APPENDIX 22: PHARMACOLOGICAL INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF BIPOLAR DISORDER – GRADE PROFILES

Lithium low dose compared with lithium standard dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium (low dose)	Lithium (standard dose)	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	21/47 (44.7%)	6/47 (12.8%)	RR 3.5 (1.55 to 7.89)	319 more per 1000 (from 70 more to 880 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	20/47 (42.6%)	3/47 (6.4%)	RR 6.67 (2.12 to 20.93)	362 more per 1000 (from 71 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/47 (2.1%)	3/47 (6.4%)	RR 0.33 (0.04 to 3.09)	43 fewer per 1000 (from 61 fewer to 133 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	11/47 (23.4%)	24/47 (51.1%)	RR 0.46 (0.25 to 0.83)	276 fewer per 1000 (from 87 fewer to 383 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium every other day compared with lithium taken daily

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium (every other day)	Lithium (daily)	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	12/25 (48%)	5/25 (20%)	RR 2.4 (0.99 to 5.81)	280 more per 1000 (from 2 fewer to 962 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	6/25 (24%)	3/25 (12%)	RR 2 (0.56 to 7.12)	120 more per 1000 (from 53 fewer to 734 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	6/25 (24%)	2/25 (8%)	RR 3 (0.67 to 13.46)	160 more per 1000 (from 26 fewer to 997 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/25 (0%)	4/25 (16%)	RR 0.11 (0.01 to 1.96)	142 fewer per 1000 (from 158	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium (every other day)	Lithium (daily)	Relative (95% CI)	Absolute		
										fewer to 154 more)		

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium compared with placebo

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		
Relapse (any) (STALLONE1973, DUNNER1976)												
2	randomised trials	serious[1]	very serious[4]	no serious indirectness	very serious[2]	reporting bias[3]	13/41 (31.7%)	36/51 (70.6%)	RR 0.41 (0.07 to 2.43)	416 fewer per 1000 (from 656 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (DUNNER1976)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/16 (6.3%)	6/24 (25%)	RR 0.25 (0.03 to 1.89)	188 fewer per 1000 (from 243 fewer to 222 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (DUNNER1976)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	9/16 (56.3%)	12/24 (50%)	RR 1.12 (0.62 to 2.03)	60 more per 1000 (from 190 fewer to 515 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (STALLONE1973, DUNNER1976)												

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		
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	9/41 (22%)	8/51 (15.7%)	RR 1.39 (0.58 to 3.34)	61 more per 1000 (from 66 fewer to 367 more)	⊕OOO VERY LOW	CRITICAL
Relapse (any) (BOWDEN2003, CALABRESE2003)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[2]	reporting bias[3]	74/167 (44.3%)	115/191 (60.2%)	RR 0.71 (0.47 to 1.06)	175 fewer per 1000 (from 319 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Relapse (any) (PRIEN1973)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	43/101 (42.6%)	84/104 (80.8%)	RR 0.53 (0.41 to 0.67)	380 fewer per 1000 (from 267 fewer to 477 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (PRIEN1973)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	27/101 (26.7%)	78/104 (75%)	RR 0.36 (0.25 to 0.5)	480 fewer per 1000 (from 375 fewer to	⊕OOO VERY LOW	CRITICAL

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		
										562 fewer)		
Relapse (any) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	28/91 (30.8%)	36/94 (38.3%)	RR 0.8 (0.54 to 1.2)	77 fewer per 1000 (from 176 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/16 (6.3%)	5/24 (20.8%)	RR 0.3 (0.04 to 2.33)	146 fewer per 1000 (from 200 fewer to 277 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (BOWDEN2003)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	8/46 (17.4%)	28/70 (40%)	RR 0.43 (0.22 to 0.87)	228 fewer per 1000 (from 52 fewer to 312 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (BOWDEN2000)												

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		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	19/91 (20.9%)	21/94 (22.3%)	RR 0.93 (0.54 to 1.62)	16 fewer per 1000 (from 103 fewer to 139 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (PRIEN1973B)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	2/18 (11.10%)	3/13 (23.1%)	RR 0.48 (0.09 to 2.48)	120 fewer per 1000 (from 210 fewer to 342 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (BOWDEN2003)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	10/46 (21.7%)	21/70 (30%)	RR 0.72 (0.38 to 1.39)	84 fewer per 1000 (from 186 fewer to 117 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (PRIEN1973)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	43/101 (42.6%)	84/104 (80.8%)	RR 0.53 (0.41 to 0.67)	380 fewer per 1000 (from 267	⊕OOO VERY LOW	CRITICAL

