[Updated 2015]

Antipsychotics and mood stabilizers (lithium, valproate, or carbamazepine) for maintenance treatment of bipolar disorder

SCOPING QUESTION: In people with bipolar disorders who require maintenance treatment, are a) antipsychotics or b) mood stabilizers (lithium, valproate or carbamazepine) effective and safe?

BACKGROUND

Bipolar disorder is a severe mental disorder associated with considerable morbidity and mortality (Hirschfeld and Vornik, 2005). It is usually characterized by recurrent manic, depressive or mixed episodes (Oswald et al., 2007). However, due to the high risk of recurrences, maintenance treatment is usually recommended (Vieta et al., 2011) and in recent years the relevance of long-term prophylaxis (i.e., maintenance treatment) has been emphasized by several guidelines. The need for maintenance treatment is supported by the desire to prevent future episodes, which cause patients and their families suffering and disrupt lives, in addition to the economic burden of direct and indirect costs associated with the disorder (Kasper, 2003). Maintenance treatment may also reduce the long-term impairment associated with the bipolar disorder. There is evidence that functional impairment in patients who have recovered from acute episodes and are asymptomatic is related to the number of previous depressive episodes (Keck, 2007). The tendency for episodes to become more frequent with time also supports the rationale for maintenance treatment (Goodwin and Jamison, 2007). A clear recommendation on mood stabilizers and antipsychotics use for maintenance treatment of bipolar disorder is critical in clinical practice.

The 2010 WHO mhGAP Intervention Guidelines recommend a mood stabilizer (i.e., lithium, valproate or carbamazepine) in the maintenance treatment of bipolar disorders. However, there have been many developments over the last five years in the field of bipolar disorder, including new placebo-controlled trials assessing maintenance treatment with antipsychotic medications (Vieta et al., 2011). Thus, the evidence profile on maintenance treatment of bipolar disorders is in need of updating.

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PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with bipolar disorder
- **Interventions:** Antipsychotic medications, mood stabilizers
- **Comparison:** Placebo
- **Outcomes:**
  - **Critical** – Prevention of relapses, adverse effects of treatment
  - **Important** – Functioning, quality of life, treatment adherence

Search strategy

The search was conducted in Week 35 of 2014 using the following databases: The Cochrane Database of Systematic Reviews, PubMED (clinical queries), the Campbell Collaboration, LILACS, PsycINFO, Embase and PILOTS. The search terms and keywords used were *"bipolar" AND (maintenance OR prevention OR recurrence OR relapse)*" AND "systematic review".* In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g., PubMED, PsycINFO and Embase) this option was selected and only the keywords *"bipolar" AND (maintenance OR prevention OR recurrence OR relapse)*"* were used. Studies were included if they were systematic reviews published from 2010 onwards.

Systematic reviews or studies included in GRADE tables or footnotes

- Berwaerts J, Melkote R, Nuamah I, Lim P (2012). A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. Journal of Affective Disorders.138(3):247-258. doi:10.1016/j.jad.2012.01.047.

- Coryell W (2009). Maintenance treatment in bipolar disorder: a reassessment of lithium as the first choice. Bipolar Disorders.11(Suppl.2):77-83. doi:10.1111/j.1399-5618.2009.00712.x.

- Smith LA, Cornelius V, Warnock A, Bell A, Young AH (2007). Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar Disorders.9(4):394-412.

- Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885.

Excluded from GRADE tables and footnotes

Macritchie K, Geddes JR, Scott J, Haslam DR, Goodwin GM (2001). Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database of Systematic Reviews. 3:CD003196.

REASON FOR EXCLUSION: All of the studies identified here were included in Vieta et al.'s (2011) meta-analysis.

PICO Table

Population 1: Adults with bipolar disorder					
Intervention	**Comparison**	**Outcome**	**Systematic reviews used for GRADE**	**Justification for systematic review used**	**Relevant GRADE Table(s)**
Aripiprazole, valproate, lamotrigine, lithium,	Placebo	Prevention of relapses	Vieta et al. (2011); Berwaerts et al. (2012) (RCT, paliperidone vs	These are the most recent, comprehensive and high quality systematic reviews	

olanzapine, quetiapine, risperidone, paliperidone			placebo)	available.	Tables 1-8, Table 10
		Functioning	No evidence available		
		Adverse effects of treatment	Vieta et al. (2011); Berwaerts et al. (2012) (RCT, paliperidone vs. placebo)	These are the most recent, comprehensive and high quality systematic reviews available.	
		Quality of life	No evidence available		
		Treatment adherence	Vieta et al. (2011); Berwaerts et al. (2012) (RCT, paliperidone vs. placebo)	These are the most recent, comprehensive and high quality systematic reviews available.	
Antipsychotic medications or mood stabilizers as a group	Placebo	Prevention of relapses	Vieta et al. (2011); Berwaerts et al. (2012) (RCT, paliperidone vs. placebo)	These are the most recent, comprehensive and high quality systematic reviews available.	Table 9
		Functioning	No evidence available		
		Adverse effects of treatment	Vieta et al. (2011); Berwaerts et al. (2012) (RCT, paliperidone vs placebo)	These are the most recent, comprehensive and high quality systematic reviews available.	
		Quality of life	No evidence available		
		Treatment adherence	Vieta et al. (2011); Berwaerts et al. (2012)	These are the most recent, comprehensive and high	

