reduced the risk of manic relapse (RR = 0.48, 95% CI = 0.09 to 2.48) and depressive relapse (RR = 0.29, 95% CI = 0.07 to 1.26), but the estimates were imprecise. At 2 years, there was very low quality evidence that continued lithium reduced the risk of discontinuation for any reason (RR = 0.12, 95% CI = 0.02 to 0.88).

One trial (N = 1,172) compared lithium, quetiapine (600 mg) and placebo (WEISLER2011). Participants were euthymic at randomisation following 4 to 24 weeks of active treatment with quetiapine. Lithium was titrated to serum levels of 0.6-1.2 mEq per litre and participants were followed for 2 years. Relapse was not reported according to the criteria set by the GDG and the number of participants relapsing in each group was not reported. Time to recurrence of a study-defined mood episode was significantly longer for continued quetiapine compared with switching to lithium (HR = 0.66, 95% CI = 0.49 to 0.88). Time to recurrence of a mood episode was significantly longer for switching to lithium compared with placebo (HR = 0.46, 95% CI = 0.36 to 0.59). At 2 years, very low quality evidence indicated evidence of benefit in favour of continued quetiapine in comparison with lithium for participants discontinuing from the study (RR = 1.62, 95% CI = 1.23 to 2.13). The lithium group had more participants discontinuing for any reason compared with placebo (RR = 1.37, 95% CI = 1.06 to 1.78).

Lithium administered at different doses

One trial (N = 94) included two groups receiving lithium at different daily doses. All participants had been euthymic for at least 2 months since the end of their index episode and were receiving lithium (GELENBERG1989). The first group received a standard dose of lithium to achieve serum levels between 0.8 and 1.0 mmol per litre. In the second, they received a low dose to achieve serum levels between 0.4 and 0.6 mmol per litre. At 1 year after randomisation, there was very low quality evidence that low dose lithium increased the risk of relapse (RR = 3.50, 95% CI = 1.55 to 7.89). There was very low quality evidence that the standard dose increased the risk of discontinuation for any reason (RR = 0.46, 95% CI = 0.25 to 0.83).

One trial (N = 50) compared 800 mg of lithium administered daily with 1200 mg administered every other day (JENSEN1995). Participants had all been euthymic for at least 4 months and had completed 3 months of active treatment with lithium administered daily. At 56 weeks after randomisation, there was very low quality evidence that lithium every other day increased the risk of relapse (RR = 2.40, 95% CI = 0.99 to 5.81) and there was very low quality evidence that lithium every other day decreased the risk of discontinuing for any reason (RR = 0.11, 95% CI = 0.01 to 1.96).

Lithium compared with carbamazepine

Three trials (N = 399) compared lithium with carbamazepine (HARTONG2003, KLEINDIENST2000, WOLF1997). At study entry participants were euthymic. In HARTONG2003 serum levels were titrated between 0.6-1.0 mmol per litre for lithium and between 6-10 mg per litre for carbamazepine. In KLEINDIENST2000 lithium serum levels were titrated between 0.6-1.2 mmol per litre and carbamazepine was administered at daily doses of 600 mg. In WOLF1997 the average daily doses of lithium and carbamazepine were 888 mg and 835 mg respectively. Participants were followed up for 52 to 130 weeks. At post-treatment, very low quality evidence indicated that lithium reduced the risk of relapse (RR = 0.73, 95% CI = 0.56 to 0.95). Two of the three trials (N = 262) reported very low quality evidence of a reduced risk of discontinuation for any reason (RR = 0.75, 95% CI = 0.16 to 3.54).

One trial (N = 31) compared lithium with carbamazepine for participants who were euthymic and had been receiving stable doses of lithium for at least 4 weeks (COXHEAD1992). Lithium was titrated to a serum level between 0.6-1.0 mmol per litre and carbamazepine was titrated to a serum level between 38-51 mmol per litre. There was very low quality evidence that was inconclusive with regard to the risk of relapse (RR = 1.25, 95% CI = 0.57 to 2.75), the study's definition of relapse was not reported. There was very low quality evidence that lithium may reduce the risk of discontinuation for any reason (RR = 0.47, 95% CI = 0.05 to 4.56).