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		
										fewer to 477 fewer)		
Relapse (depression) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	9/91 (9.9%)	15/94 (16%)	RR 0.62 (0.29 to 1.34)	61 fewer per 1000 (from 113 fewer to 54 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (PRIEN1973B)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	2/18 (11.1%)	5/13 (38.5%)	RR 0.29 (0.07 to 1.26)	273 fewer per 1000 (from 358 fewer to 100 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (BOWDEN2003, CALABRESE2003)												
2	randomised trials	serious[1]	very serious[4]	no serious indirectness	serious[2]	reporting bias[3]	71/167 (42.5%)	64/191 (33.5%)	RR 1.38 (0.78 to 2.45)	127 more per 1000 (from 74 fewer to 486 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (BOWDEN2000)												

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		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	41/91 (45.1%)	35/94 (37.2%)	RR 1.21 (0.86 to 1.71)	78 more per 1000 (from 52 fewer to 264 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (PRIEN1973)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	23/101 (22.8%)	57/104 (54.8%)	RR 0.42 (0.28 to 0.62)	318 fewer per 1000 (from 208 fewer to 395 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (PRIEN1973B)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/18 (5.6%)	6/13 (46.2%)	RR 0.12 (0.02 to 0.88)	406 fewer per 1000 (from 55 fewer to 452 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (WEISLER2011)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	99/364 (27.2%)	80/404 (19.8%)	RR 1.37 (1.06 to 1.78)	73 more per 1000 (from 12 more to 154 more)	⊕⊕OO LOW	CRITICAL

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		
Discontinuation (due to side effects) (BOWDEN2003, CALABRESE2003)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	35/167 (21%)	22/191 (11.5%)	RR 1.95 (1.2 to 3.17)	109 more per 1000 (from 23 more to 250 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects) (WEISLER2011)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/364 (5.5%)	10/404 (2.5%)	RR 2.22 (1.05 to 4.68)	30 more per 1000 (from 1 more to 91 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	31/91 (34.1%)	11/94 (11.7%)	RR 2.91 (1.56 to 5.44)	224 more per 1000 (from 66 more to 520 more)	⊕OOO VERY LOW	CRITICAL
Suicide												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/18 (0%)	1/13 (7.7%)	RR 0.25 (0.01 to 5.59)	58 fewer per 1000 (from 76 fewer to 353 more)	⊕OOO VERY LOW	CRITICAL
Mortality												

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		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/18 (5.6%)	1/13 (7.7%)	RR 0.72 (0.05 to 10.52)	22 fewer per 1000 (from 73 fewer to 732 more)	⊕OOO VERY LOW	CRITICAL
Global Assessment Scale (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	164	184	-	SMD 0.2 higher (0.01 lower to 0.42 higher)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium compared with carbamazepine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Carbamazepine	RR (95% CI)	Absolute		
Relapse (any) (HARTONG2003, KLEINDIENST2000, WOLF1997)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	60/195 (30.8%)	84/204 (41.2%)	RR 0.73 (0.56 to 0.95)	111 fewer per 1000 (from 21 fewer to 181 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (any) (COXHEAD1992)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	8/16 (50%)	6/15 (40%)	RR 1.25 (0.57 to 2.75)	100 more per 1000 (from 172 fewer to 700 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	5/16 (31.3%)	5/15 (33.3%)	RR 0.94 (0.34 to 2.6)	20 fewer per 1000 (from 220 fewer to 533 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Carbamazepine	RR (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	4/44 (9.10)	8/50 (20%)	RR 0.45 (0.15 to 1.35)	110 fewer per 1000 (from 170 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	7/44 (15.9%)	11/50 (22%)	RR 0.72 (0.31 to 1.7)	62 fewer per 1000 (from 152 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (COXHEAD1992)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/16 (6.3%)	2/15 (13.3%)	RR 0.47 (0.05 to 4.65)	71 fewer per 1000 (from 127 fewer to 487 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (HARTONG2003, KLEINDIENST2000, WOLF1997)												
3	randomised trials	serious[1]	no serious inconsistency	very serious[4]	serious[2]	reporting bias[3]	36/186	58/190	RR 0.62 (0.23	116 fewer per 1000	⊕OOO	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Carbamazepine	RR (95% CI)	Absolute		
							(19.4%)	(30.5%)	to 1.66)	(from 235 fewer to 201 more)	VERY LOW	
Discontinuation (due to side effects) (HARTONG2003, WOLF1997)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	17/128	9/134	RR 1.96 (0.9 to 4.27)	64 more per 1000 (from 7 fewer to 220 more)	⊕OOO	CRITICAL
							(13.3%)	(6.7%)			VERY LOW	
Discontinuation (due to side effects) (COXHEAD1992)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/16	2/5	RR 0.19 (0.01 to 3.63)	108 fewer per 1000 (from 132 fewer to 351 more)	⊕OOO	CRITICAL
							0%	(13.3%)			VERY LOW	