			(RCT, paliperidone vs. placebo)	quality systematic reviews available.	
Carbamazepine	Placebo	Prevention of relapses	Smith et al. (2007)	This is the only systematic review that includes a trial with carbamazepine (which is not included in the most recent systematic review provided by Vieta et al., 2010).	Table 11
		Functioning	No evidence available		
		Adverse effects of treatment	No evidence available		
		Quality of life	No evidence available		
		Treatment adherence	No evidence available		

Narrative description of the studies that went into analysis

Vieta et al. (2011) included 14 comparisons with monotherapies (aripiprazole N = 1; valproate N = 1; lamotrigine N = 3; lithium N = 3; olanzapine N = 1; quetiapine 300 mg N = 2; quetiapine 600 mg N = 2; risperidone LAI N = 1) vs. placebo used as bipolar maintenance or relapse/recurrence prevention. All patients (N = 2501) were stabilized at randomization and index episodes were depressive (N = 6), manic/hypomanic/mixed (N = 7) or any (N = 1) episode. Study duration was from 26-104 weeks, with six 52-weeks comparisons. Mean age ranged from 38 to 44 years, with 33-51% male patients. Relapse was defined as requiring intervention for a mood episode, hospital admission or DSM-IV criteria for any mood episode. All

monotherapies had relative risks (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).

The aim of the RCT by Berwaerts et al. (2012) was to assess paliperidone extended-release's (ER) efficacy in maintenance treatment of clinically stable patients with bipolar disorder. Acute phase responders, aged 18 to 65 years, were randomized to paliperidone ER (n=152) or placebo (n=148) and concluded that paliperidone reduced the time to recurrence any mood symptoms vs. placebo.

Smith et al. (2007) included one small study by Okuma et al. (1981) that randomized 22 patients to carbamazepine (200-600 mg) and 10 to placebo for one year. Diagnoses were bipolar disorder or manic-type endogenous manic–depressive psychosis, according to ICD-9. Medication was started when participants were free from manic or depressive symptoms. Okuma et al. (1981) reported that carbamazepine was effective in 6 of 10 participants and placebo was effective in 2 of 9 participants. Smith et al. (2007) calculated RR as 2.70 (95% CI ¼ 0.72–10.14) and found that the difference was not statically significant, despite the results favouring carbamazepine.

GRADE Tables

Table 1. Aripiprazole vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should aripiprazole vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aripiprazole	Placebo	Relative (95% CI)	Absolute		
Prevention of relapses – Any mood episode (follow-up 100 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	45/187 (24.1%)	36/94 (38.3%)	RR 0.63 (0.44 to 0.9)[3]	142 fewer per 1000 (from 38 fewer to 214 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses – Manic or mixed episode (follow-up 100 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	13/77 (16.9%)	28/83 (33.7%)	RR 0.50 (0.28 to 0.89)[3]	169 fewer per 1000 (from 37 fewer to 243 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses – Depressive episode (follow-up 100 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[4]	None	11/77 (14.3%)	13/83 (15.7%)	RR 0.91 (0.43 to 1.91)[3]	14 fewer per 1000 (from 89 fewer to 143 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

Functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events of treatment – Discontinuation due to adverse events (follow-up 100 weeks)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[5]	None	1/39 (2.6%)	0/27 (0%)	-[6]	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence – All cause discontinuation (follow-up 100 weeks)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[5]	None	32/39 (82.1%)	22/27 (81.5%)	RR 1.01 (0.8 to 1.27)[6]	8 more per 1000 (from 163 fewer to 220 more)	⊕OOO VERY LOW	IMPORTANT
								0%		-		

[1] Dropout rate > 30%.
[2] Only study contributed to the analysis.
[3] Estimates <1 favour treatment.
[4] 95% CI includes both no effect and significant benefit.
[5] Only one study with less than 100 patients.
[6] Not reported.

[Updated 2015]

Table 2. Valproate vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should valproate vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Valproate**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Prevention of relapses – Any mood episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	25/77 (32.5%)	43/83 (51.8%)	RR 0.63 (0.43 to 0.92)[3]	192 fewer per 1000 (from 41 fewer to 295 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses – Manic or mixed episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[4]	None	33/187 (17.6%)	21/94 (22.3%)	RR 0.79 (0.49 to 1.29)[3]	47 fewer per 1000 (from 114 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses – Depressive episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	12/187 (6.4%)	15/94 (16%)	RR 0.40 (0.2 to 0.82)[3]	96 fewer per 1000 (from 29 fewer to 128 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Functioning												

0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events of treatment – Discontinuation due to intolerance (follow-up 52 weeks)												
1	Randomized trials	Very serious[1]	no serious inconsistency	Serious[2]	No serious imprecision	None	41/187 (21.9%)	11/94 (11.7%)	-[5]	117 fewer per 1000 (from 117 fewer to 117 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence – all cause discontinuation (follow-up 52 weeks)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	116/187 (62%)	71/94 (75.5%)	RR 0.83 (0.71 to 0.98)[5]	128 fewer per 1000 (from 15 fewer to 219 fewer)	⊕OOO VERY LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Dropout rate > 30%.
[2] Only one study contributed to the analysis.
[3] Estimates <1 favour treatment.
[4] 95% CI includes both no effect and significant benefit.
[5] Not reported.