Lithium compared with lamotrigine

One trial (N = 122) compared lithium with lamotrigine (400 mg) for participants who were not experiencing an acute episode at randomisation. Serum levels of lithium were maintained between 0.5-1.0 mmol per litre (LICHT2010). There was very low quality evidence suggesting little difference in the risk of relapse (RR = 0.97, 95% CI = 0.69 to 1.36), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting little difference in discontinuation for any reason (RR = 1.09, 95% CI = 0.64 to 1.87).

Lithium compared with valproate

One trial (N = 185) compared lithium with valproate as part of a three-arm trial (BOWDEN2000; see above for the comparison of lithium with placebo). Participants were not experiencing an acute episode at randomisation, but had experienced the onset of a manic episode within 3 months. Serum levels were maintained between 0.8-1.2 mmol per litre for lithium and 71 to 125 ug per mL for valproate. There was very low quality evidence suggesting lithium produced a small increase in the risk of relapse (RR = 1.28, 95% CI = 0.86 to 1.91), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence

suggesting little difference in discontinuation for any reason (RR = 1.19, 95% CI = 0.89 to 1.59).

One trial (N = 60) compared lithium (1400 mg) with valproate (1600 mg) for participants who were euthymic and had been receiving active treatment with lithium and valproate for 6 months (CALABRESE2005C). There was very low quality evidence suggesting little difference in the risk of relapse (RR = 1.13, 95% CI = 0.70 to 1.82), and a possible increase in the risk of discontinuation for any reason (RR = 1.46, 95% CI = 0.61 to 3.50).

Lithium compared with valproate and lithium and valproate combined

One three-arm trial (N = 330) compared lithium, valproate and the combination of lithium and valproate for participants who were not experiencing an acute episode following active treatment of lithium and valproate in combination for four to 8 weeks (GEDDES2010). Lithium serum levels were maintained between 0.4-1.0 mmol per litre for lithium and 750-1250 mg of valproate were administered daily for a total of 2 years. At post-treatment, there was low quality evidence favouring lithium over valproate for study-defined relapse (RR = 0.85, 95% CI = 0.70 to 1.05) and hospitalisation (RR = 0.88, 95% CI = 0.53 to 1.46), and little evidence of a difference in discontinuation for any reason (RR = 1.02, 95% CI = 0.78 to 1.34). For lithium compared with the combination therapy, there was low quality evidence of a small difference favouring continued combination therapy for study-defined relapse (RR = 1.10, 95% CI = 0.87 to 1.40) and hospitalisation (RR = 1.38, 95% CI = 0.76 to 2.47), and there was little evidence of a difference in discontinuation for any reason (RR = 0.96, 95% CI = 0.74 to 1.26). There was low quality evidence favouring continued combination therapy over valproate alone for study-defined relapse (RR = 1.29, 95% CI = 1.04 to 1.61) and hospitalisation (RR = 1.56, 95% CI = 0.88 to 2.76), and little evidence of a difference in discontinuation for any reason (RR = 0.95, 95% CI = 0.72, 1.24).

Olanzapine compared with lithium

One trial (N = 431) compared olanzapine (10 mg) with lithium (1000 mg) for participants who were no longer experiencing an acute episode following 6 to 12 weeks of active treatment with olanzapine and lithium (TOHEN2005). At 1 year after randomisation, there was very low quality evidence suggesting continued olanzapine reduced the risk of relapse (RR = 0.76, 95% CI = 0.56 to 1.03) and discontinuation due to any reason (RR = 0.79, 95% CI = 0.68 to 0.93).

Antipsychotics

Aripiprazole compared with placebo

One trial (N = 351) compared aripiprazole (20 mg) with placebo for participants who were taking lamotrigine (CARLSON2012). At randomisation, participants had been euthymic for 8 weeks following active treatment with aripiprazole and lamotrigine for 9 to 24 weeks. There was very low quality evidence suggesting aripiprazole reduced the risk of relapse (RR = 0.69, 95% CI = 0.49 to 0.98), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting little difference in discontinuation for any reason (RR = 0.92, 95% CI = 0.79 to 1.06).

One trial (N = 337) compared aripiprazole (15 mg) with placebo for participants who were taking lithium or valproate (MARCUS2011). All participants had not responded to initial treatment with lithium or valproate for a manic or mixed episode. Subsequently, they were administered aripiprazole in addition to lithium or valproate, and participants who were symptom free for 12 consecutive weeks were randomised. There was very low quality evidence suggesting aripiprazole reduced the risk of relapse (RR = 0.58, 95% CI = 0.38 to 0.91), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting that aripiprazole may decrease the risk of discontinuation for any reason (RR = 0.82, 95% CI = 0.64 to 1.05).