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium compared with valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Valproate	Relative (95% CI)	Absolute		
Relapse (any) (CALABRESE2005C)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	18/32 (56.3%)	14/28 (50%)	RR 1.12 (0.7 to 1.82)	60 more per 1000 (from 150 fewer to 410 more)	⊕OOO VERY LOW	CRITICAL
Relapse (any) (GEDDES2010)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	64/110 (58.2%)	75/110 (68.2%)	RR 0.85 (0.7 to 1.05)	102 fewer per 1000 (from 205 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Relapse (any) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	28/91 (30.8%)	45/187 (24.1%)	RR 1.28 (0.86 to 1.91)	67 more per 1000 (from 34 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	22/110 (20%)	25/110 (22.7%)	RR 0.88 (0.53 to 1.46)	27 fewer per 1000 (from 107	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Valproate	Relative (95% CI)	Absolute		
										fewer to 105 more)		
Relapse (mania) (GEDDES2010)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	40/110 (36.4%)	49/110 (44.5%)	RR 0.82 (0.59 to 1.13)	80 fewer per 1000 (from 183 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
Relapse (mania) (CALABRESE2005C)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	7/32 (21.9%)	6/28 (21.4%)	RR 1.02 (0.39 to 2.68)	4 more per 1000 (from 131 fewer to 360 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	19/91 (20.9%)	33/187 (17.6%)	RR 1.18 (0.71 to 1.96)	32 more per 1000 (from 51 fewer to 169 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (GEDDES2010)												
1	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	35/110 (31.8%)	50/110 (45.5%)	RR 0.7 (0.5 to 0.99)	136 fewer per 1000	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Valproate	Relative (95% CI)	Absolute		
		bias								(from 5 fewer to 227 fewer)		
Relapse (depression) (CALABRESE2005C)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	11/32 (34.4%)	8/28 (28.6%)	RR 1.2 (0.56 to 2.56)	57 more per 1000 (from 126 fewer to 446 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	9/91 (9.9%)	12/187 (6.4%)	RR 1.54 (0.67 to 3.52)	35 more per 1000 (from 21 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (BOWDEN2000)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	41/91 (45.1%)	71/187 (38%)	RR 1.19 (0.89 to 1.59)	72 more per 1000 (from 42 fewer to 224 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (CALABRESE2005c)												
1	randomised	serious[1]	no serious	no serious	very	reporting bias[3]	10/32	6/28	RR 1.46	99 more	⊕OOO	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Valproate	Relative (95% CI)	Absolute		
	trials		inconsistency	indirectness	serious[2]		(31.3%)	(21.4%)	(0.61 to 3.5)	per 1000 (from 84 fewer to 536 more)	VERY LOW	
Discontinuation (for any reason) (GEDDES2010)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	54/110 (49.1%)	53/110 (48.2%)	RR 1.02 (0.78 to 1.34)	10 more per 1000 (from 106 fewer to 164 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects) (GEDDES2010)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	10/110 (9.1%)	6/110 (5.5%)	RR 1.67 (0.63 to 4.43)	37 more per 1000 (from 20 fewer to 187 more)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium compared with lithium and valproate combination

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Lithium + Valproate	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	64/110 (58.2%)	58/110 (52.7%)	RR 1.1 (0.87 to 1.4)	53 more per 1000 (from 69 fewer to 211 more)	⊕⊕OO LOW	CRITICAL
Relapse (mania)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	40/110 (36.4%)	30/110 (27.3%)	RR 1.33 (0.9 to 1.97)	90 more per 1000 (from 27 fewer to 265 more)	⊕⊕OO LOW	CRITICAL
Relapse (depression)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	35/110 (31.8%)	39/110 (35.5%)	RR 0.9 (0.62 to 1.3)	35 fewer per 1000 (from 135 fewer to 106 more)	⊕⊕OO LOW	CRITICAL
Hospitalisation												
1	randomised	no	no serious	no serious	serious[2]	reporting bias[3]	22/110	16/110	RR 1.38	55 more	⊕⊕OO	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Lithium + Valproate	Relative (95% CI)	Absolute		
	trials	serious risk of bias	inconsistency	indirectness			(20%)	(14.5%)	(0.76 to 2.47)	per 1000 (from 35 fewer to 214 more)	LOW	
Discontinuation (for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	54/110 (49.1%)	56/110 (50.9%)	RR 0.96 (0.74 to 1.26)	20 fewer per 1000 (from 132 fewer to 132 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	10/110 (9.1%)	16/110 (14.5%)	RR 0.62 (0.3 to 1.32)	55 fewer per 1000 (from 102 fewer to 47 more)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Valproate compared with lithium and valproate combination

