# APPENDIX 21: INTERVENTIONS FOR LONG-TERM MANAGEMENT – FOREST PLOTS

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#### Abbreviations

**BRMaS** Bech-Rafaelsen Mania Scale **BRMeS** Bech-Rafaelsen Melancholia Scale

CGI(-BP, -C, -S) Clinical Global Impressions (-Bipolar, -Children, -Severity)

confidence interval CI

DSM(-III, -IV, -TR) Diagnostic and Statistical Manual of Mental Disorders (3rd edition, 4th edition, Text

Revision)

**ECT** electroconvulsive therapy

GAF Global Assessment of Functioning scale

**GAS** Global Assessment Scale

intravariance IV number of studies K

**MADRS** Montgomery Åsberg Depression Rating Scale

Mantel-Haenszel М-Н Mania Rating Scale **MRS** not reported NR RR risk ratio

SD standard deviation **TAU** treatment as usual

**YMRS** Young Mania Rating Scale

#### 1.1 LITHIUM

## 1.1.1 Outcomes for low dose of lithium compared with standard dose

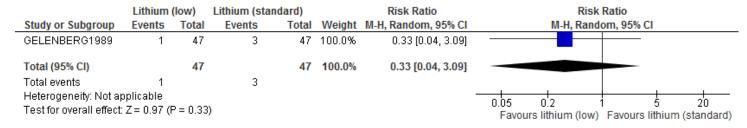
#### Number of participants who relapsed (any type)

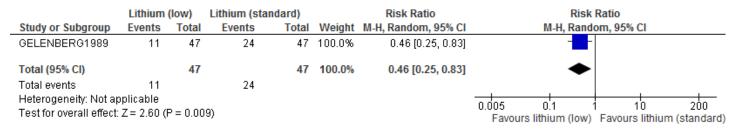


#### Number of participants who relapsed (mania)



#### Number of participants who relapsed (depression)





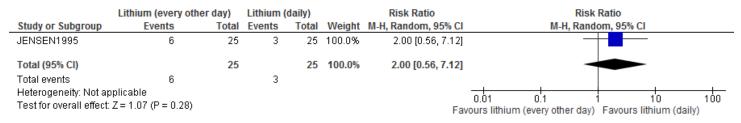
<sup>&</sup>lt;sup>1</sup> The definition of relapse differs between studies. Please refer to Table 1.6 below for a full definition.

## 1.1.2 Outcomes for lithium every other day compared with lithium daily

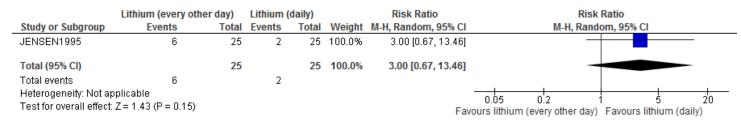
#### Number of participants who relapsed (any type)