Olanzapine compared with placebo

One trial (N = 68) compared olanzapine with placebo for participants who were all taking lithium or valproate (TOHEN2004). Participants were euthymic following 6 weeks of active treatment with olanzapine and either lithium or valproate. There was very low quality evidence that olanzapine might be associated with a reduction relapse (RR = 0.66, 95% CI = 0.38 to 1.15), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that olanzapine reduces the risk of discontinuation (RR = 0.77, 95% CI = 0.62 to 0.94).

One trial (VIETA2012; N = 278) compared olanzapine (10 mg) with placebo as part of a three-arm trial that also included risperidone long-acting injectable). (Additional comparisons are described below.) Participants were randomised once euthymic following 12 weeks of active treatment with risperidone long-acting injectable. There was low quality evidence that olanzapine reduced the risk of relapse (RR = 0.42, 95% CI = 0.30 to 0.59), but the definition of relapse did not meet the criteria set by the GDG. There was low quality evidence of no difference or a small difference in discontinuation for any reason (RR = 1.10, 95% CI = 0.66 to 1.85). The GDG noted that the published report for the trial is not consistent with unpublished company reports.

Paliperidone compared with placebo

One trial (N = 68) compared paliperidone extended release (6 mg) with placebo for participants who were euthymic following 6 weeks of active treatment with paliperidone (BERWAERTS2012). At 129 weeks after randomisation there was very low quality evidence that continued paliperidone was not associated with a reduction in relapse (RR = 0.83, 95% CI = 0.66 to 1.06), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence of no difference in discontinuation (RR = 1.05, 95% CI = 0.78 to 1.42).

Quetiapine compared with placebo

One trial (N = 585) compared quetiapine (300 mg or 600 mg) with placebo for participants who were euthymic following 8 weeks of active treatment with quetiapine (YOUNG2012). At 1 year after randomisation there was very low quality evidence that continued quetiapine may be associated with a reduction in relapse (RR = 0.59, 95% CI = 0.46 to 0.76), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting that quetiapine increased the risk of discontinuation (RR = 1.23, 95% CI = 1.05 to 1.43).

One trial (WEISLER2011; N = 808) compared quetiapine with placebo as part of a three-arm trial that also included lithium (see above). Participants were randomised if they were euthymic for at least 4 weeks following 4 to 24 weeks of active treatment quetiapine. Relapse was not reported according to the criteria set by the GDG and the number of participants relapsing in each group was not reported. The authors reported that time to recurrence of a mood episode was significantly longer for the continued quetiapine group compared with placebo (HR = 0.29, 95% CI = 0.23 to 0.38). At 2 years, very low quality evidence indicated that continued quetiapine when compared with placebo increased the risk of discontinuing for any reason (RR = 1.23, 95% CI = 1.05 to 1.43).

Two trials (N = 1,326) compared quetiapine with placebo for participants who were also taking lithium or valproate (SUPPES2009, VIETA2008B). Participants were randomised if they were euthymic for at least 12 weeks following active treatment with quetiapine and either lithium or valproate for 12 to 36 weeks. At 2 years after randomisation there was low quality evidence that continued quetiapine may be associated with a reduction in relapse (RR = 0.38, 95% CI = 0.32 to 0.46), but the definition of relapse did not meet the criteria set by the GDG. There was low quality evidence continued quetiapine may increase the risk of discontinuation for any reason (RR = 1.53, 95% CI = 1.24 to 1.89).

Quetiapine compared with valproate

One trial (LANGOSCH2008; N = 38) compared quetiapine (500 mg) with valproate (1300 mg) for participants with rapid-cycling bipolar disorder who had remitted or partly remitted from an acute episode. At 1 year after randomisation, there was very low quality evidence of no difference in discontinuation for any reason (RR = 0.95, 95% CI = 0.64 to 1.41). Relapse was not reported; however, the authors reported the mean number of mood swings per month, defined as (1) a change from a (sub)depressive to a manic or hypomanic state and vice versa, or (2) a change from an euthymic to an acute state and vice versa. Over the 12-month study period, the authors report there was no significant difference between groups in the frequency of mood swings. The quetiapine group had significantly fewer days with moderate to severe depressive symptoms.