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Lithium + Valproate	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	75/110 (68.2%)	58/110 (52.7%)	RR 1.29 (1.04 to 1.61)	153 more per 1000 (from 21 more to 322 more)	⊕⊕OO LOW	CRITICAL
Hospitalisation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	25/110 (22.7%)	16/110 (14.5%)	RR 1.56 (0.88 to 2.76)	81 more per 1000 (from 17 fewer to 256 more)	⊕⊕OO LOW	CRITICAL
Relapse (mania)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	49/110 (44.5%)	30/110 (27.3%)	RR 1.63 (1.13 to 2.36)	172 more per 1000 (from 35 more to 371 more)	⊕⊕OO LOW	CRITICAL
Relapse (depression)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	50/110 (45.5%)	39/110 (35.5%)	RR 1.28 (0.93 to 1.77)	99 more per 1000 (from 25 fewer to 273 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Lithium + Valproate	Relative (95% CI)	Absolute		
Discontinuation (for any reason)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	53/110 (48.2%)	56/110 (50.9%)	RR 0.95 (0.72 to 1.24)	25 fewer per 1000 (from 143 fewer to 122 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	53/110 (48.2%)	56/110 (50.9%)	RR 0.95 (0.72 to 1.24)	25 fewer per 1000 (from 143 fewer to 122 more)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium compared with lamotrigine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Lamotrigine	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	31/60 (51.7%)	33/62 (53.2%)	RR 0.97 (0.69 to 1.36)	16 fewer per 1000 (from 165 fewer to 192 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	19/60 (31.7%)	18/62 (29%)	RR 1.09 (0.64 to 1.87)	26 more per 1000 (from 105 fewer to 253 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lithium compared with quetiapine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	Quetiapine	Relative (95% CI)	Absolute		
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	99/364 (27.2%)	68/404 (16.8%)	RR 1.62 (1.23 to 2.13)	104 more per 1000 (from 39 more to 190 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/364 (5.5%)	14/404 (3.5%)	RR 1.59 (0.81 to 3.09)	20 more per 1000 (from 7 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Olanzapine compared with lithium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine	Lithium	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	53/217 (24.4%)	69/214 (32.2%)	RR 0.76 (0.56 to 1.03)	77 fewer per 1000 (from 142 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	25/217 (11.5%)	53/214 (24.8%)	RR 0.47 (0.3 to 0.72)	131 fewer per 1000 (from 69 fewer to 173 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	28/217 (12.9%)	16/214 (7.5%)	RR 1.73 (0.96 to 3.1)	55 more per 1000 (from 3 fewer to 157 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	116/217 (53.5%)	144/214 (67.3%)	RR 0.79 (0.68 to 0.93)	141 fewer per 1000	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine	Lithium	Relative (95% CI)	Absolute		
										(from 47 fewer to 215 fewer)		
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	41/217 (18.9%)	55/214 (25.7%)	RR 0.74 (0.51 to 1.05)	67 fewer per 1000 (from 126 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Weight (mean change in kg; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	217	214	-	SMD 0.07 higher (0.12 lower to 0.26 higher)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Aripiprazole compared with placebo (all participants taking lamotrigine)

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		
Relapse (any)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	40/178 (22.5%)	56/173 (32.4%	RR 0.69 (0.49 to 0.98)	100 fewer per 1000 (from 6 fewer to 165 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	16/178 (9%)	27/173 (15.6%)	RR 0.58 (0.32 to 1.03)	66 fewer per 1000 (from 106 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	24/178 (13.5%)	29/173 (16.8%)	RR 0.8 (0.49 to 1.32)	34 fewer per 1000 (from 85 fewer to 54 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	113/178 (63.5%)	120/173 (69.4%)	RR 0.92 (0.79 to 1.06)	55 fewer per 1000 (from 146	⊕OOO VERY LOW	CRITICAL