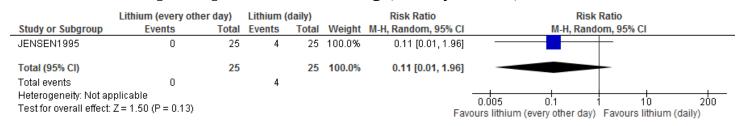


## 1.1.3 Number of participants who relapsed (mania)



## 1.1.4 Number of participants who relapsed (depression)





## 1.2 OUTCOMES FOR LITHIUM COMPARED WITH PLACEBO

## 1.2.1 Number of participants who relapsed (any type)

Study or Subgroup   Events   Total   Events   Total   Events   Total   Events   Total   Events   Eve		Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Total (95% CI)  Total (95% CI)  Total events  All 1 51 100.0% 0.41 [0.07, 2.43]  Total events  Test for overall effect: Z = 0.98 (P = 0.33)    Calcaborate   Find   Find	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Total (95% CI)	DUNNER1976	10	16	18	24	53.9%	0.83 [0.53, 1.30]	-
Total events	STALLONE1973	3	25	18	27	46.1%	0.18 [0.06, 0.54]	<del></del>
Heterogeneity: Tau² = 1.47; Chi² = 9.11, df = 1 (P = 0.003); i² = 89%   Test for overall effect: Z = 0.98 (P = 0.33)	Total (95% CI)		41		51	100.0%	0.41 [0.07, 2.43]	
Study or Subgroup   Lithium   Placebo   Risk Ratio   Risk Ratio   M-H, Random, 95% Cl	Total events	13		36				
Test for overall effect Z = 0.98 (P = 0.33)			0.05 0.2 1 5 20					
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl	Test for overall effect:	Z = 0.98 (						
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl		Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
BOWDEN2003	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	
Total (95% CI)         167         191         100.0%         0.71 [0.47, 1.06]           Total events         74         115           Heterogeneity: Tau² = 0.06; Chi² = 3.10, df = 1 (P = 0.08); I² = 68%         0.05 0.2 1 5 20           Test for overall effect: Z = 1.66 (P = 0.10)         Placebo         Risk Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% CI           PRIEN1973         43         101         84         104         100.0%         0.53 [0.41, 0.67]         M-H, Random, 95% CI           Total (95% CI)         101         104         100.0%         0.53 [0.41, 0.67]         Total (95% CI)         1.5 2         Favours lithium Favours placebo           Study or Subgroup         Events         Total         Placebo         Risk Ratio         Risk Ratio         Risk Ratio         Risk Ratio         M-H, Random, 95% CI         M-H, Random, 95% CI         M-H, Random, 95% CI         M-H, Random, 95% CI         Do.5 0.7 1 1.5 2         Favours lithium Favours placebo         Risk Ratio         M-H, Random, 95% CI         M-H, Ran	•							
Total events         74         115           Heterogeneity: Tau² = 0.06; Chi² = 3.10, df = 1 (P = 0.08); I² = 68%           Test for overall effect: Z = 1.66 (P = 0.10)           Risk Ratio           Study or Subgroup         Lithium         Placebo         Risk Ratio           PRIEN1973         43         101         84         100.0%         0.53 [0.41, 0.67]           Total (95% Cl)         101         104         100.0%         0.53 [0.41, 0.67]           Total events         43         84           Heterogeneity: Not applicable         Placebo         Risk Ratio           Total events         Total Events         Total Weight M-H, Random, 95% Cl           BOWDEN2000         28         91         94         100.0%         0.80 [0.54, 1.20]           Total (95% Cl)         91         94         100.0%         0.80 [0.54, 1.20]           Total (95% Cl)         91         94	CALABRESE2003	56	121	66	121	56.7%	0.85 [0.66, 1.09]	<b>=</b>
Total events         74         115           Heterogeneity: Tau² = 0.06; Chi² = 3.10, df = 1 (P = 0.08); I² = 68%           Test for overall effect: Z = 1.66 (P = 0.10)           Risk Ratio           Study or Subgroup         Lithium         Placebo         Risk Ratio           M-H, Random, 95% CI           PRIEN1973         43         101         104         100.0%         0.53 [0.41, 0.67]           Total (95% CI)         101         104         100.0%         0.53 [0.41, 0.67]           Total events         43         84           Heterogeneity: Not applicable         Risk Ratio           Total events         7 Total Events         Total Weight M-H, Random, 95% CI           BOWDEN2000         28         94         100.0%         0.80 [0.54, 1.20]           Total (95% CI)         91         94         100.0%         0.80 [0.54, 1.20]           Total (95% CI)         91         94								
Heterogeneity: Tau² = 0.06; Chi² = 3.10, df = 1 (P = 0.08); i² = 68%  Test for overall effect: Z = 1.66 (P = 0.10)    Comparison   Com			167		191	100.0%	0.71 [0.47, 1.06]	•
Test for overall effect: Z = 1.66 (P = 0.10)    Lithium   Placebo   Risk Ratio   Risk Ratio   M-H, Random, 95% CI								
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% CI					P = 0.0	8); I²= 68	%	0.05 0.2 1 5 20
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% CI	Test for overall effect:	Z = 1.66 (	P = 0.1	0)				
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% CI								
PRIEN1973         43         101         84         104         100.0%         0.53 [0.41, 0.67]           Total (95% CI)         101         104         100.0%         0.53 [0.41, 0.67]           Total events         43         84           Heterogeneity: Not applicable         0.5         0.7         1         1.5         2           Test for overall effect: Z = 5.12 (P < 0.00001)		Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Total events	Study or Subgroup					Weight		
Total events		Events	Total	Events	Total		M-H, Random, 95% CI	
Heterogeneity: Not applicable   Test for overall effect: Z = 5.12 (P < 0.00001)	PRIEN1973	Events	Total 101	Events	Total 104	100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67]	
Test for overall effect: Z = 5.12 (P < 0.00001)    Lithium   Placebo   Risk Ratio   Risk Ratio   M-H, Random, 95% CI	PRIEN1973 Total (95% CI)	Events 43	Total 101	Events 84	Total 104	100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67]	
Study or Subgroup   Lithium   Placebo   Risk Ratio   Risk Ratio   M-H, Random, 95% Cl	PRIEN1973  Total (95% CI)  Total events	43 43	Total 101	Events 84	Total 104	100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67]	
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% CI         M-H, Random, 95% CI           BOWDEN2000         28         91         36         94         100.0%         0.80 [0.54, 1.20]           Total (95% CI)         91         94         100.0%         0.80 [0.54, 1.20]           Total events         28         36           Heterogeneity: Not applicable         0.05         0.2         1         5         20	PRIEN1973  Total (95% CI)  Total events  Heterogeneity: Not as	43 pplicable	101 101	84 84	Total 104	100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67]	M-H, Random, 95% CI
BOWDEN2000 28 91 36 94 100.0% 0.80 [0.54, 1.20]  Total (95% CI) 91 94 100.0% 0.80 [0.54, 1.20]  Total events 28 36  Heterogeneity: Not applicable  Total for everyll effect 7 = 1.97 (D = 0.20)	PRIEN1973  Total (95% CI)  Total events  Heterogeneity: Not as	43 pplicable	101 101	84 84	Total 104	100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67]	M-H, Random, 95% CI
Total (95% CI) 91 94 100.0% 0.80 [0.54, 1.20]  Total events 28 36  Heterogeneity: Not applicable  Test for everyll effect: 7= 1.97 (R = 0.20)	PRIEN1973  Total (95% CI)  Total events  Heterogeneity: Not as	43 pplicable Z = 5.12 (	Total 101 101 P < 0.0	84 84 0001)	104 104	100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67]	M-H, Random, 95% CI  O.5 0.7 1 1.5 2  Favours lithium Favours placebo
Total events 28 36 Heterogeneity: Not applicable 0.05 0.2 1 5 20	PRIEN1973  Total (95% CI)  Total events  Heterogeneity: Not ap  Test for overall effect:	43 pplicable Z = 5.12 ( Lithiu	Total 101 101 P < 0.0	84 84 00001)	Total 104 104 bo	100.0% 100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67] Risk Ratio	M-H, Random, 95% CI  0.5 0.7 1.5 2 Favours lithium Favours placebo  Risk Ratio
Total events 28 36 Heterogeneity: Not applicable 0.05 0.2 1 5 20	PRIEN1973  Total (95% CI)  Total events Heterogeneity: Not as Test for overall effect:  Study or Subgroup	43 pplicable Z = 5.12 ( Lithiu Events	Total 101 101 P < 0.0 m Total	84 84 00001) Place Events	Total 104 104 bo Total	100.0% 100.0% Weight	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67] Risk Ratio M-H, Random, 95% CI	M-H, Random, 95% CI  0.5 0.7 1.5 2 Favours lithium Favours placebo  Risk Ratio
Heterogeneity: Not applicable 0.05 0.2 1 5 20	PRIEN1973  Total (95% CI) Total events Heterogeneity: Not as Test for overall effect:  Study or Subgroup BOWDEN2000	43 pplicable Z = 5.12 ( Lithiu Events	Total 101 101 P < 0.0 m Total 91	84 84 00001) Place Events	Total 104 104 bo Total 94	100.0% 100.0% Weight 100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67]  Risk Ratio M-H, Random, 95% CI 0.80 [0.54, 1.20]	M-H, Random, 95% CI  0.5 0.7 1.5 2 Favours lithium Favours placebo  Risk Ratio
Toot for our roll off cet 7 - 4.07 /D = 0.203	PRIEN1973  Total (95% CI) Total events Heterogeneity: Not as Test for overall effect:  Study or Subgroup BOWDEN2000  Total (95% CI)	43 pplicable Z = 5.12 ( Lithiu Events	Total 101 101 P < 0.0 m Total 91	84 84 00001) Place Events 36	Total 104 104 bo Total 94	100.0% 100.0% Weight 100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67]  Risk Ratio M-H, Random, 95% CI 0.80 [0.54, 1.20]	M-H, Random, 95% CI  0.5 0.7 1.5 2 Favours lithium Favours placebo  Risk Ratio
Favours lithium Favours placebo	PRIEN1973  Total (95% CI) Total events Heterogeneity: Not ap Test for overall effect:  Study or Subgroup BOWDEN2000  Total (95% CI) Total events	43 pplicable Z = 5.12 ( Lithiu Events 28	Total 101 101 P < 0.0 m Total 91	84 84 00001) Place Events 36	Total 104 104 bo Total 94	100.0% 100.0% Weight 100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67]  Risk Ratio M-H, Random, 95% CI 0.80 [0.54, 1.20]	M-H, Random, 95% CI  0.5 0.7 1.5 2 Favours lithium Favours placebo  Risk Ratio M-H, Random, 95% CI
	PRIEN1973  Total (95% CI) Total events Heterogeneity: Not ap Test for overall effect:  Study or Subgroup BOWDEN2000  Total (95% CI) Total events Heterogeneity: Not ap	43 pplicable Z = 5.12 ( Lithiu Events 28 pplicable	Total 101 P < 0.0 m Total 91	84 84 00001) Place Events 36	Total 104 104 bo Total 94	100.0% 100.0% Weight 100.0%	M-H, Random, 95% CI 0.53 [0.41, 0.67] 0.53 [0.41, 0.67]  Risk Ratio M-H, Random, 95% CI 0.80 [0.54, 1.20]	M-H, Random, 95% CI  0.5 0.7 1 1.5 2 Favours lithium Favours placebo  Risk Ratio M-H, Random, 95% CI

## Number of participants who relapsed (mania)

	•			•			
	Lithiu		Place			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2000	19	91	21	94	100.0%	0.93 [0.54, 1.62]	<b>—</b>
Total (95% CI)		91		94	100.0%	0.93 [0.54, 1.62]	<b>*</b>
Total events	19		21				
Heterogeneity: Not ap	•						0.05 0.2 1 5 20
Test for overall effect:	Z = 0.24 (		Favours lithium Favours placebo				
	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2003	8	46	28	70	100.0%	0.43 [0.22, 0.87]	-
Total (95% CI)		46		70	100.0%	0.43 [0.22, 0.87]	•
Total events	8		28			- / -	
Heterogeneity: Not ap	plicable						
Test for overall effect:	-	P = 0.0	)2)				0.05 0.2 1 5 20
			•				Favours lithium Favours placebo
	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
DUNNER1976	1	16	6	24	100.0%	0.25 [0.03, 1.89]	
Total (95% CI)		16		24	100.0%	0.25 [0.03, 1.89]	
Total events	1		6				
Heterogeneity: Not ap	plicable						
Test for overall effect:	-	(P = 0.1	8)				0.05 0.2 1 5 20 Favours lithium Favours placebo
	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRIEN1973B	2	18	3	13	100.0%	0.48 [0.09, 2.48]	
Total (95% CI)		18		13	100.0%	0.48 [0.09, 2.48]	
Total events	2		3		1001070	0110 [0100, 2110]	
Heterogeneity: Not ap	_		,				
Test for overall effect:	-	P=n3	38)				0.05 0.2 1 5 20
1 COLIOI OVCIAII CIICUL	2-0.01 (	, - 0.0	,0,				Favours lithium Favours placebo
	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total			Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRIEN1973	27	101	78	104	100.0%	0.36 [0.25, 0.50]	-
Total (95% CI)		101		104	100.0%	0.36 [0.25, 0.50]	•
Total events	27		78				
Heterogeneity: Not ap			-				
Test for overall effect:	•	P < 0.0	00001)				0.2 0.5 1 2 5 Favours lithium Favours placebo
		-					ravours minum ravours placebo