Risperidone long-acting injectable compared with placebo

One trial (VIETA2012; N = 273) compared risperidone long-acting injectable (25 mg) with placebo as part of a three-arm trial (see above). Participants were randomised when euthymic following 12 weeks of active treatment with risperidone long-acting injectable. At 78 weeks after randomisation there was very low quality evidence that risperidone may be associated with a reduction in relapse (RR = 0.69, 95% CI = 0.53 to 0.90), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that risperidone may increase the risk of discontinuation for any reason (RR = 1.33, 95% CI = 0.82 to 2.17). The GDG noted that the published report for the trial is not consistent with unpublished company reports.

One trial (N = 303) compared risperidone long-acting injectable (25 mg) for participants who were euthymic following 3 weeks of active treatment with oral risperidone and 12 weeks with risperidone long-acting injectable (QUIROZ2010). At 2 years after randomisation there was very low quality evidence that risperidone may be associated with a reduction in relapse (RR = 0.56, 95% CI = 0.42 to 0.75), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence of a small effect in favour of risperidone on discontinuation for any reason (RR = 0.89, 95% CI = 0.61 to 1.32).

Risperidone long-acting injectable in addition to treatment as usual compared treatment as usual

One trial (N = 124) compared risperidone long-acting injectable (12.5 mg) with a placebo injection for participants who were receiving treatment as usual (MACFADDEN). Participants were randomised when euthymic for at least 4 weeks following 16 weeks of active treatment with risperidone long-acting injectable. At 1 year after randomisation, there was very low quality evidence that risperidone may be associated with a reduction in relapse (RR = 0.50, 95% CI = 0.30 to 0.85), but the definition of relapse did not meet

the criteria set by the GDG. There was very low quality evidence that risperidone may increase the risk of discontinuation for any reason (RR = 1.27, 95% CI = 0.61 to 2.64).

One trial (BOBO2011B; N = 50) compared risperidone long-acting injectable (27 mg) in addition to treatment as usual with treatment as usual alone. Participants were randomised when not in acute episode, and participants were required a history of four or more episodes in the previous year. Relapse was not reported according to the criteria set by the GDG and the number of participants relapsing in each group was not reported. The authors reported a higher mean number of study-defined mood events in the treatment as usual group between baseline and 12 months, however the authors report that this was not statistically significant. There was very low quality evidence that risperidone may increase the risk of discontinuation (RR = 1.50, 95% CI = 0.63 to 3.59).

Anticonvulsants

Oxcarbazepine compared with placebo

One trial (N = 55) compared oxcarbazepine (1200 mg) with placebo for participants who had been euthymic for 6 months (VIETA2008). During the trial, all participants were also taking lithium. At 1 year after randomisation, there was very low quality evidence that oxcarbazepine may be associated with a reduction in relapse (RR = 0.50, 95% CI = 0.26 to 0.94), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence of no effect or a small increase in discontinuation for any reason (RR = 1.12, 95% CI = 0.55 to 2.24).

Gabapentin compared with placebo

One trial (N = 25) compared gabapentin (300 mg) with placebo for participants who were euthymic but had experienced an acute episode within 6 months (VIETA2006). All participants continued taking lithium, valproate, carbamazepine or any combination of these medications. The number of people in each group who experienced a relapse was not reported. The authors reported no significant difference between groups for time to first new episode (HR = 1.34, p=0.67). There was very low quality evidence of no difference in discontinuation for any reason (RR = 1.08, 95% CI = 0.51 to 2.30). The GDG noted that the published report for the trial is not consistent with unpublished company reports.

Lamotrigine compared with placebo

Two trials (BOWDEN2003, CALABRESE2003; N = 471) compared lamotrigine (200 mg) as part of a three-arm trial (also including lithium as described above). Participants were euthymic at randomisation following 8 to 16 weeks of active treatment with lamotrigine alone or in addition to other psychotropic

medication. At approximately 74 weeks after randomisation there was low quality evidence that continued lamotrigine may be associated with a reduction in relapse (RR = 0.82, 95% CI = 0.59 to 1.14), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was low quality evidence of a small or no effect of lamotrigine on discontinuation (RR = 1.14, 95% CI = 0.64 to 2.06).