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		
										fewer to 42 more)		
Discontinuation (due to side effects)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	16/178 (9%)	10/173 (5.8%)	RR 1.56 (0.73 to 3.33)	32 more per 1000 (from 16 fewer to 135 more)	⊕OOO VERY LOW	CRITICAL
Weight (mean change in kg; better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	160	161	-	SMD 0.08 higher (0.14 lower to 0.29 higher)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Aripiprazole compared with placebo (all participants taking lithium or valproate)

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		
Relapse (any)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[2]	25/168 (14.9%)	43/169 (25.4%)	RR 0.58 (0.38 to 0.91)	107 fewer per 1000 (from 23 fewer to 158 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	11/168 (6.5%)	25/169 (14.8%)	RR 0.44 (0.23 to 0.87)	83 fewer per 1000 (from 19 fewer to 114 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[2]	14/168 (8.3%)	18/169 (10.7%)	RR 0.78 (0.4 to 1.52)	23 fewer per 1000 (from 64 fewer to 55 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	65/168 (38.7%)	80/169 (47.3%)	RR 0.82 (0.64 to 1.05)	85 fewer per 1000 (from 170	⊕OOO VERY LOW	CRITICAL

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		
										fewer to 24 more)		
Discontinuation (due to side effects)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	19/168 (11.3%)	15/169 (8.9%)	RR 1.27 (0.67 to 2.42)	24 more per 1000 (from 29 fewer to 126 more)	⊕OOO VERY LOW	CRITICAL
Weight (mean change in kg; better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	160	161	-	SMD 0.08 higher (0.14 lower to 0.29 higher)	⊕OOO VERY LOW	CRITICAL
Suicide												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/168 (0.6%)	0/169 (0%)	RR 3.04 (0.12 to 75.05)	-	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Olanzapine compared with placebo (all participants taking lithium or valproate)

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		
Relapse (any)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	11/30 (36.7%)	21/38 (55.3%)	RR 0.66 (0.38 to 1.15)	188 fewer per 1000 (from 343 fewer to 83 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	6/30 (20%)	11/38 (28.9%)	RR 0.69 (0.29 to 1.65)	90 fewer per 1000 (from 206 fewer to 188 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	7/30 (23.3%)	15/38 (39.5%)	RR 0.59 (0.28 to 1.26)	162 fewer per 1000 (from 284 fewer to 103 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												

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		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	35/51 (68.6%)	43/48 (89.6%)	RR 0.77 (0.62 to 0.94)	206 fewer per 1000 (from 54 fewer to 340 fewer)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	5/51 (9.8%)	8/48 (16.7%)	RR 0.59 (0.21 to 1.67)	68 fewer per 1000 (from 132 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Olanzapine compared with placebo

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**		
Relapse (any)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	32/137 (23.4%)	77/138 (55.8%)	RR 0.42 (0.3 to 0.59)	324 fewer per 1000 (from 229 fewer to 391 fewer)	⊕⊕OO LOW	CRITICAL
Relapse (mania)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[2]	20/137 (14.6%)	54/138 (39.1%)	RR 0.37 (0.24 to 0.59)	247 fewer per 1000 (from 160 fewer to 297 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	12/137 (8.8%)	23/138 (16.7%)	RR 0.53 (0.27 to 1.01)	78 fewer per 1000 (from 122 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (for any reason)												

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**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	25/138 (18.1%)	23/140 (16.4%)	RR 1.1 (0.66 to 1.85)	16 more per 1000 (from 56 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	4/138 (2.9%)	2/140 (1.4%)	RR 2.03 (0.38 to 10.9)	15 more per 1000 (from 9 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Paliperidone compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paliperidone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse (any)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	66/152 (43.4%)	77/148 (52%)	RR 0.83 (0.66 to 1.06)	88 fewer per 1000 (from 177 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	56/152 (36.8%)	52/148 (35.1%)	RR 1.05 (0.78 to 1.42)	18 more per 1000 (from 77 fewer to 148 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	5/152 (3.3%)	4/148 (2.7%)	RR 1.22 (0.33 to 4.44)	6 more per 1000 (from 18 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
Weight (mean change in kg; better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	146	144	-	SMD 0.21 higher (0.03 lower to 0.44	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paliperidone	Placebo	Relative (95% CI)	Absolute		
										higher)		