[Updated 2015]

Table 3. Lamotrigine vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should lamotrigine vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamotrigine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Prevention of relapses - Any mood episode (follow-up 26-76 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
3	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	169/363 (46.6%)	179/275 (65.1%)	RR 0.83 (0.68 to 1)[2]	111 fewer per 1000 (from 208 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Prevention of relapses - Manic episode (follow-up 26-76 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	58/273 (21.2%)	47/188 (25%)	RR 0.96 (0.68 to 1.34)[2]	10 fewer per 1000 (from 80 fewer to 85 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 26-76 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
2	Randomized trials	Very serious[1]	Serious[3]	No serious indirectness	Serious[4]	None	85/273 (31.1%)	68/188 (36.2%)	RR 0.70 (0.36 to 1.36)[2]	109 fewer per 1000 (from 231 fewer to 130 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Functioning												
0	No evidence					None	-	-	-	-		IMPORTANT

	available							0%		-		
Adverse events of treatment - Discontinuation due to adverse events (follow-up 26 to 76 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	23/221 (10.4%)	15/131 (11.5%)	-[5]	115 fewer per 1000 (from 115 fewer to 115 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - All cause discontinuation (follow-up 26-76 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	239/280 (85.4%)	179/191 (93.7%)	RR 0.94 (0.89 to 0.99)[5]	56 fewer per 1000 (from 9 fewer to 103 fewer)	⊕⊕OO LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Dropout rate > 30% in all studies.
[2] Estimates <1 favour treatment.
[3] I^2= 67.1%.
[4] 95% CI includes both no effect and significant benefit.
[5] Not reported.

[Updated 2015]

Table 4. Lithium vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui

Question: Should lithium vs. placebo be used for maintenance treatment of bipolar disorder in adults?

Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Placebo	Relative (95% CI)	Absolute		
Prevention of relapses - Any mood episode (follow-up 52-76 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
3	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	112/269 (41.6%)	151/282 (53.5%)	RR 0.75 (0.6 to 0.94)[2]	134 fewer per 1000 (from 32 fewer to 214 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Prevention of relapses - Manic episode (follow-up 52-76 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
3	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	37/255 (14.5%)	68/282 (24.1%)	RR 0.63 (0.39 to 1.01)[2]	89 fewer per 1000 (from 147 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 52-76 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
3	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	65/255 (25.5%)	83/282 (29.4%)	RR 0.88 (0.67 to 1.15)[2]	35 fewer per 1000 (from 97 fewer to 44 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Functioning												
0	No evidence					None	-	-	-	-		IMPORTANT

	available							0%		-		
Adverse events of treatment - Discontinuation due to adverse events (follow-up 52-76 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	62/258 (24%)	26/285 (9.1%)	-[4]	91 fewer per 1000 (from 91 fewer to 91 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - all cause discontinuation (follow-up 52-76 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	226/271 (83.4%)	250/285 (87.7%)	RR 0.97 (0.92 to 1.01)[4]	26 fewer per 1000 (from 70 fewer to 9 more)	⊕⊕OO LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Dropout rate > 30% in all studies.

[2] Estimates <1 favour treatment.

[3] 95% CI includes both no effect and significant benefit.

[4] Not reported.

[5] Coryell et al. (2009) reviewed five early (1973-1976) randomized placebo-controlled trials with lithium in stabilized patients with bipolar disorder. Pooled success rates were 120/160 (75%) with lithium and 66/168 (39.3%) with placebo. Discontinuation due to adverse events rates was 23/160 (14.4%) with lithium and 29/168 (17.3%) with placebo.

[Updated 2015]

Table 5. Olanzapine vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should olanzapine vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Olanzapine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Prevention of relapses - Any mood episode (follow-up 48 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	105/225 (46.7%)	109/136 (80.1%)	RR 0.58 (0.49 to 0.69)[2]	337 fewer per 1000 (from 248 fewer to 409 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Prevention of relapses - Manic or mixed episode (follow-up 48 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	27/225 (12%)	44/136 (32.4%)	RR 0.40 (0.28 to 0.57)[2]	194 fewer per 1000 (from 139 fewer to 233 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 48 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	68/225 (30.2%)	53/136 (39%)	RR 0.78 (0.58 to 1.04)[2]	86 fewer per 1000 (from 164 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		

Adverse events of treatment - Discontinuation due to adverse events (follow-up 48 weeks)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	17/225 (7.6%)	0/136 (0%)	-[3]	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - All cause discontinuation (follow-up 48 weeks)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	72/225 (32%)	18/136 (13.2%)	RR 2.42 (1.51 to 3.87)[2]	188 more per 1000 (from 67 more to 380 more)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
								0%		-		

[1] Only one study contributed to the analysis.

[2] Estimates <1 favour treatment.

[3] Not reported.