## Number of participants who relapsed (depression)

Study on Subanna	Lithiu		Place		W-:-b4	Risk Ratio	W CI	Risk Ratio
Study or Subgroup						M-H, Random, 95		M-H, Random, 95% CI
BOWDEN2000	9	91	15	94	100.0%	0.62 [0.29, 1	1.34]	
Total (95% CI)		91		94	100.0%	0.62 [0.29, 1	1.34]	•
Total events			15					
Heterogeneity: Not a							_	0.05 0.2 1 5 20
Test for overall effect	Z = 1.21 (	P = 0.2	(3)					Favours lithium Favours placebo
	Lithium	Р	lacebo		F	Risk Ratio		Risk Ratio
Study or Subgroup				l Wei		Random, 95% CI		M-H, Random, 95% CI
BOWDEN2003		46		100.0		0.72 [0.38, 1.39]		<del>-</del>
Total (95% CI)		46		100.	0%	0.72 [0.38, 1.39]		<b>→</b>
Total events	10		21					
Heterogeneity: Not app		0.00				_	0.05	0.2 1 5 20
Test for overall effect: Z	= 0.96 (P =	0.33)					Favours	s lithium (low) Favours lithium(standard)
	Lithiu	m	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95	5% CI	M-H, Random, 95% CI
DUNNER1976	9	16	12	24	100.0%	1.13 [0.62, 3	2.03]	
							•	T
Total (95% CI)		16		24	100.0%	1.13 [0.62, 2	2.03]	<b>*</b>
Total events	9		12					
Heterogeneity: Not a	pplicable						-	0.05 0.2 1 5 20
Test for overall effect	Z = 0.39 (	P = 0.7	'0)					Favours lithium Favours placebo
	Lithiu	m	Place	ho		Risk Ratio		Risk Ratio
Study or Subgroup					Weight	M-H, Random, 95	5% CI	M-H, Random, 95% CI
PRIEN1973B	2	18	5		100.0%			m-n, Kandoni, 93% Ci
FRIENTS/3D	2	10	9	13	100.070	0.29 [0.07, 1	1.20]	_
Total (95% CI)		18		13	100.0%	0.29 [0.07, 1	1.26]	
Total events	2		5					
Heterogeneity: Not a	pplicable						-	0.05 0.2 1 5 20
Test for overall effect	: Z = 1.65 (I	P = 0.1	0)					0.05 0.2 1 5 20 Favours lithium Favours placebo
	Lithiu		Placel			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95	% CI	M-H, Random, 95% CI
PRIEN1973	43	101	84	104	100.0%	0.53 [0.41, 0	0.67]	_
Total (95% CI)		101		104	100.0%	0.53 [0.41, 0	1 671	
Total events	43	.01	84	104	100.070	0.55 [0.41, 0	]	
Heterogeneity: Not a			04				_	
Test for overall effect		pynn	100043					0.5 0.7 1 1.5 2
restion overall effect	. 2 – 3.12 (1	- 0.0	,5001)					Favours lithium Favours placebo

Study or Subgroup	Number of participants discontinuing (for any reason)												
DUNIER1976   3   16   4   24   41.5%   1.13   0.29, 4.37		Lithiu	m	Place	bo		Risk Ratio	Risk Ratio					
STALLONE1973   6   25   4   27   58.5%   1.62   0.52   5.08	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI					
Total (95% CI)	DUNNER1976	3	16	4	24	41.5%	1.13 [0.29, 4.37]	<del>-</del>					
Total events	STALLONE1973	6	25	4	27	58.5%	1.62 [0.52, 5.08]	<del>-</del>					
Total events													
Heterogeneity: Tau" = 0.00; Chi" = 0.16, off = 1 (P = 0.69); P = 0.5   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.74 (P = 0.46)   Test for overall effect: Z = 0.09 (P = 0.27)   Test for overall effect: Z = 0.13; Chi" = 4.39, df = 1 (P = 0.04); P = 77.5   Test for overall effect: Z = 1.09 (P = 0.27)   Test for overall effect: Z = 1.09 (P = 0.27)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 1.09 (P = 0.28)   Test for overall effect: Z = 4.31 (P < 0.0001)   Test for overall effect: Z = 4.31 (P < 0.0001)   Test for overall effect: Z = 4.31 (P < 0.0001)   Test for overall effect: Z = 4.31 (P < 0.0001)   Test for overall effect: Z = 0.001   Test f			41	_	51	100.0%	1.39 [0.58, 3.34]	<b>—</b>					
Study or Subgroup   Lithium   Placebo   Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% CI   M-H, Random, 95% CI		-		_									
Study or Subgroup   Cents   Total   Events   Events   Total   Events   Total   Events   Even			0.005 0.1 1 10 200										
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl   M-H, Random, 95% Cl	rest for overall effect	1651101 Overall BIBUL Z = 0.74 (F = 0.40)											
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl   M-H, Random, 95% Cl		l ithiu	m	Place	bo		Risk Ratio	Risk Ratio					
BOWDEN2003   26 46 21 70 47.0%   1.88 [12.2.9.2]   Total (95% CI)   167    191 100.0%   1.38 [0.78, 2.45]   Total (95% CI)   167    191 100.0%   1.38 [0.78, 2.45]   Total (95% CI)   Total events   71    64    Heterogeneity, Tau" = 0.13; Chi" = 4.39, df = 1 (P = 0.04); P = 77%   Test for overall effect. Z = 1.09 (P = 0.27)   Z = 1.09 (P = 0.27)   Total (95% CI)   Total (95% CI)   91    91    35    94    100.0%   1.21 [0.86, 1.71]   Total (95% CI)   91    94    100.0%   1.21 [0.86, 1.71]   Total (95% CI)   91    94    100.0%   1.21 [0.86, 1.71]   Total events   41    35    Heterogeneity, Not applicable   Test for overall effect. Z = 1.08 (P = 0.28)   Total (95% CI)   Total events   Total   Even	Study or Subgroup					Weight							
Total (95% CI)													
Total (95% CI)								<b>+</b>					
Total events													
Note   Companies   Companies	Total (95% CI)		167		191	100.0%	1.38 [0.78, 2.45]	<b>◆</b>					
Study or Subgroup   Events   Total   Events   Events   Total   Events   E													
Study or Subgroup   Cevents   Total   Events   Total		-			P = 0.0	4); $I^2 = 77$	%	0.01 0.1 1 10 100					
Study or Subgroup	Test for overall effect:	Z = 1.09	(P = 0.2)	27)									
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl								•					
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl		Lithiu	m	Dlace	ho		Rick Ratio	Rick Ratio					
Total (95% CI)	Study or Subgroup					Weight							
Total (95% CI)								-					
Total events	D011D2112000	71	٠,		01	100.070	1.21 [0.00, 1.11]						
Heterogeneity: Not applicable   Test for overall effect   Z = 1.08 (P = 0.28)   Placebox   Risk Ratio   Favours lithium   Favours placebox   Risk Ratio   Risk	Total (95% CI)		91		94	100.0%	1.21 [0.86, 1.71]	<b>◆</b>					
Test for overall effect   Z = 1.08 (P = 0.28)	Total events	41		35									
Study or Subgroup   Events   Total   Events   Eve	Heterogeneity: Not ap	plicable						01.03 05 1 3 5 10					
Study or Subgroup   Cevents   Total   Events   Total   Veight   M-H, Random, 95% CI   M-H, Random, 95% CI	Test for overall effect:	Z = 1.08	(P = 0.2)	28)									
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% CI		1.246.2		Diagram			Dial Datia						
PRIEN1973         23         101         57         104         100.0%         0.42 [0.28, 0.62]           Total (95% CI)         101         104         100.0%         0.42 [0.28, 0.62]           Total events         23         57           Heterogeneity: Not applicable         10.2         0.5         1         2         5           Favours lithium         Placebo         Risk Ratio         Risk Ratio         M-H, Random, 95% CI           PRIEN1973B         1         18         6         13         100.0%         0.12 [0.02, 0.88]           Total (95% CI)         18         13         100.0%         0.12 [0.02, 0.88]         0.002 0.1         10         500           Total events         1         6         Risk Ratio         No.002 0.1         10         500         Favours lithium         Favours lithium         Favours placebo         Risk Ratio         No.002 0.1         10         500         Favours lithium         Fa	Ctudy or Cubarous					Weight							
Total (95% CI)         101         104         100.0%         0.42 [0.28, 0.62]           Total events         23         57           Heterogeneity: Not applicable         Test for overall effect: Z = 4.31 (P < 0.0001)								M-H, Random, 95% Ci					
Total events   23   57   Heterogeneity: Not applicable   Test for overall effect: Z = 4.31 (P < 0.0001)	PRIENT9/3	23	101	57	104	100.0%	0.42 [0.28, 0.62]						
Total events   23   57   Heterogeneity: Not applicable   Test for overall effect: Z = 4.31 (P < 0.0001)	Total (95% CI)		101		104	100.0%	0.42 [0.28, 0.62]	•					
Heterogeneity: Not applicable Test for overall effect: Z = 4.31 (P < 0.0001)    Column		23		57									
Test for overall effect: Z = 4.31 (P < 0.0001)				٥.				<del></del>					
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% CI   M-H, Random, 95% CI		-	(P < 0.0	001)									
Study or Subgroup   Events   Total   Events   Total   Weight   M-H, Random, 95% Cl			•	•				Favours littlium Favours placebo					
PRIEN1973B													
Total (95% CI)         18         13         100.0%         0.12 [0.02, 0.88]           Total events         1         6           Heterogeneity: Not applicable         0.002 0.1 1 0 500           Test for overall effect: Z = 2.08 (P = 0.04)         Risk Ratio           Study or Subgroup         Events Total Events Total Veight M-H, Random, 95% CI           WEISLER2011         99 364         80 404 100.0%         1.37 [1.06, 1.78]           Total (95% CI)         364 404 100.0%         1.37 [1.06, 1.78]           Total events         99 80         80           Heterogeneity: Not applicable         0.5 0.7 1 1.5 2								M-H, Random, 95% CI					
Total events 1 6  Heterogeneity: Not applicable Test for overall effect: Z = 2.08 (P = 0.04)    Column	PRIEN1973B	1	18	6	13	100.0%	0.12 [0.02, 0.88]						
Total events 1 6  Heterogeneity: Not applicable Test for overall effect: Z = 2.08 (P = 0.04)    Column	Total (05% CI)		40		42	100.0%	0.42 [0.02 0.00]						
Heterogeneity: Not applicable Test for overall effect: Z = 2.08 (P = 0.04)    Lithium   Placebo   Risk Ratio   Risk Ratio		4	10	c	13	100.0%	0.12 [0.02, 0.88]						
Test for overall effect: Z = 2.08 (P = 0.04)    Lithium   Placebo   Risk Ratio   Risk Ratio   Risk Ratio   M-H, Random, 95% CI		-		ь									
Lithium   Placebo   Risk Ratio   Risk Ratio   M-H, Random, 95% CI		•	/P = 0.0	M									
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% CI         M-H, Random, 95% CI           WEISLER2011         99         364         80         404         100.0%         1.37 [1.06, 1.78]           Total (95% CI)         364         404         100.0%         1.37 [1.06, 1.78]           Total events         99         80           Heterogeneity: Not applicable         0.5 0.7 1 1.5 2	restion overall ellect.	2-2.00	(1 – 0.0	,4)				Favours lithium Favours placebo					
WEISLER2011 99 364 80 404 100.0% 1.37 [1.06, 1.78]  Total (95% CI) 364 404 100.0% 1.37 [1.06, 1.78]  Total events 99 80  Heterogeneity: Not applicable  Tost for everall effect: 7 = 2.41 (P = 0.02)		Lithiu	m	Place	bo		Risk Ratio	Risk Ratio					
Total (95% CI) 364 404 100.0% 1.37 [1.06, 1.78]  Total events 99 80  Heterogeneity: Not applicable  Tost for everall effect: 7 = 3.41 (P = 0.03)	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI					
Total events 99 80  Heterogeneity: Not applicable 0.5 0.7 1 1.5 2	WEISLER2011	99	364	80	404	100.0%	1.37 [1.06, 1.78]	-					
Total events 99 80  Heterogeneity: Not applicable 0.5 0.7 1 1.5 2													
Heterogeneity: Not applicable  Out for everall effect: Z = 3.41 /B = 0.03 \ 0.5 0.7 1 1.5 2			364		404	100.0%	1.37 [1.06, 1.78]	<b>—</b>					
Toot for everall effect 7 = 2.44 /P = 0.02\				80									
restrur overall ellect: Z = 2.41 (P = 0.02)  Favours lithium Favours placebo		-	/D = 0.0	121				0.5 0.7 1 1.5 2					
	restror overall ellect	Z - Z.41 I	(r = 0.0	12)				Favours lithium Favours placebo					