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Quetiapine compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
Relapse (any)(YOUNG2012)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	69/291 (23.7%)	118/294 (40.1%)	RR 0.59 (0.46 to 0.76)	165 fewer per 1000 (from 96 fewer to 217 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (YOUNG2012)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	170/291 (58.4%)	140/294 (47.6%)	RR 1.23 (1.05 to 1.43)	110 more per 1000 (from 24 more to 205 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (for any reason) (WEISLER2011)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	68/404 (16.8%)	80/404 (19.8%)	RR 0.85 (0.63 to 1.14)	30 fewer per 1000 (from 73 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects) (YOUNG2012)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	12/291 (4.1%)	10/294 (3.4%)	RR 1.21 (0.53 to 2.76)	7 more per 1000 (from 16 fewer to	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
										60 more)		
Discontinuation (due to side effects) (WEISLER2011)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	14/404 (3.5%)	10/404 (2.5%)	RR 1.4 (0.63 to 3.11)	10 more per 1000 (from 9 fewer to 52 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Quetiapine compared with placebo (all participants taking lithium or valproate)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
Relapse (any)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	125/646 (19.3%)	343/680 (50.4%)	RR 0.38 (0.32 to 0.46)	313 fewer per 1000 (from 272 fewer to 343 fewer)	⊕⊕OO LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	197/646 (30.5%)	134/680 (19.7%)	RR 1.53 (1.24 to 1.89)	104 more per 1000 (from 47 more to 175 more)	⊕⊕OO LOW	CRITICAL
Discontinuation (due to side effects)												
2	randomised trials	serious[1]	serious[5]	no serious indirectness	serious[2]	reporting bias[3]	42/646 (6.5%)	14/680 (2.1%)	RR 2.53 (0.75 to 8.53)	32 more per 1000 (from 5 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL
Weight (mean change in kg)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	310	313	-	SMD 0.43 higher	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
										(0.27 to 0.59 higher)		
Suicide												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/336 (0.3%)	1/367 (0.27%)	RR 1.09 (0.07 to 16.79)	0 more per 1000 (from 3 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/336 (0%)	2/367 (0.54%)	RR 0.22 (0.01 to 4.45)	4 fewer per 1000 (from 5 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Quetiapine compared with valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quetiapine**	**Valproate**	**Relative (95% CI)**	**Absolute**		
Discontinuation (for any reason)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	15/21 (71.4%)	12/16 (75%)	RR 0.95 (0.64 to 1.41)	38 fewer per 1000 (from 270 fewer to 307 more)	⊕OOO VERY LOW	CRITICAL

Risperidone long-acting injectable compared with placebo injection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Placebo	Relative (95% CI)	Absolute		
Relapse (any) (VIETA2012)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	52/135 (38.5%)	77/138 (55.8%)	RR 0.69 (0.53 to 0.9)	173 fewer per 1000 (from 56 fewer to 262 fewer)	⊕⊕OO LOW	CRITICAL
Relapse (any) (QUIROZ2010)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	45/154 (29.2%)	78/149 (52.3%)	RR 0.56 (0.42 to 0.75)	230 fewer per 1000 (from 131 fewer to 304 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania) (VIETA2012)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	27/135 (20%)	54/138 (39.1%)	RR 0.51 (0.34 to 0.76)	192 fewer per 1000 (from 94 fewer to 258 fewer)	⊕⊕OO LOW	CRITICAL
Relapse (mania) (QUIROZ2010)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	45/154 (29.2%)	78/149 (52.3%)	RR 0.56 (0.42 to 0.75)	230 fewer per 1000 (from 131 fewer to 304 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (depression) (VIETA2012)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	25/135 (18.5%)	23/138 (16.7%)	RR 1.11 (0.66 to 1.86)	18 more per 1000 (from 57 fewer to 143 more)	⊕⊕OO LOW	CRITICAL
Relapse (depression) (QUIROZ2010)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	45/154 (29.2%)	78/149 (52.3%)	RR 0.56 (0.42 to 0.75)	230 fewer per 1000 (from 131 fewer to 304 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason) (VIETA2012)												
1	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	30/137 (21.9%)	23/140 (16.4%)	RR 1.33 (0.82 to 2.17)	54 more per 1000 (from 30	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Placebo	Relative (95% CI)	Absolute		
		bias								fewer to 192 more)		
Discontinuation (for any reason) (QUIROZ2010)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	37/154 (24%)	40/149 (26.8%)	RR 0.89 (0.61 to 1.32)	30 fewer per 1000 (from 105 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects) (VIETA2012)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	6/137 (4.4%)	2/140 (1.4%)	RR 3.07 (0.63 to 14.93)	30 more per 1000 (from 5 fewer to 199 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects) (QUIROZ2010)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/154 (0.65%)	1/149 (0.67%)	RR 0.97 (0.06 to 15.33)	0 fewer per 1000 (from 6 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Risperidone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse (any)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	15/65 (23.1%)	27/59 (45.8%)	RR 0.5 (0.3 to 0.85)	229 fewer per 1000 (from 69 fewer to 320 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	7/65 (10.80)	16/59 (27.1%)	RR 0.4 (0.18 to 0.9)	163 fewer per 1000 (from 27 fewer to 222 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	8/65 (12.3%)	11/59 (18.6%)	RR 0.66 (0.29 to 1.53)	63 fewer per 1000 (from 132 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	14/65 (21.5%)	Oct-59 (16.9%)	RR 1.27 (0.61 to	46 more per 1000	⊕OOO VERY	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Placebo	Relative (95% CI)	Absolute		
									2.64)	(from 66 fewer to 278 more)	LOW	
Discontinuation (due to side effects)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	3/65 (4.6%)	1/59 (1.7%)	RR 2.72 (0.29 to 25.47)	29 more per 1000 (from 12 fewer to 415 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Risperidone long-acting injectable with treatment as usual compared with treatment as usual alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Risperidone + TAU**	**TAU**	**Relative (95% CI)**	**Absolute**		
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	9/25 (36%)	6/25 (24%)	RR 1.5 (0.63 to 3.59)	120 more per 1000 (from 89 fewer to 622 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	-	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Few trials in this area have been registered
[4] Substantial and significant heterogeneity.