[Updated 2015]

Table 6. Quetiapine (300 mg) vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should quetiapine (300 mg) vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quetiapine 300 mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Prevention of relapses - Any mood episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-[2,3,4]	-	RR 0.67 (0.49 to 0.9)[5]	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Prevention of relapses - Manic or mixed episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-[2]	-	RR 0.98 (0.55 to 1.74)[5]	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 52 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-[2,6,7]	-	RR 0.55 (0.36 to 0.83)[5]	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events of treatment												

0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - all cause discontinuation (follow-up 52 weeks)												
2	Randomized trials	very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/141 (48.9%)	139/247 (56.3%)	RR 0.78 (0.65 to 0.95)[5]	124 fewer per 1000 (from 28 fewer to 197 fewer)	⊕⊕OO LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Dropout rate > 30% in all studies.
[2] Not reported.
[3] Hazard ratio for the time to recurrence of a mood event of 0.56 (95% CI 0.39 to 0.82) for both quetiapine 300 mg and 600 mg (Young et al.,2008).
[4] Hazard ratio for the time to recurrence of a mood event of 0.43 (95% CI 0.27 to 0.69) for both quetiapine 300 mg and 600 mg (McElroy et al., 2008).
[5] Estimates <1 favour treatment.
[6] Hazard ratio for the time to recurrence of a depressive event of 0.48 (95% CI 0.29–0.77) for both quetiapine 300 mg and 600 mg (Young et al., 2008)
[7] Hazard ratio for the time to recurrence of a depressive event of 0.36 (95% CI 0.21 to 0.63) for both quetiapine 300 mg and 600 mg (McElroy et al., 2008).

Table 7. Quetiapine (600 mg) vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should quetiapine (600 mg) vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quetiapine 600 mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Prevention of relapses - Any mood episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-[2,3,4]	151/0 (0%)[2]	RR 0.54 (0.36 to 0.81)[5]	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Prevention of relapses - Manic or mixed episode (follow-up 52 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	-[2]	-	RR 0.80 (0.43 to 1.47)[5]	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 52 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-[2,7,8]	-	RR 0.45 (0.27 to 0.75)[5]	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Functioning												

0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events of treatment												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - All cause discontinuation (follow-up 52 weeks)												
2	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	71/150 (47.3%)	140/247 (56.7%)	RR 0.76 (0.63 to 0.92)[5]	136 fewer per 1000 (from 45 fewer to 210 fewer)	⊕⊕OO LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Dropout rate > 30% in all studies.
[2] Not reported.
[3] Hazard ratio for the time to recurrence of a mood event of 0.56 (95% CI 0.39 to 0.82) for both quetiapine 300 mg and 600 mg (Young et al., 2008)
[4] Hazard ratio for the time to recurrence of a mood event of 0.43 (95% CI 0.27 to 0.69) for both quetiapine 300 mg and 600 mg (McElroy et al., 2008).
[5] Estimates <1 favour treatment.
[6] 95% CI includes both no effect and significant benefit.
[7] Hazard ratio for the time to recurrence of a depressive event of 0.48 (95% CI 0.29–0.77) for both quetiapine 300 mg and 600 mg (Young et al., 2008).
[8] Hazard ratio for the time to recurrence of a depressive event of 0.36 (95% CI 0.21 to 0.63) for both quetiapine 300 mg and 600 mg (McElroy et al., 2008).

[Updated 2015]

Table 8. Risperidone in long-acting injection (LAI) form vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should risperidone LAI vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone LAI	Placebo	Relative (95% CI)	Absolute		
Prevention of relapses - Any mood episode (follow-up 104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	42/135 (31.1%)	76/133 (57.1%)	RR 0.54 (0.41 to 0.73)[2]	263 fewer per 1000 (from 154 fewer to 337 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Prevention of relapses - Manic or mixed episode (follow-up 104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	22/135 (16.3%)	62/133 (46.6%)	RR 0.35 (0.23 to 0.53)[2]	303 fewer per 1000 (from 219 fewer to 359 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[3]	None	20/135 (14.8%)	14/133 (10.5%)	RR 1.41 (0.74 to 2.67)[2]	43 more per 1000 (from 27 fewer to 176 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Functioning												
0	No evidence					None	-	-	-	-		IMPORTANT

	available							0%		-		
Adverse events of treatment - Discontinuation due to adverse events (follow-up 104 weeks)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	33/154 (21.4%)	15/149 (10.1%)	-[4]	101 fewer per 1000 (from 101 fewer to 101 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - all cause discontinuation (follow-up 104 weeks)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	40/154 (26%)	37/149 (24.8%)	RR 1.05 (0.71 to 1.54)[2]	12 more per 1000 (from 72 fewer to 134 more)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
								0%		-		

[1] Only one study contributed to the analysis.
[2] Estimates <1 favour treatment.
[3] 95% CI includes both no effect and significant harm.
[4] Not reported.

[Updated 2015]

Table 9. Antipsychotics and mood stabilizers vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should antipsychotics and mood stabilizers vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Åström M, Paulsson B (2011). Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology.14(8):1029-1049. doi:10.1017/S1461145711000885.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotics and mood stabilizers	Placebo	Relative (95% CI)	Absolute		
Prevention of relapses - Any mood episode (follow-up 26-104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
14	Randomized trials	Very serious[1]	Serious[2]	No serious indirectness	No serious imprecision	None	488/1152 (42.4%)	594/1003 (59.2%)	RR 0.68 (0.6 to 0.77)[3]	190 fewer per 1000 (from 136 fewer to 237 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses - Manic or mixed episode (follow-up 26-104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
13	Randomized trials	Very serious[1]	Serious[4]	No serious indirectness	No serious imprecision	None	190/1152 (16.5%)	291/916 (31.8%)	RR 0.65 (0.51 to 0.84)[3]	111 fewer per 1000 (from 51 fewer to 156 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 26-104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
13	Randomized trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	327/1152 (28.4%)	316/916 (34.5%)	RR 0.70 (0.58 to 0.85)[3]	103 fewer per 1000 (from 52 fewer to 145 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Functioning												