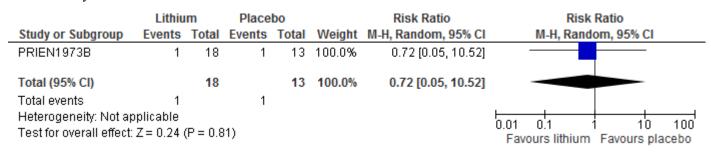
## Number of participants discontinuing due to side effects

	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2003	16	46	10	70	48.6%	2.43 [1.21, 4.89]	-
CALABRESE2003	19	121	12	121	51.4%	1.58 [0.80, 3.12]	<del>  -</del>
Total (95% CI)		167		191	100.0%	1.95 [1.20, 3.17]	•
Total events	35		22				
Heterogeneity: Tau² =	0.00; Chi	z = 0.76	3, df = 1 (	P = 0.3	8);	6	0.005 0.1 1 10 200
Test for overall effect:	Z = 2.70 (	P = 0.0	107)				Favours lithium Favours placebo
	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2000	31	91	11	94	100.0%	2.91 [1.56, 5.44]	
Total (95% CI)		91		94	100.0%	2.91 [1.56, 5.44]	•
Total events	31		11				
Heterogeneity: Not ap	plicable						0.005 0.1 1 10 200
Test for overall effect:	Z= 3.35 (	P = 0.0	008)				Favours lithium Favours placebo
	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
WEISLER2011	20	364	10	404	100.0%	2.22 [1.05, 4.68]	-
Total (95% CI)		364		404	100.0%	2.22 [1.05, 4.68]	•
Total events	20		10				
Heterogeneity: Not ap			.0				<u> </u>
Test for overall effect:	-	P = 0.0	4)				0.005 0.1 1 10 200 Favours lithium Favours placebo

#### Number of suicides

	Lithiu	m	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRIEN1973B	0	18	1	13	100.0%	0.25 [0.01, 5.59]	
Total (95% CI)		18		13	100.0%	0.25 [0.01, 5.59]	
Total events	0		1				
Heterogeneity: Not ap	plicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.88 (	(P = 0.3)	88)				0.01 0.1 1 10 100 Favours lithium Favours placebo

## Number of deaths

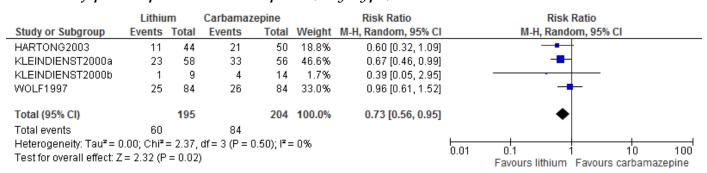


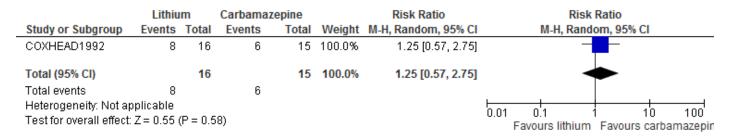
#### Psychosocial functioning (Global Assessment Scale)<sup>2</sup>

	Li	ithium		PI	acebo		;	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
BOWDEN2003	10	17.5	44	11	14	69	31.6%	-0.06 [-0.44, 0.31]	_
CALABRESE2003	4.1	9.6	120	6.9	11.1	115	68.4%	-0.27 [-0.53, -0.01]	-
Total (95% CI)			164			184	100.0%	-0.20 [-0.42, 0.01]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	-	-1 -0.5 0 0.5 1						
Test for overall effect:	Z = 1.89	(P = 0	0.06)						Favours lithium Favours placebo

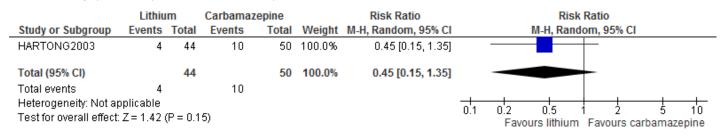
## 1.2.2 Outcomes for lithium compared with carbamazepine