Lamotrigine compared with placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamotrigine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse (any)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	143/280 (51.1%)	115/191 (60.2%)	RR 0.82 (0.59 to 1.14)	108 fewer per 1000 (from 247 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	20/59 (33.9%)	28/70 (40%)	RR 0.85 (0.54 to 1.34)	60 fewer per 1000 (from 184 fewer to 136 more)	⊕⊕OO LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	8/59 (13.6%)	21/70 (30%)	RR 0.45 (0.22 to 0.94)	165 fewer per 1000 (from 18 fewer to 234 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	96/280 (34.3%)	64/191 (33.5%)	RR 1.14 (0.64 to 2.06)	47 more per 1000 (from 121 fewer to 355 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamotrigine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	26/280 (9.3%)	22/191 (11.5%)	RR 0.84 (0.48 to 1.46)	18 fewer per 1000 (from 60 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Global Assessment Scale (Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[4]	219	184	-	SMD -0.21 lower (-0.56 lower to 0.15 higher)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Oxcarbazepine compared with placebo (all participants were taking lithium)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxcarbazepine	Placebo	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	8/26 (30.8%)	18/29 (62.1%)	RR 0.5 (0.26 to 0.94)	310 fewer per 1000 (from 37 fewer to 459 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	5/26 (19.2%)	9/29 (31%)	RR 0.62 (0.24 to 1.61)	118 fewer per 1000 (from 236 fewer to 189 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	3/26 (11.5%)	9/29 - (31%)	RR 0.37 (0.11 to 1.23)	196 fewer per 1000 (from 276 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxcarbazepine	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	10/26 (38.5%)	10/29 (34.5%)	RR 1.12 (0.55 to 2.24)	41 more per 1000 (from 155 fewer to 428 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	3/26 (11.5%)	2/29 (6.9%)	RR 1.67 (0.3 to 9.24)	46 more per 1000 (from 48 fewer to 568 more)	⊕OOO VERY LOW	CRITICAL
Psychosocial functioning (GAF; better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	26	29	-	SMD 0.27 higher (0.26 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Weight (Mean change in kg; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	26	29	-	SMD 0.16 lower (0.69 lower to 0.37 higher)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Valproate compared with placebo

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**		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	45/187 (24.1%)	36/94 (38.3%)	RR 0.63 (0.44 to 0.9)	142 fewer per 1000 (from 38 fewer to 214 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	33/187 (17.6%)	21/94 (22.3%)	RR 0.79 (0.49 to 1.29)	47 fewer per 1000 (from 114 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[4]	12/187 (6.4%)	15/94 (16%)	RR 0.4 (0.2 to 0.82)	96 fewer per 1000 (from 29 fewer to 128 fewer)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	71/187 (38%)	35/94 (37.2%)	RR 1.02 (0.74 to 1.4)	7 more per 1000 (from 97 fewer to 149	⊕OOO VERY LOW	CRITICAL