0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events of treatment - Discontinuation due to adverse events (follow-up 26-104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
10	Randomized trials	Very serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	159/1084 (14.7%)	86/822 (10.5%)	-[3,6]	105 fewer per 1000 (from 105 fewer to 105 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - All cause discontinuation (follow-up 26-104 weeks; assessed with requiring intervention/hospital admission/DSM-IV criteria for any mood episode)												
13	Randomized trials	Very serious[1]	Serious[7]	No serious indirectness	No serious imprecision	None	738/1319 (56%)	813/1344 (60.5%)	RR 0.93 (0.87 to 0.99)[3]	42 fewer per 1000 (from 6 fewer to 79 fewer)	⊕OOO VERY LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Droput > 30% in 12 studies.
[2] I^2 = 52.3%
[3] Estimates <1 favour treatment.
[4] I^2 = 56.6%
[5] Droput > 30% in eight studies.
[6] Not reported.
[7] I^2 = 64%

[Updated 2015]

Table 10. Paliperidone extended-release (ER) vs. placebo for maintenance treatment of bipolar disorder.

Authors: L Tarsitani and C Barbui
Question: Should paliperidone ER vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Berwaerts J, Melkote R, Nuamah I, Lim P (2012). A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar disorder after an acute manic or mixed episode. Journal of Affective Disorders.138(3):247-258. doi:10.1016/j.jad.2012.01.047.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paliperidone ER	Placebo	Relative (95% CI)	Absolute		
Prevention of relapses - Any mood episode (follow-up 24 months; assessed with YMRS≥15 and Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S) for mania≥4; YMRS<15, MADRS≥16 and CGI-BP-S for depression≥4; hospitalization or intervention)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	84/146 (57.5%)	105/144 (72.9%)	HR 1.43 (1.03 to 1.98)[3]	116 more per 1000 (from 10 more to 196 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses - Manic or mixed episode (follow-up 24 months; assessed with YMRS≥15 and Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S) for mania≥4; hospitalization or intervention)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	31/146 (21.2%)	51/144 (35.4%)	HR 2.06 (1.32 to 3.22)[3]	240 more per 1000 (from 84 more to 401 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses - Depressive episode (follow-up 24 months; assessed with YMRS<15, MADRS≥16 and CGI-BP-S for depression≥4; hospitalization or intervention)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	35/146 (24%)	26/144 (18.1%)	HR 0.88 (0.53 to 1.46)[3]	20 fewer per 1000 (from 80 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Functioning												

0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events of treatment - Discontinuation due to adverse events (follow-up 24 months) [5]												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	2/147 (1.4%)	3/149 (2%)	-[4]	20 fewer per 1000 (from 20 fewer to 20 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence - All cause discontinuation (follow-up 24 months)												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	56/152 (36.8%)	52/148 (35.1%)	-[4]	351 fewer per 1000 (from 351 fewer to 351 fewer)	⊕OOO VERY LOW	IMPORTANT
								0%		-		
								0%		-		

[1] Dropout rate is > 30%.

[2] Only one study contributed to the analysis.

[3] Estimates >1 favour treatment.

[4] Not reported.

[5] Maintenance phase.

[Updated 2015]

Table 11. Carbamazepine vs. placebo for maintenance treatment of bipolar disorder

Authors: L Tarsitani and C Barbui
Question: Should carbamazepine vs. placebo be used for maintenance treatment of bipolar disorder in adults?
Bibliography: Smith LA, Cornelius V, Warnock A, Bell A, Young AH (2007). Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar Disorders.9(4):394-412.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbamazepine	Placebo	Relative (95% CI)	Absolute		
Relapse prevention												
1	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Reporting bias[2]	6/10 (60%)	2/9 (22.2%)	RR 2.70 (0.72 to 10.14)	378 more per 1000 (from 62 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Disability and functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse effects												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Treatment adherence												

0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		

[1] Single study with a dropout rate of 32%.
[2] Only one study contributed to the analysis.
[3] Sample size is very low (N=19) and CI crosses 1 and 2.0.

Additional evidence not mentioned in GRADE tables

Carbamazepine

Goodwin FK and Jamison KR. Maintenance medical treatment. In: Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression (2nd ed.). Oxford: Oxford University Press; 2007.

This chapter reviews five prospective, parallel, randomized, double-blind trials comparing carbamazepine with lithium as a prophylactic agent in treating bipolar disorder (Placidi et al., 1986; Watkins et al., 1987; Coxhead et al., 1992; Denicoff et al., 1997; Greil et al., 1997; Greil and Kleindienst, 1999). Carbamazepine is similarly effective or slightly less effective than acute treatment with lithium, but appears to be similarly effective and tolerated in the maintenance treatment of bipolar disorder.

First-Generation Antipsychotics

Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR (2011). Comparative efficacy and acceptability of antimanic medications in acute mania: a multiple-treatments meta-analysis. Lancet.378(9799):1306-1315. doi:10.1016/S0140-6736(11)60873-8.