#### Number of participants who relapsed (any type)





#### Number of participants who relapsed (mania)

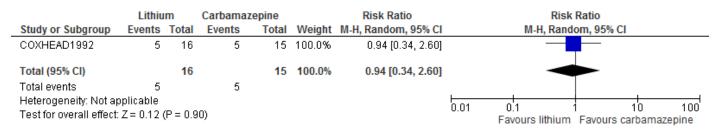


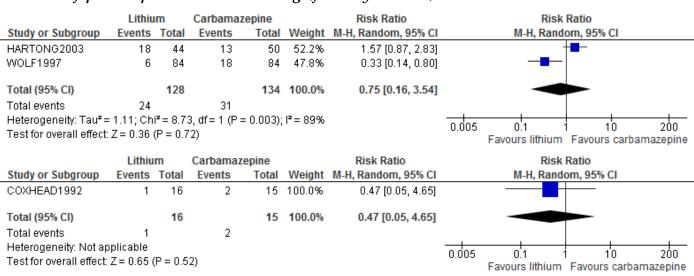
<sup>&</sup>lt;sup>2</sup> Scores have been reversed so that higher change scores indicate a worsening of functioning.

#### Number of participants who relapsed (depression)

	Lithiur	m	Carbama	zepine		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
HARTONG2003	7	44	11	50	100.0%	0.72 [0.31, 1.70]			
Total (95% CI)		44		50	100.0%	0.72 [0.31, 1.70]			
Total events	7		11						
Heterogeneity: Not ap Test for overall effect:		P = 0.4	6)				0.1 0.2 0.5 1 2 5 10 Favours lithium Favours carbamazepine		

#### Number of participants who were hospitalised





#### Number of participants discontinuing due to side effects

	Lithium			epine		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events</b>	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
HARTONG2003	5	44	4	50	38.9%	1.42 [0.41, 4.96]	<del></del>
WOLF1997	12	84	5	84	61.1%	2.40 [0.88, 6.51]	<del></del>
Total (95% CI)		128		134	100.0%	1.96 [0.90, 4.27]	•
Total events	17		9				
Heterogeneity: Tau² =	0.00; Chi	z = 0.41	, df = 1 (P =	: 0.52); l <sup>2</sup>	= 0%		0.005 0.1 1 10 200
Test for overall effect:	Z=1.69 (	P = 0.0	9)				Favours lithium Favours carbamazepine
	Lithiu	m	Carbama	zepine		Risk Ratio	Risk Ratio
Study or Subgroup	Lithiu Events	m Total	Carbama: Events	zepine Total	Weight		
Study or Subgroup COXHEAD1992				·	Weight 100.0%	M-H, Random, 95% CI	M-H, Random, 95% CI
	Events	Total	Events	Total	100.0%	M-H, Random, 95% CI 0.19 [0.01, 3.63]	M-H, Random, 95% CI
COXHEAD1992	Events	Total 16	Events	Total 15	100.0%	M-H, Random, 95% CI 0.19 [0.01, 3.63]	M-H, Random, 95% CI
COXHEAD1992 Total (95% CI)	Events 0 0	Total 16	Events 2	Total 15	100.0%	M-H, Random, 95% CI 0.19 [0.01, 3.63]	M-H, Random, 95% CI

## 1.2.3 Outcomes for lithium compared with lamotrigine

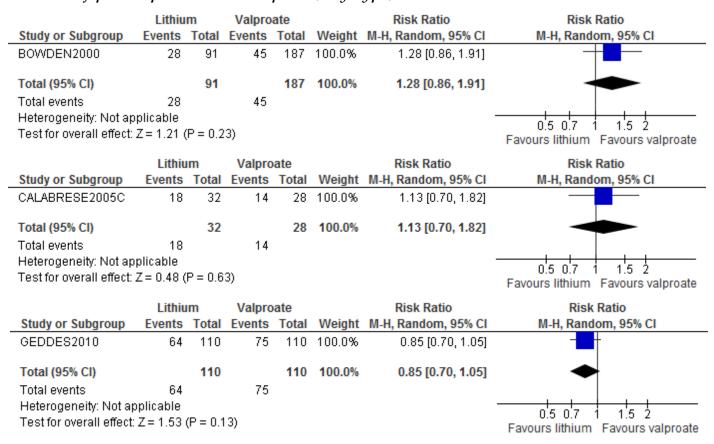
## Number of participants who relapsed (any type)

	Lithiu	m	Lamotri	igine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
LICHT2010	31	60	33	62	100.0%	0.97 [0.69, 1.36]	-
Total (95% CI)		60		62	100.0%	0.97 [0.69, 1.36]	<b>*</b>
Total events	31		33				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 0.17 (	(P = 0.8)	36)				Favours lithium Favours lamotrigine

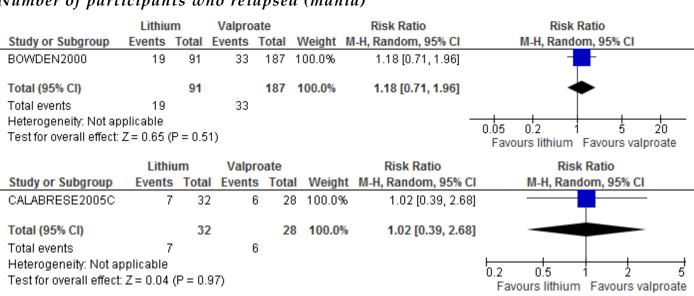


### 1.2.4 Outcomes for lithium compared with valproate

#### Number of participants who relapsed (any type)

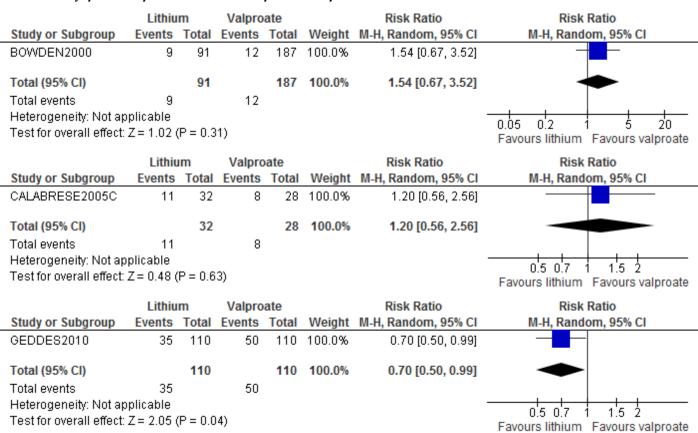


#### Number of participants who relapsed (mania)



	Lithiu	m	Valpro	ate		Risk Ratio		Risk Ratio			
Study or Subgroup	Events Total Events Total		Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			CI			
GEDDES2010	40	110	49	110	100.0%	0.82 [0.59, 1.13]					
Total (95% CI)		110		110	100.0%	0.82 [0.59, 1.13]		•	-		
Total events	40		49								
Heterogeneity: Not ap	plicable						0.2	l.5 1	+	-	ļ.
Test for overall effect:	Z = 1.23	(P = 0.2)	(2)						Favours	valproate	9

#### Number of participants who relapsed (depression)



#### Number of participants who were hospitalised

Study or Subgroup	Lithium				Weight	Risk Ratio	Risk Ratio
Study or Subgroup	Events	TOTAL	Events	TOTAL	vveigni	M-H, Random, 95% CI	M-H, Random, 95% CI
GEDDES2010	22	110	25	110	100.0%	0.88 [0.53, 1.46]	-
Total (95% CI)		110		110	100.0%	0.88 [0.53, 1.46]	•
Total events	22		25				
Heterogeneity: Not ap	plicable						<del>1. 1. 1. 1. 1</del>
	m – o e	-23				0.1 0.2 0.5 1 2 5 10	
Test for overall effect:	,P = 0.6	(2)				Favours lithium Favours valproate	