Valproate compared with placebo

One trial (BOWDEN2000; N = 281) compared valproate with placebo as part of a three-arm trial (also including lithium as described above). Participants were not experiencing an acute episode at randomisation, but had experienced the onset of a manic episode within 3 months. Valproate was titrated to serum levels of 71 to 125 ug per millilitre and participants were followed for 1 year. There was low quality evidence that valproate was associated with a reduction in the risk of relapse (RR = 0.63, 95% CI = 0.44 to 0.90). There was very low quality evidence of little effect of valproate on discontinuation for any reason (RR = 1.02, 95% CI = 0.74 to 1.40).

Antidepressants

Imipramine compared with placebo

One trial (PRIEN1973B; N = 26) compared imipramine (125 mg) with placebo as part of a three-arm trial (also including lithium as described above). At randomisation, participants had remitted from a manic episode and were receiving stable doses of lithium. Study-defined relapse was reported separately for manic and depressive episodes, but the definition of relapse did not meet the criteria set by the GDG. Estimates were very imprecise for study-defined manic (RR = 2.00, 95% CI = 0.63 to 6.34) and depressive relapses (RR = 0.09, 95% CI = 0.01 to 1.49). At 2 years, there was very low quality evidence of little effect on discontinuation (RR = 1.17, 95% CI = 0.54 to 2.53).

One three-arm trial (PRIEN1984; N = 78) compared lithium, imipramine (150 mg) and the combination of lithium and imipramine. At randomisation participants were euthymic following 2 months of active treatment with combined lithium and imipramine. Lithium serum levels were maintained between 0.4 to 1.0 mmol per litre. At 2 years after randomisation, there was very low quality evidence that imipramine when compared with lithium increased the risk of relapse (RR = 1.47, 95% CI = 1.07 to 2.02), but the definition of relapse did not meet the criteria set by the GDG. Only the number of participants discontinuing due to side effects was reported and no one withdrew for this reason in either the lithium or imipramine groups. For the combination therapy compared with imipramine, very low quality evidence indicated that the combination therapy may be associated with a reduction in the risk of study-defined relapse (RR = 0.62, 95% CI = 0.43 to

0.89), but for a possible increase in the risk of discontinuation for any reason (RR = 5.81, 95% CI = 0.29 to 117.23). For the combination therapy compared with lithium there was little evidence of an important effect for study-defined relapse (RR = 0.91, 95% CI = 0.60 to 1.40). For discontinuation, the results were inconclusive (RR = 5.81, 95% CI = 0.29 to 117.23).

One trial (QUITKIN1981; N = 75) compared imipramine (125 mg) with placebo for participants who were all taking lithium. At randomisation participants had been euthymic for at least 6 weeks while receiving stable doses of lithium. At 129 weeks after randomisation in the results were inconclusive for relapse (RR = 1.54, 95% CI = 0.71 to 3.33) and discontinuation for any reason (RR = 0.86, 95% CI = 0.65 to 1.13), but the quality of the evidence was very low.

Antidepressants compared with placebo

One trial (GHAEMI2010; N = 70) compared antidepressant continuation with discontinuation for participants who were also taking mood stabilisers. All participants had responded to active treatment with antidepressants and mood stabilisers for an acute depressive episode and had been euthymic for at least 2 months when randomised. Outcomes were reported in insufficient detail to allow extraction and analysis. The authors reported no difference between groups in the occurrence of manic, depressive or mixed episodes from baseline to 12 months. There was no difference in time to the occurrence of a manic episode, however the delay in occurrence of a depressive episode was significantly longer for the continuation group (HR = 2.13, 95% CI = 1.00 to 4.56).