In this multiple-treatment meta-analysis, the authors systematically reviewed six randomized placebo-controlled trials of haloperidol at therapeutic dose range for the treatment of acute mania in 1285 adults. The overall quality of studies was rated as good, even though some studies did not record details about randomization and allocation concealment and there were only a few RCTs at low risk of bias. Mean change scores on the Young Mania Rating Scale (YMRS) and dropout rates (i.e., treatment discontinuation) were chosen as primary outcomes to represent the most sensible and

sensitive estimates of acute treatment efficacy and acceptability. Haloperidol was significantly more effective than placebo (SMD −0.56; 95% CI −0·69 to −0·43). In terms of dropout rate, haloperidol was not significantly superior to placebo (OR 0.85; 95% CI 0.62 to 1.15). Moreover, this review included 14 head-to-head comparisons of haloperidol vs. aripiprazole (N=2 studies, n=679 patients), carbamazepine (N=3, n=70), lithium (N=2, n=44), olanzapine (N=2, n=578), quetiapine (N=1, n=201), risperidone (N=3, n=433), ziprasidone (N=1, n=350) and haloperidol was among most effective evidence-based options for the treatment of manic episodes.

Although these cannot be viewed as straightforward studies of maintenance treatment of bipolar disorder, they may support some prophylactic benefit for haloperidol.

Littlejohn R, Leslie F, Cookson J (1994). Depot antipsychotics in the prophylaxis of bipolar affective disorder. British Journal of Psychiatry.165(6):827-829.

This is a retrospective chart review of 18 bipolar disorder patients using five first-generation depot antipsychotics (i.e., fluphenazine, flupenthixol, haloperidol, pipothiazine and zuclopenthixol.) for 8 years. The number of weeks hospitalized annually per patient decreased from 11. 4 to 1.5 weeks ($p< 0.001$). Decreases were also found in time hospitalized for mania (9.1weeks vs 1.0 weeks, $p < 0.001$), depression (1.4 weeks vs 0.2 weeks, $p < 0.05$) and mixed episodes (1.0 weeks vs 0 weeks, $p< 0.01$).

Ahlfors UG, Baastrup PC, Dencker SJ, Elgen K, Lingjaerde O, Pedersen V, Schou M, Aaskoven O (1981). Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. Acta Psychiatrica Scandinavica.64(3):226-37.

This study had two groups of patients. In Group I the patients were allocated randomly to maintenance treatment with either lithium or flupenthixol decanoate. The patients in Group II had previously been given lithium and were switched to flupenthixol decanoate because of unsatisfactory prophylactic effect of lithium, doubtful compliance or side effects. The study was not blind. In Group I neither lithium treatment (14 patients) nor treatment with flupenthixol decanoate (19 patients) led to a significant fall of mean episode frequency. In Group II (93 patients) treatment with flupenthixol decanoate was associated with significant falls in the frequency of manic episodes and per-cent time ill in mania and with significant rises in the frequency of depressive episodes and per-cent time ill in depression. Increase of depressive morbidity was seen only in patients who had been given lithium during the pre-trial period and was presumably a result of the discontinuation of lithium. The authors state that flupenthixol decanoate may be worth trying in patients whose disorders are dominated more by mania episodes versusdepressive recurrences, and who do not respond to lithium or do not tolerate it.

National Institute for Health and Care Excellence (NICE). 2014. *Managing bipolar disorder in adults in the longer term in secondary care*. In: Bipolar disorder: The assessment and management of bipolar disorder in adults, children and young people in primary and secondary care [CG185]. [online]. London: NICE. Available from: http://www.nice.org.uk/guidance/cg185/chapter/recommendations#how-to-use-medication (accessed Autumn 2014).

The NICE guidelines advise the following:

- Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder;
- If lithium is ineffective, consider adding valproate. If lithium is poorly tolerated or is not suitable (for example, because the person does not agree to routine blood monitoring), consider valproate or olanzapine instead or consider adding quetiapine if lithium has been effective during an episode of mania or bipolar depression; and
- Discuss with the person the possible benefits and risks of each medication for them.

Use among pregnant and lactating women

National Collaborating Centre for Mental Health (NCCMH). 2007. *Antenatal and Postnatal Mental Health: The NICE Clinical Management and Service Guidance* [CG45]. Leicester: The British Psychological Society & The Royal College of Psychiatrists.

These guidelines make the following recommendations:

- Valproate should not be routinely prescribed to women of childbearing potential. If there is no effective alternative, the risks of taking valproate during pregnancy and the importance of using adequate contraception should be explained; and
- Lithium should not be routinely prescribed for pregnant women, particularly in the first trimester of pregnancy (because of the risk of cardiac malformations in the fetus) or during breastfeeding (because of high levels in breast milk).