#### Number of participants discontinuing (for any reason)

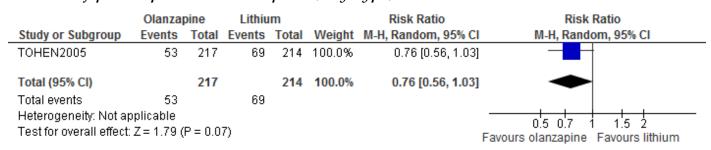
	Lithium Valproate					Risk Ratio	Risk Ratio		
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
BOWDEN2000	41	91	71	187	100.0%	1.19 [0.89, 1.59]	m-n, Kandoni, 33% Ci		
BOVVDEIN2000	41	31	( )	107	100.0%	1.13 [0.03, 1.33]	_		
Total (95% CI)		91		187	100.0%	1.19 [0.89, 1.59]	<b>•</b>		
Total events	41		71						
Heterogeneity: Not ap	plicable						0.005 0.1 1 10 200		
Test for overall effect:	Z=1.15 (	P = 0.2	!5)				0.005 0.1 1 10 200 Favours lithium Favours valproate		
	Lithiu	ım	Valpro	ate		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
CALABRESE2005C	10	32	6	28	100.0%	1.46 [0.61, 3.50]	-		
							_		
Total (95% CI)		32		28	100.0%	1.46 [0.61, 3.50]	<b>*</b>		
Total events	10		6						
Heterogeneity: Not ap	plicable						0.005 0.1 1 10 200		
Test for overall effect:	Z = 0.84 (	P = 0.4	0)				Favours lithium Favours valproate		
							•		
	Lithiu		Valpro			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
GEDDES2010	54	110	53	110	100.0%	1.02 [0.78, 1.34]			
Total (95% CI)		110		110	100.0%	1.02 [0.78, 1.34]	•		
Total events 54 53									
Heterogeneity: Not ap	plicable						0.005 0.1 1 10 200		
Test for overall effect: $Z = 0.13$ (P = 0.89)							Favours lithium Favours valproate		

## Number of participants discontinuing due to side effects

	Lithium Valproate			ate		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
GEDDES2010	10	110	6	110	100.0%	1.67 [0.63, 4.43]	-			
Total (95% CI)		110		110	100.0%	1.67 [0.63, 4.43]	•			
Total events	10		6							
Heterogeneity: Not applicable							0.005 0.1 1 10 200			
Test for overall effect:	Z = 1.02	(P = 0.3)	31)				Favours lithium Favours valproate			

## 1.2.5 Outcomes for olanzapine compared with lithium

#### Number of participants who relapsed (any type)



#### Number of participants who relapsed (mania)

	Olanzapine		Lithium		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
TOHEN2005	25	217	53	214	100.0%	0.47 [0.30, 0.72]	
Total (95% CI)		217		214	100.0%	0.47 [0.30, 0.72]	-
Total events	25		53				
Heterogeneity: Not ap	plicable						05 07 1 15 2
Test for overall effect:	Z = 3.44 (	P = 0.0	006)				Favours olanzapine Favours lithium

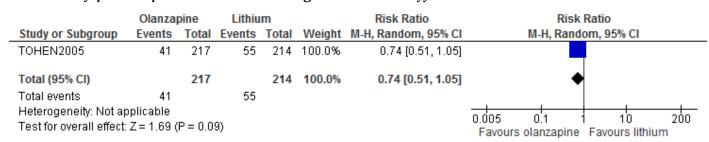
#### Number of participants who relapsed (depression)

	Olanzapine		Lithium		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
TOHEN2005	28	217	16	214	100.0%	1.73 [0.96, 3.10]	
Total (95% CI)		217		214	100.0%	1.73 [0.96, 3.10]	
Total events	28		16				
Heterogeneity: Not ap Test for overall effect:		P = 0.0	7)				0.5 0.7 1 1.5 2 Favours olanzapine Favours lithium

#### Number of participants discontinuing (for any reason)



#### Number of participants discontinuing due to side effects



#### Change in weight (kg)

	Olar	ızapir	1e	Lit	hium	1		Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
TOHEN2005	1.8	5.8	217	1.4	5	214	100.0%	0.07 [-0.12, 0.26]	_		
Total (95% CI)			217			214	100.0%	0.07 [-0.12, 0.26]	-		
Heterogeneity: Not ap Test for overall effect:			0.44)						-0.5 -0.25 0 0.25 0.5 Favours olanzapine Favours lithium		

## 1.2.6 Outcomes for valproate compared with lithium and valproate combination

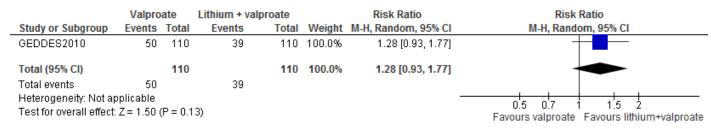
## Number of participants who relapsed (any type)

	Valproate Lithium		Lithium + val	oroate		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total Events Total		Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
GEDDES2010	75	110	58	110	100.0%	1.29 [1.04, 1.61]	-
Total (95% CI)		110		110	100.0%	1.29 [1.04, 1.61]	•
Total events Heterogeneity: Not ap Test for overall effect:		(P = 0.0	58				0.5 0.7 1 1.5 2 Favours valproate Favours lithium+vaproate

#### Number of participants who relapsed (mania)

	Valproate Lithium + valproate				Risk Ratio Risk Ratio				
Study or Subgroup	Events Total Events Total			Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
GEDDES2010	49	110	30	110	100.0%	1.63 [1.13, 2.36]			
Total (95% CI)		110		110	100.0%	1.63 [1.13, 2.36]	-		
Total events	49		30						
Heterogeneity: Not ap Test for overall effect:		P = 0.0	109)				0.5 0.7 1 1.5 2 Favours valproate Favours lithium+valproate		

#### Number of participants who relapsed (depression)



#### Number of participants who were hospitalised

	Valproate Lithium + valproate				Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
GEDDES2010	25	110	16	110	100.0%	1.56 [0.88, 2.76]		+
Total (95% CI)		110		110	100.0%	1.56 [0.88, 2.76]		-
Total events	25		16					
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.1	2)				0.1	0.2 0.5 1 2 5 10 Favours valproate Favours lithium+valproate

#### Number of participants discontinuing (for any reason)

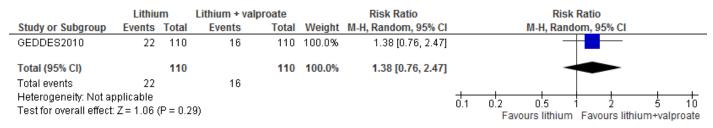
	Valpro	ate	ate Lithium + valproate			Risk Ratio	Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ran	dom, 95% CI	
GEDDES2010	53	110	56	110	100.0%	0.95 [0.72, 1.24]				
Total (95% CI)		110		110	100.0%	0.95 [0.72, 1.24]			<b>*</b>	
Total events	53		56							
Heterogeneity: Not ap Test for overall effect:	(P = 0.6	i9)				0.005 Fav	0.1 ours valproate	1 10 Favours lithiu	200 m+valproate	

#### Number of participants discontinuing due to side effects

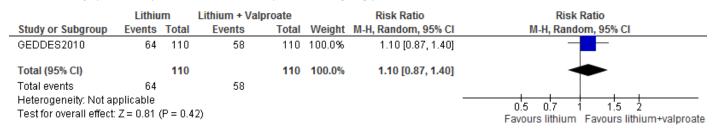
	Valpro	ate	Lithium + va	Iproate		Risk Ratio	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% CI	
GEDDES2010	53	110	56	110	100.0%	0.95 [0.72, 1.24]				
Total (95% CI)		110		110	100.0%	0.95 [0.72, 1.24]		•	•	
Total events	53		56							
Heterogeneity: Not ap Test for overall effect:	(P = 0.6	9)				0.005	0.1 Favours vaproate	1 10 Favours lithium	200 n+valproate	

## 1.2.7 Outcomes for lithium compared with lithium and valproate combination

#### Number of participants who were hospitalised



#### Number of participants who relapsed (any type)



#### Number of participants who relapsed (mania)

	Lithiu	m	Lithium + valproate			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
GEDDES2010	40	110	30	110	100.0%	1.33 [0.90, 1.97]	+
Total (95% CI)		110		110	100.0%	1.33 [0.90, 1.97]	
Total events	40		30				
Heterogeneity: Not ap Test for overall effect:	•	P = 0.1	5)				0.5 0.7 1 1.5 2 Favours lithium Favours lithium+valproate