Table 12: Summary of evidence for pharmacological interventions for the long-term management of bipolar disorder

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Pharmacological Interventions							
Lithium							
Lithium (low dose) compared with lithium (standard dose)	94	1	RR = 3.50 (1.55, 7.89)	Research diagnostic criteria or DSM-III criteria for mania or depression	RR = 0.46 (0.25, 0.83)	52	GELENBERG1989
Lithium every other day compared with lithium daily)	50	1	RR = 2.40 (0.99, 5.81)	Manic or depressive relapse was defined as the DSM-III-R criteria for mania or major depression and a BRMAS score ≥10 or a BRMES score ≥10, respectively	RR = 0.11 (0.01, 1.96)	56	JENSEN1995
Lithium compared with placebo (participants were euthymic at study entry)	92	2	RR = 0.41 (0.07, 2.43)	Extra medication required to treat symptoms	RR = 1.39 (0.58, 5.08)	121, 69	STALLONE1973, DUNNER1976
Lithium compared with placebo (participants first received open-label lamotrigine – alone or in combination with other psychotropic drugs - for 8 to 16 weeks and were randomised once euthymic)	358	2	RR = 0.71 (0.47, 1.06)	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.38 (0.78, 2.45)	72, 76	CALABRESE2003, BOWDEN2003

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Lithium compared with placebo (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)	185	1	RR = 0.80 (0.54, 1.20)	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.21 (0.86, 1.71)	52	BOWDEN2000
Lithium compared with placebo (following remission of a manic episode and prior to discharge patients were stabilised on maintenance doses of lithium)	205	1	RR = 0.53 (0.41, 0.67)	Manic or depressive attack requiring hospitalisation or supplementary drugs	RR = 0.42 (0.28, 0.62)	104	PRIEN1973
Lithium compared with placebo (following remission from a depressive episode, patients were stabilised on lithium or imipramine)	31	1	NR	Manic or depressive attack requiring hospitalisation or supplementary drugs	RR = 0.12 (0.02, 0.88)	104	PRIEN1973B
Lithium compared with placebo (participants received open-label quetiapine for 4 to 24 weeks and were	768 δ	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or	RR = 1.37 (1.06, 1.78)	104	WEISLER2011

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
randomised once euthymic)				MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania			
Lithium compared with carbamazepine (participants were euthymic and were ready to start prophylactic treatment)	399	3	RR = 0.73 (0.56, 0.95)	Recurrence of an affective episode	RR = 0.75 (0.16, 3.54)	52, 104, 130	WOLF1997, HARTONG2003, KLEINDIENST2000
Lithium compared with carbamazepine (participants were euthymic and all on stable doses of lithium)	31	1	RR = 1.25 (0.57, 2.75)	Not defined	RR = 0.47 (0.05, 4.56)	52	COXHEAD1992
Lithium compared with quetiapine (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)	768[δ]	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.62 (1.23, 2.13)	104	WEISLER2011

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Lithium compared with valproate (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)	278	1	RR = 1.28 (0.86, 1.91)	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.19 (0.89, 1.59)	52	BOWDEN2000
Lithium compared with valproate (participants were randomised when euthymic and after 6 months of active treatment with lithium and valproate)	60	1	RR = 1.13 (0.70, 1.82)	Patients who met criteria for mania (a total Young Mania Rating Scale score ≥20 for up to 8 weeks) or depression (a 24-item Hamilton depression scale score ≥20 for 8 weeks) were considered to have relapsed.	RR = 1.46 (0.61, 3.50)	80	CALABRESE2005C
Lithium compared with valproate (participants were randomised whilst euthymic and after 4 to 8 weeks of active treatment with lithium and valproate)	220[β]	1	RR = 0.85 (0.70, 1.05)	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 1.02 (0.78, 1.34)	104	GEDDES2010
Lithium compared with lithium and valproate combination	220[β]	1	RR = 1.10 (0.87, 1.40)	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 0.96 (0.74, 1.26)	104	GEDDES2010

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Valproate compared with lithium and valproate combination	220[β]	1	RR = 1.29 (1.04, 1.61)	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 0.95 (0.72, 1.24)	104	GEDDES2010
Olanzapine compared with lithium	431	1	RR = 0.76 (0.56, 1.03)	DSM-IV criteria for a depressive, manic or mixed episode.	RR = 0.79 (0.68, 0.93)	52	TOHEN2005
Antipsychotics							
Aripiprazole compared with placebo (all participants taking lamotrigine)	351	1	RR = 0.69 (0.49, 0.98)	One or more of the following events: hospitalisation for a manic or mixed episode; a serious adverse event or worsening disease during the study; or discontinuation due to a lack of efficacy (as determined by the investigator). For the latter two criteria, patients also needed to have a YMRS total score ≥14 and a MADRS total score ≤16 for a relapse to a manic episode; a YMRS total score ≥14 and a MADRS total score ≥16 for a relapse to a mixed episode; and a YMRS total score ≤14 and a MADRS total score ≥16 for a relapse to a depressive episode	RR = 0.92 (0.79, 1.06)	52	CARLSON2012