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Quantitative summary of evidence table

Outcomes	**Aripiprazole (ARI)** *(Number of studies, RR [95%CI], quality)*	**Valproate (VAL)** *(Number of studies, RR [95%CI], quality)*	**Lamotrigine** *(Number of studies, RR [95%CI], quality)*	**Lithium (LIT)** *(Number of studies, RR [95%CI], quality)*	**Olanzapine (OLA)** *(Number of studies, RR [95%CI], quality)*	**Quetiapine (QUE) 300 mg** *(Number of studies, RR [95%CI], quality)*	**Quetiapine (QUE) 600 mg** *(Number of studies, RR [95%CI], quality)*	**Risperidone (RIS) LAI** *(Number of studies, RR [95%CI], quality)*	**Antipsychotics/ stabilizers as a group (AP or ST)** *(Number of studies, RR [95%CI], quality)*	**Paliperidone ER (PAL)** *(Number of studies, HR [95%CI], quality)*	**Carbamazepine (CAR)** *(Number of studies, RR [95%CI], quality)*
Prevention of relapses - Any mood episode	1 study, RR 0.63 (0.44 to 0.9) In favour of ARI, VERY LOW	1 study, RR 0.63 (0.43 to 0.92) In favour of VAL, VERY LOW	3 studies, RR 0.83 (0.68 to 1), LOW	3 studies, RR 0.75 (0.6 to 0.94) In favour of LIT, LOW	1 study, RR 0.58 (0.49 to 0.69) In favour of OLA, MODERATE	2 studies, RR 0.67 (0.49 to 0.9) In favour of QUE, LOW	2 studies, RR 0.54 (0.36 to 0.81) In favour of QUE , LOW	1 study, RR 0.54 (0.41 to 0.73) In favour of RIS, MODERATE	14 studies, RR 0.68 (0.6 to 0.77) In favour of AP or ST, VERY LOW	1 study, HR 1.43 (1.03 to 1.98) In favour of PAL, VERY LOW	1 study, RR 2.70 (0.72 to 10.14). VERY LOW
Prevention of relapses – Manic/mixed episode	1 study, RR 0.50 (0.28 to 0.89) In favour of	1 study, RR 0.79 (0.49 to 1.29),	2 studies, RR 0.96 (0.68 to 1.34),	3 studies, RR 0.63 (0.39 to 1.01),	1 study, RR 0.40 (0.28 to 0.57) In favour of	2 studies, RR 0.98 (0.55 to 1.74).	2 studies, RR 0.80 (0.43 to 1.47),	1 study, RR 0.35 (0.23 to 0.53) In favour of	13 studies, RR 0.65 (0.51 to 0.84) In favour of AP or	1 study, HR 2.06 (1.32 to 3.22) In favour of	

	ARI, VERY LOW	VERY LOW	LOW	VERY LOW	OLA, MODERATE	LOW	LOW	RIS, MODERATE	MS, VERY LOW	PAL, VERY LOW	
Prevention of relapses – Depressive episode	1 study, RR 0.91 (0.43 to 1.91), VERY LOW	1 study, RR 0.40 (0.2 to 0.82) In favour of VAL, VERY LOW	2 studies, RR 0.70 (0.36 to 1.36), VERY LOW	3 studies, RR 0.88 (0.67 to 1.15), LOW	1 study, RR 0.78 (0.58 to 1.04), MODERATE	2 studies, RR 0.55 (0.36 to 0.83) In favour of QUE, LOW	2 studies, RR 0.45 (0.27 to 0.75) In favour of QUE, LOW	1 study, RR 1.41 (0.74 to 2.67), LOW	13 studies, RR 0.70 (0.58 to 0.85) In favour of AP/MS, LOW	1 study, HR 0.88 (0.53 to 1.46), VERY LOW	
Functioning	No evidence available										
Discontinuation due to adverse events	1 study, Treatment 2.6% Placebo 0% VERY LOW	1 study, Treatment 21.9% Placebo 11.7% VERY LOW	2 studies Treatment 10.4% Placebo 11.5% LOW	2 studies Treatment 24% Placebo 9.1% LOW	1 study, Treatment 7.6% Placebo 0% MODERATE			1 study, Treatment 21.4% Placebo 10.1% MODERATE	10 studies, Treatment 14.7% Placebo 10.5% LOW	1 study, Treatment 1.4% Placebo 2% VERY LOW	
Quality of life	No evidence available										

Treatment adherence - All cause discontinuation	1 study, RR 1.01 (0.8 to 1.27), VERY LOW	1 study, RR 0.83 (0.71 to 0.98) In favour of VAL, VERY LOW	2 studies, RR 0.94 (0.89 to 0.99) In favour of LAM, LOW	2 studies, RR 0.88 (0.67 to 1.15), LOW	1 study, RR 2.42 (1.51 to 3.87) In favour of PLA MODERATE	2 studies, RR 0.78 (0.65 to 0.95) In favour of QUE, LOW	2 studies, RR 0.76 (0.63 to 0.92) In favour of QUE, LOW	1 study, RR 1.05 (0.71 to 1.54), MODERATE	13 studies, RR 0.93 (0.87 to 0.99) In favour of AP/MS, VERY LOW	1 study, Treamtent 36.8% Placebo 35.1% VERY LOW	