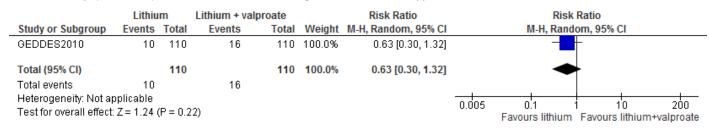
## Number of participants who relapsed (depression)

	Lithiu	m	Lithium + val	proate		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
GEDDES2010	35	110	39	110	100.0%	0.90 [0.62, 1.30]	
Total (95% CI)		110		110	100.0%	0.90 [0.62, 1.30]	
Total events	35		39				
Heterogeneity: Not ap Test for overall effect:	•	P = 0.5	i7)				0.5 0.7 1 1.5 2 Favours lithium Favours lithium+valproate

## Number of participants discontinuing (for any reason)

	Lithiu	m	Lithium + val	proate		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	dom, 95% CI	
GEDDES2010	54	110	56	110	100.0%	0.96 [0.74, 1.26]				
Total (95% CI)		110		110	100.0%	0.96 [0.74, 1.26]			<b>•</b>	
Total events	54		56							
Heterogeneity: Not a Test for overall effect		(P = 0.7	'9)				0.005	0.1 Favours lithium	1 10 Favours lithin	200 um+valproate

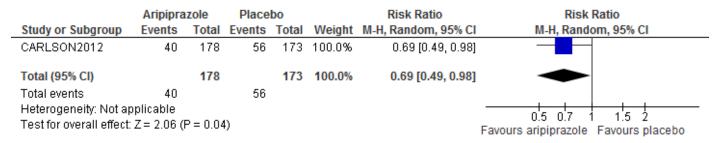
#### Number of participants discontinuing due to side effects



#### 1.3 ANTIPSYCHOTICS

# 1.3.1 Outcomes for aripiprazole compared with placebo (all participants taking lamotrigine)

#### Number of participants who relapsed (any type)



#### Number of participants who relapsed (mania)

	Aripipra	zole	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CARLSON2012	16	178	27	173	100.0%	0.58 [0.32, 1.03]	
Total (95% CI)		178		173	100.0%	0.58 [0.32, 1.03]	
Total events	16		27				
Heterogeneity: Not ap Test for overall effect:	•	P = 0.06	6)				0.5 0.7 1 1.5 2 Favours aripiprazole Favours placebo

#### Number of participants who relapsed (depression)

	Aripipra	zole	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CARLSON2012	24	178	29	173	100.0%	0.80 [0.49, 1.32]	
Total (95% CI)		178		173	100.0%	0.80 [0.49, 1.32]	
Total events	24		29				
Heterogeneity: Not ap	oplicable						0.5 0.7 1 1.5 2
Test for overall effect:	Z = 0.86 (1	P = 0.39	3)				Favours aripiprazole Favours placebo



#### Number of participants discontinuing due to side effects

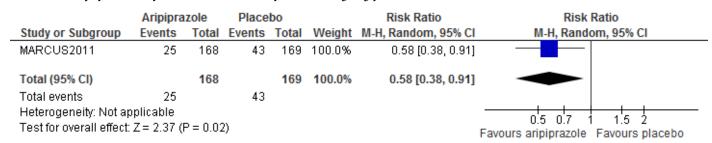
	Aripipra	zole	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CARLSON2012	16	178	10	173	100.0%	1.56 [0.73, 3.33]	-
Total (95% CI)		178		173	100.0%	1.56 [0.73, 3.33]	<b>◆</b>
Total events	16		10				
Heterogeneity: Not ap	plicable						0.005 0.1 1 10 200
Test for overall effect:	Z = 1.14 (1	P = 0.26	5)				Favours aripiprazole Favours placebo

#### Change in weight (kg)

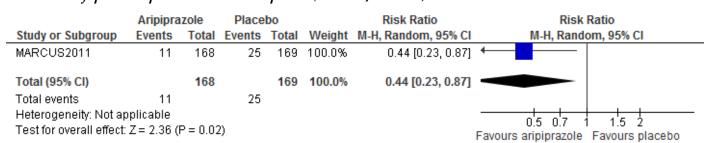
	Arip	iprazo	le	PI	acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
CARLSON2012	0.43	5.78	151	-1.81	5.74	143	100.0%	0.39 [0.16, 0.62]	•
Total (95% CI)			151			143	100.0%	0.39 [0.16, 0.62]	•
Heterogeneity: Not ap Test for overall effect:			0.0010)						-2 -1 0 1 2 Favours aripiprazole Favours placebo

# 1.3.2 Outcomes for aripiprazole compared with placebo (all participants taking lithium or valproate)

#### Number of participants who relapsed (any type)



#### Number of participants who relapsed (mania/mixed)



#### Number of participants who relapsed (depression)

	Aripipra	zole	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
MARCUS2011	14	168	18	169	100.0%	0.78 [0.40, 1.52]	<del></del>
Total (95% CI)		168		169	100.0%	0.78 [0.40, 1.52]	
Total events	14		18				
Heterogeneity: Not as	plicable						05 07 1 15 2
Test for overall effect:	Z = 0.72 (1	P = 0.47	?)				Favours aripiprazole Favours placebo

## Number of participants discontinuing (for any reason)

	Aripipra	zole	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
MARCUS2011	65	168	80	169	100.0%	0.82 [0.64, 1.05]	<b>-</b>
Total (95% CI)		168		169	100.0%	0.82 [0.64, 1.05]	•
Total events	65		80				
Heterogeneity: Not as	oplicable						0.005 0.1 1 10 200
Test for overall effect:	Z = 1.59 (	$P = 0.1^{\circ}$	1)				Favours aripiprazole Favours placebo

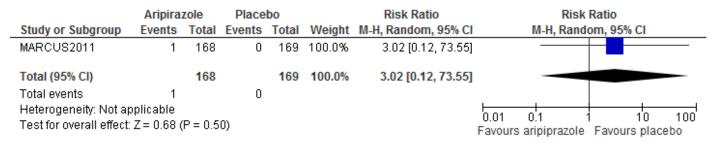
#### Number of participants discontinuing due to side effects

	Aripipra	zole	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% C	I
MARCUS2011	19	168	15	169	100.0%	1.27 [0.67, 2.42]	<b>-</b>	
Total (95% CI)		168		169	100.0%	1.27 [0.67, 2.42]	•	
Total events	19		15					
Heterogeneity: Not ap Test for overall effect:	•	P = 0.48	6)				0.005 0.1 1 10 Favours aripiprazole Favours g	200 placebo

## Change in weight (kg)

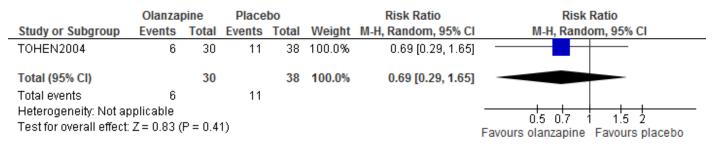
	Aripi	ргахо	ole	PI	acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
MARCUS2011	1.07	6.2	160	0.6	6.22	161	100.0%	0.08 [-0.14, 0.29]	_
Total (95% CI)			160			161	100.0%	0.08 [-0.14, 0.29]	-
Heterogeneity: Not a Test for overall effect			0.50)						-0.5 -0.25 0 0.25 0.5 Favours aripiprazole Favours placebo

#### Number of suicides



# 1.3.3 Outcomes for olanzapine compared with placebo (all participants taking lithium or valproate)

#### Number of participants who relapsed (mania)



#### Number of participants who relapsed (depression)

	Olanza	pine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
TOHEN2004	7	30	15	38	100.0%	0.59 [0.28, 1.26]	
Total (95% CI)		30		38	100.0%	0.59 [0.28, 1.26]	
Total events	7		15				
Heterogeneity: Not ap	plicable						05 07 1 15 2
Test for overall effect:	Z = 1.36 (	P = 0.1	7)				Favours olanzapine Favours placebo

#### Number of participants discontinuing (for any reason)

	Olanza	pine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
TOHEN2004	35	51	43	48	100.0%	0.77 [0.62, 0.94]	•
Total (95% CI)		51		48	100.0%	0.77 [0.62, 0.94]	•
Total events	35		43				
Heterogeneity: Not ap	plicable						0.005 0.1 1 10 200
Test for overall effect:	Z = 2.50 (	P = 0.0	1)				Favours olanzapine Favours placebo