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Aripiprazole compared with placebo (all participants taking lithium or valproate)	337	1	RR = 0.58 (0.38, 0.91)	One or more of the following: hospitalisation for a manic, mixed or depressive episode; a serious adverse event of worsening disease accompanied by a YMRS total score ≥16 and/or a MADRS total score ≥16; discontinuation due to lack of efficacy, as determined by the investigator, accompanied by a YMRS total score ≥16 and / or a MADRS total score ≥16	RR = 0.82 (0.64, 1.05)	52	MARCUS2011
Olanzapine compared with placebo (all participants taking lithium or valproate)	68	1	RR = 0.66 (0.38, 1.15)	YMRS total score ≥15, symptomatic relapse of depression defined as an HRSD–21 total score ≥15	RR = 0.77 (0.62, 0.94)	78	TOHEN2004
Olanzapine compared with placebo	278	1	RR = 0.42 (0.30, 0.59)	*1*) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalisation for any bipolar mood episode; 4) had YMRS score ≥12, MADRS score ≥12, or CGI-S scale score ≥4 at any visit	RR = 1.10 (0.66, 1.85)	78	VIETA2012

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Paliperidone compared with placebo	300	1	RR = 0.83 (0.66, 1.06)	(1) YMRS ≥15 and CGI-BP-S for mania ≥4 ; YMRS ≥15, MADRS ≥16 and CGI-BP-S for depression ≥4; voluntary or involuntary hospitalisation for any mood symptoms; therapeutic intervention to prevent or treat an impending mood episode; another therapeutic measure; any other clinically relevant event suggestive of a recurrent mood episode*	RR = 1.05 (0.78, 1.42)	129	BERWAERTS2012
Quetiapine compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with quetiapine)	585	1	RR = 0.59 (0.49, 0.76)	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.23 (1.05, 1.43)	52	YOUNG2012
Quetiapine compared with placebo (participants were randomised when euthymic after 4 to 24 weeks of active treatment with quetiapine)	808[δ]	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 20; or	RR = 0.85 (0.63, 1.14)	104	WEISLER2011

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
				discontinuation due to depression and/or mania or hypomania			
Quetiapine compared with placebo (all participants were taking lithium or valproate)	1,326	2	RR = 0.38 (0.29, 0.48)	Initiation of any medication to treat mixed, manic, or depressive symptoms, including an antipsychotic, antidepressant, or mood-stabilising agent other than lithium or divalproex or an anxiolytic other than lorazepam; psychiatric hospitalisation; YMRS or MADRS total scores ≥20 at two consecutive assessments; or discontinuation from the study because of a mood event (as determined by the investigator)	RR = 1.53 (1.24, 1.89)	104	SUPPES2009, VIETA2008B
Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with risperidone)	273	1	RR = 0.69 (0.53, 0.90)	1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalisation for any bipolar mood episode; 4) had YMRS score ≥12, MADRS	RR = 1.33 (0.82, 2.17)	78	VIETA2012

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
				score ≥12, or CGI-S scale score ≥4 at any visit			
Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 3 weeks of active treatment with oral risperidone and 26 weeks of risperidone long-acting injectable)	303	1	RR = 0.63 (0.51, 0.77)	1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalisation for any bipolar mood episode; 4) had YMRS score ≥12, MADRS score ≥12, or CGI-S scale score ≥4 at any visit	RR = 0.89 (0.61, 1.32)	104	QUIROZ2010

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual and were euthymic as randomisation following 16 weeks of active treatment with risperidone long-acting injectable)	124	1	RR = 0.50 (0.30, 0.85)	DSM-IV-TR criteria for an acute mood episode in the setting of adequate compliance with oral TAU. Additionally, at least one of the following three conditions was satisfied: (i) Clinical worsening, with the addition of a new mood stabiliser, antidepressant or antipsychotic or a > 20% dose increase of existing oral TAU medication, and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score ≥ 4 or CGI-BP-C score ≥ 6 or GAF score decreased by > 10 points from baseline; (ii) hospitalisation for worsening of manic or depressive symptoms and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score ≥ 4 or CGI-BP-C score ≥ 6 or GAF score decreased by > 10 points from baseline; (iii) hospitalisation for worsening of manic or depressive symptoms and having significant suicidal ideation	RR = 1.27 (0.61, 2.64)	52	MACFADDEN2009