Evidence to recommendation table

Benefits	In terms of the proportion of patients relapsing for any mood episode, there is some evidence that aripiprazole, valproate, lamotrigine, lithium olanzapine, quetiapine (300mg and 600mg), risperidone LAI and paliperidone ER were significantly more effective than placebo in maintenance treatment of bipolar disorder. There is very limited evidence suggesting that carbamazepine may be more effective than placebo in the maintenance treatment of bipolar disorder, although the difference was not statistically significant (i.e., one small RCT). There is evidence from five randomized, double-blind trials that carbamazepine is similarly effective or slightly less effective than lithium and equally tolerated in the maintenance treatment of bipolar disorder. In terms of manic or mixed relapses, there is evidence that aripiprazole, olanzapine, risperidone LAI and paliperidone ER were significantly more effective than placebo. There is limited evidence for

	valproate, lamotrigine, lithium, quetiapine 300 mg and quetiapine 600 mg for this outcome. No evidence is available for carbamazepine. In terms of depressive relapses, there is evidence that valproate and quetiapine 300 mg and 600 mg were significantly more effective than placebo. Aripiprazole, lamotrigine, lithium, olanzapine, risperidone LAI and paliperidone ER were no better than placebo. The overall estimate for antipsychotics and mood stabilizers considered as a group is RR 0.70 (0.58 to 0.85) (in 13 studies, except paliperidone LAI). No evidence is available for carbamazepine. In terms of treatment adherence, only valproate, lamotrigine, quetiapine 300 mg and quetiapine 600 significantly reduced total dropouts when compared to placebo. Olanzapine increased total dropouts. No evidence is available for carbamazepine. In terms of symptoms severity, functioning, quality of life, or user and family satisfaction with care, there was no evidence available for maintenance treatment of bipolar disorder. No direct evidence is available for first-generation antipsychotic medications for the maintenance treatment of bipolar disorder. However, in six randomized placebo-controlled trials and 14 head-to-head comparisons for the treatment of acute mania, haloperidol was among most effective treatments.
Harms	There is no evidence about adverse events compared to placebo. The overall dropout rate for adverse events was 14.7% in patients treated with antipsychotics or mood stabilizers and 10.5% in patients treated with placebo (except paliperidone ER). Lithium, valproate and olanzapine significantly increase the risk of withdrawal for adverse events compared to placebo. Lamotrigine does not appear to increase dropout due to adverse events. Risperidone LAI was associated with treatment emergent extrapyramidal symptoms, weight gain and

	prolactin increase. The short- and long-term tolerability profile of antipsychotics may be indirectly inferred from studies conducted in other patient populations.
Summary of the quality of evidence	The quality of evidence was VERY LOW for aripiprazole, valproate and carbamazepine; VERY LOW-to-LOW for lamotrigine, lithium and quetiapine; MODERATE-to-LOW for risperidone LAI and MODERATE for olanzapine.

Value and preferences	
In favour	Important issues include the short and long term consequences of disability and the lack of functioning and discrimination associated with manic or depressive relapse. In addition, both manic and depressive episodes can be life-threatening conditions. Long-term treatment of bipolar disorder may prevent future episodes that tend to cause patients and their familites suffering and dirupt their lives, in addition to the economic burden of direct and indirect costs. Maintenance treatment may reduce long-term impairment associated with bipolar disorder. The tendency for episodes to become more frequent with time also supports the rationale for maintenance treatment.
Against	There are significant concerns about safety and tolerability associated with long-term treatment with antipsychotics and mood stabilizers. In terms of tolerability, both lithium and valproate have a narrow

	therapeutic index and can be toxic to multiple organ systems. A further important issue is the burden of taking mood stabilizers that requires regular blood monitoring.
Uncertainty or variability?	The capacity of monitoring adverse effects of different antipsychotics varies between countries.

Feasibility (including resource use considerations)	Lithium, valproate, carbamazepine and first-generation antipsychotics are associated with low acquisition costs. The cost of second-generation antipsychotics may be more than ten times the cost of generic first-generation antipsychotics. Lithium treatment requires periodic blood level monitoring that may not be available, except in secondary care settings, and increases treatment costs. In many LAMICs, continuous availability of antipsychotics (especially second-generation antipsychotics) and mood stabilizers in non-specialized health care is a challenge. Lithium, valproate and carbamazepine are included in the WHO Essential Medicine List as mood stabilizers medicines.

	Haloperidol, chlorpromazine and risperidone are also available in the WHO Essential Medicine List.
Uncertainty or variability?	Overall the availability and technical capacity to administer antipsychotics varies between countries and the level of care provided by health centres.

Recommendation and remarks

Recommendation

Lithium or valproate or certain second-generation antipsychotics (aripiprazole, olanzapine, paliperidone extended release, quetiapine, and risperidone long acting injection release) can be offered for the maintenance treatment of bipolar disorder. If treatment with one of these agents is not feasible, first-generation antipsychotics or carbamazepine may be used. Maintenance treatment should be offered in primary health care settings under supervision of a specialist.

Rationale: Although there are concerns about safety and tolerability associated with long-term treatment with antipsychotics and mood stabilizers, there is low-quality evidence suggesting that the benefits of lithium, valproate and certain second-generation antipsychotics outweigh their harms. In terms of tolerability, both lithium and valproate have a narrow therapeutic index and can be toxic to multiple organ systems. A further important issue is the burden of taking mood stabilizers that requires regular blood monitoring.

Remarks

Treatment with lithium should be initiated only in those settings where personnel and facilities for close clinical and laboratory monitoring are available.

All studies evaluating antipsychotic treatment have investigated the efficacy and tolerability profile of second-generation antipsychotics, while no direct evidence is available for first-generation antipsychotics. Evidence was considered for certain second-generation antipsychotics (aripiprazole, olanzapine, paliperidone extended release, quetiapine, and risperidone long acting injection release).

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate **X Low** □ Very low
Balance of benefits vs. harms	**X Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	□ Less resource-intensive **X More resource-intensive**
Strength	**CONDITIONAL**

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