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		
										more)		
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	41/187 (21.9%)	Nov-94 (11.7%)	RR 1.87 (1.01 to 3.47)	102 more per 1000 (from 1 more to 289 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Gabapentin compared with placebo (all participants were taking a mood stabiliser)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	Gabapentin	Placebo	Relative (95% CI)	Absolute		
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	7/13 (53.8%)	6/12 (50%)	RR 1.08 (0.51 to 2.3)	40 more per 1000 (from 245 fewer to 650 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	1/13 (7.7%)	1/12 (8.3%)	RR 0.92 (0.06 to 13.18)	7 fewer per 1000 (from 78 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Imipramine in combination with lithium compared with lithium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine + lithium	Lithium	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	18/36 (50%)	23/42 (54.8%)	RR 0.91 (0.6 to 1.4)	49 fewer per 1000 (from 219 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	10/36 (27.8%)	11/42 (6.2%)	RR 1.06 (0.51 to 2.2)	16 more per 1000 (from 128 fewer to 314 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	8/36 (22.2%)	12/42 (28.6%)	RR 0.78 (0.36 to 1.69)	63 fewer per 1000 (from 183 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	2/36 (5.6%)	0/42 (0%)	RR 5.81 (0.29 to 117.23)	-	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Imipramine and lithium compared with imipramine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine + lithium	Imipramine	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	18/36 (50%)	29/36 (80.6%)	RR 0.62 (0.43 to 0.89)	306 fewer per 1000 (from 89 fewer to 459 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	10/36 (27.8%)	19/36 (52.8%)	RR 0.53 (0.29 to 0.97)	248 fewer per 1000 (from 16 fewer to 375 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	8/36 (22.2%)	10/36 (27.8%)	RR 0.8 (0.36 to 1.79)	56 fewer per 1000 (from 178 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												

1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	2/36 (5.6%)	0/42 (0%)	RR 5.81 (0.29 to 117.23)	-	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Imipramine compared with lithium

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Imipramine**	**Lithium**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	29/36 (80.6%)	23/42 (54.8%)	RR 1.47 (1.07 to 2.02)	257 more per 1000 (from 38 more to 559 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	19/36 (52.8%)	11/42 (26.2%)	RR 2.02 (1.11 to 3.65)	267 more per 1000 (from 29 more to 694 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	10/36 (27.8%)	12/42 (28.6%)	RR 0.97 (0.48 to 1.98)	9 fewer per 1000 (from 149 fewer to 280 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/36 (0%)	0/42 (0%)	not pooled	not pooled	⊕OOO VERY LOW	CRITICAL

1 Risk of bias in several domains.
2 Substantial and significant heterogeneity.
3 Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
4 Few trials in this area have been registered

Imipramine compared with placebo (all participants were taking lithium)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine	Placebo	Relative (95% CI)	Absolute		
Relapse (any)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	12/37 (32.4%)	8/38 (21.1%)	RR 1.54 (0.71 to 3.33)	114 more per 1000 (from 61 fewer to 491 more)	⊕OOO VERY LOW	CRITICAL
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	9/37 (24.3%)	5/38 (10.5%)	RR 2.31 (0.78 to 6.85)	138 more per 1000 (from 23 fewer to 616 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	3/37 (8.1%)	5/38 (10.5%)	RR 0.77 (0.18 to 3.21)	24 fewer per 1000 (from 86 fewer to 233 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	25/37 (67.6%)	30/38 (78.9%)	RR 0.86 (0.65 to 1.13)	111 fewer per 1000 (from 276	⊕OOO VERY LOW	CRITICAL

										fewer to 103 more)		
Discontinuation (due to side effects)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	1/37 (2.7%)	1/38 (2.6%)	RR 1.03 (0.07 to 15.82)	1 more per 1000 (from 24 fewer to 390 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered

Imipramine compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine	Placebo	Relative (95% CI)	Absolute		
Relapse (mania)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	6/13 (46.2%)	3/13 (23.1%)	RR 2 (0.63 to 6.34)	231 more per 1000 (from 85 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Relapse (depression)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/13 (0%)	5/13 (38.5%)	RR 0.09 (0.01 to 1.49)	350 fewer per 1000 (from 381 fewer to 188 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation (for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	7/13 (53.8%)	6/13 (46.2%)	RR 1.17 (0.54 to 2.53)	78 more per 1000 (from 212 fewer to 706 more)	⊕OOO VERY LOW	CRITICAL
Suicide												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	0/13 (0%)	1/13 (7.7%)	RR 0.33 (0.01 to 7.5)	52 fewer per 1000 (from 76 fewer to 500 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	2/13 (15.4%)	1/13 (7.7%)	RR 2 (0.21 to 19.44)	77 more per 1000 (from 61 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias in several domains.
[2] Substantial and significant heterogeneity.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Few trials in this area have been registered