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Risperidone long-acting injectable in addition to treatment as usual compared with treatment as usual (all participants had rapid cycling bipolar disorder and were not in an acute episode at randomisation)	50	1	NR	Occurrence of any of the following at any study visit: (1) a YMRS score >14 or a MADRS score >15; (2) 20% or greater increase in YMRS or MADRS scores from the previous study visit for patients with a MADRS score ≥10 or a YMRS score ≥8 at the current study visit; (3) urgent care visit/referral (psychiatric hospitalisation; emergency department visit; or referral for respite care, partial hospitalisation, or intensive outpatient treatment) due to worsening mood symptoms; (4) a CGI-S score ≥4; (5) syndromal relapse (DSM-IV-TR criteria for manic, hypomanic, major depressive, or mixed episode met); (6) withdrawal from the study due to inefficacy; and (7) necessary clinical medication adjustments	RR = 1.50 (0.63, 3.59)	52	BOBO2011B
Anticonvulsants							
Oxcarbazepine compared with placebo	55	1	RR = 0.50 (0.26, 0.94)	DSM-IV-TR criteria for a manic, hypomanic, mixed or depressive episode or scoring ≥12 in the YMRS or ≥20 in the MADRS	RR = 1.12 (0.55, 2.24)	52	VIETA2008
Gabapentin compared with placebo	25	1	NR	NR	RR = 1.08 (0.51, 2.30)	52	VIETA2006

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Lamotrigine compared with placebo	471	2	RR = 0.82 (0.59, 1.14)	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.14 (0.64, 2.06)	76, 78	CALABRESE2003, BOWDEN2003
Valproate compared with placebo	281	1	RR = 0.63 (0.44, 0.90)	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.02 (0.74, 1.40)	52	BOWDEN2000
Antidepressants							
Imipramine compared with placebo (all participants were taking lithium)	75	1	RR = 1.54 (0.71, 3.33)	Research diagnostic criteria for mania or major depressive disorder	RR = 0.86 (0.65, 1.13)	129	QUITKIN1981
Imipramine compared with placebo	26	1	RR = 0.75 (0.36, 1.55)	Manic or depressive attack requiring hospitalisation or supplementary drugs (that is, psychopharmacologic agents other than the patient's assigned treatment)	RR = 1.17 (0.54, 2.53)	104	PRIEN1973B
Imipramine and lithium combination compared with lithium	78[µ]	1	RR = 0.68 (0.49, 0.93)	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive	RR[∂]= 5.81 (0.29, 117.23)	104	PRIEN1984

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
				disorder or mania and yielded a GAS rating of 60 or less.			
Imipramine and lithium combination compared with imipramine	72[μ]	1	RR = 0.62 (0.43, 0.89)	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	RR[∂] = 5.81 (0.29, 117.23)	104	PRIEN1984
Imipramine compared with lithium	78[μ]	1	RR = 1.47 (1.07, 2.02)	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	There was no discontinuation in either group.	104	PRIEN1984
Antidepressants compared with placebo	70	1	NR	NR	NR	52	GHAEMI2010

Note. CI = Confidence interval; k = Number of studies; N = Sample size; NR = Not reported; RR = Relative risk.

†A relative risk (RR) of less than 1 favours the first treatment named

‡Cells containing definitions of relapse which do not meet the criteria set by the GDG have been shaded grey

ΔLength of follow-up reported in number of weeks

[β]GEDDES2010 is a three-arm trial including lithium, valproate and the combination of lithium and valproate. The overall number of participants is 330. All three comparisons have been included in this table so the number of participants has been double-counted.

[δ]WEISLER2011 is a three-arm trial including lithium, quetiapine and placebo. The overall number of participants is 1,172. All three comparisons have been included in this table so the number of participants has been double-counted.

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
µPRIEN1984 is a three-arm trial including imipramine, lithium and the combination of imipramine and lithium. The overall number of participants is 114. All three comparisons have been included in this table so the number of participants has been double-counted.							
∂ Discontinuation due to side effects. No other reasons for discontinuation were reported.							