### Number of participants discontinuing due to side effects

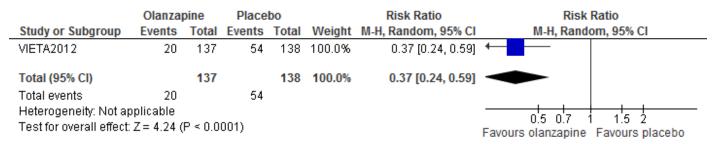


### 1.3.4 Outcomes for olanzapine compared with placebo

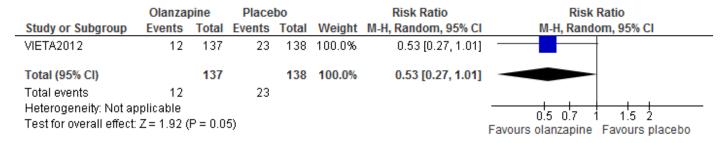
#### Number of participants who relapsed (any type)

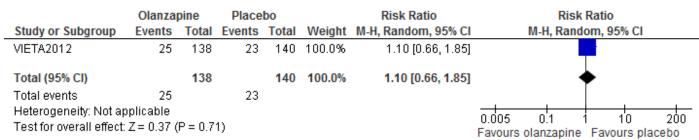
	Olanza	pine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
VIETA2012	32	137	77	138	100.0%	0.42 [0.30, 0.59]	_
Total (95% CI)		137		138	100.0%	0.42 [0.30, 0.59]	•
Total events	32		77				
Heterogeneity: Not ap	plicable						05 07 1 15 2
Test for overall effect:	Z = 5.05 (	P < 0.0	0001)				Favours olanzapine Favours placebo

#### Number of participants who relapsed (mania)



#### Number of participants who relapsed (depression)





#### Number of participants discontinuing due to side effects

	Olanza	pine	Place	bo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI	
VIETA2012	4	138	2	140	100.0%	2.03 [0.38, 10.90]	_		
Total (95% CI)		138		140	100.0%	2.03 [0.38, 10.90]	-		
Total events	4		2						
Heterogeneity: Not ap	plicable						0.005 0.1	1 10	200
Test for overall effect:	Z = 0.82 (	P = 0.4	1)				Favours olanzapine		

## 1.3.5 Outcomes for paliperidone compared with placebo

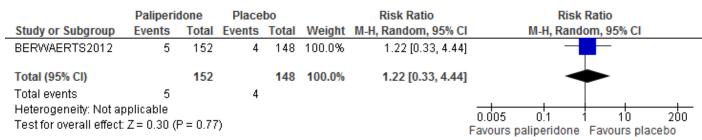
## Number of participants who relapsed (any type)

	Paliperio	done	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BERWAERTS2012	66	152	77	148	100.0%	0.83 [0.66, 1.06]	
Total (95% CI)		152		148	100.0%	0.83 [0.66, 1.06]	•
Total events	66		77				
Heterogeneity: Not ap	plicable						05 07 1 15 2
Test for overall effect:	Z = 1.49 (F	P = 0.14	<b>!</b> )				Favours paliperidone Favours placebo

## Number of participants discontinuing (for any reason)

	Paliperi	Paliperidone Placebo		bo		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	M-H, Rand	om, 95% CI		
BERWAERTS2012	56	152	52	148	100.0%	1.05 [0.78, 1.42	]				
Total (95% CI)		152		148	100.0%	1.05 [0.78, 1.42]	]	•			
Total events	56		52								
Heterogeneity: Not ap	oplicable						0.005	01	10	200	
Test for overall effect:	Z = 0.31 (	P = 0.78	6)					o.i paliperidone			

## Number of participants discontinuing due to side effects



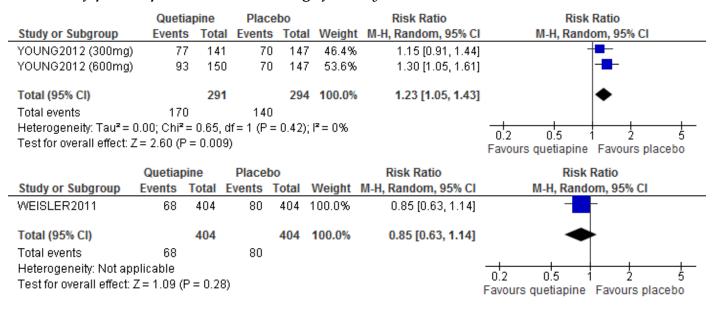
#### Change in weight (kg)

	Palij	Paliperidone Placebo						Std. Mean Difference	Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
BERWAERTS2012	0.5	5.18	146	-0.6	5.51	144	100.0%	0.21 [-0.03, 0.44]	+			
Total (95% CI)			146			144	100.0%	0.21 [-0.03, 0.44]	•			
Heterogeneity: Not ap Test for overall effect:			0.08)					ı	-1 -0.5 0 0.5 1 Favours paliperidone Favours placebo			

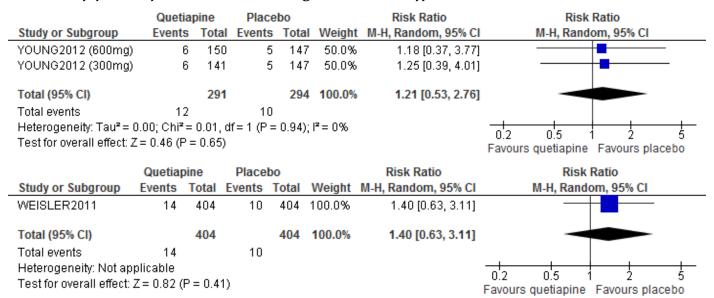
## 1.3.6 Outcomes for quetiapine compared with placebo

#### Number of participants who relapsed (any type)

	Quetia	pine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
YOUNG2012 (300mg)	37	141	59	147	53.6%	0.65 [0.47, 0.92]	<b></b>
YOUNG2012 (600mg)	32	150	59	147	46.4%	0.53 [0.37, 0.77]	<del></del>
Total (95% CI)		291		294	100.0%	0.59 [0.46, 0.76]	•
Total events	69		118				
Heterogeneity: Tau <sup>2</sup> = 0.1	00; Chi²=	0.66, d	f=1 (P=	0.42);	l² = 0%		05 07 1 15 2
Test for overall effect: Z=	= 4.10 (P <	< 0.000	1)				Favours quetiapine Favours placebo

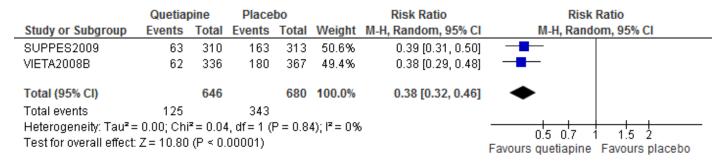


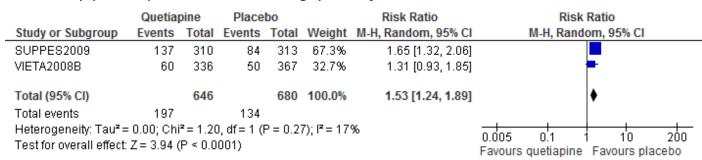
#### Number of participants discontinuing due to side effects



## 1.3.7 Outcomes for quetiapine compared with placebo (all participants were taking lithium or valproate)

#### Number of participants who relapsed (any type)





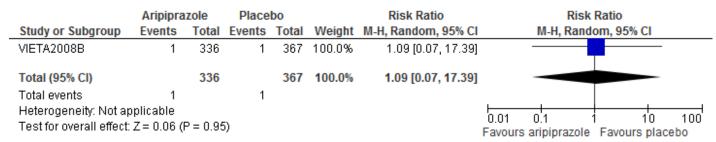
#### Number of participants discontinuing due to side effects

	Quetia	pine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
SUPPES2009	35	310	8	313	55.0%	4.42 [2.08, 9.37]	-
VIETA2008B	7	336	6	367	45.0%	1.27 [0.43, 3.75]	<del>-</del>
Total (95% CI)		646		680	100.0%	2.53 [0.75, 8.53]	•
Total events	42		14				
Heterogeneity: Tau² = Test for overall effect:				P = 0.0	6); I² = 71	%	0.005 0.1 1 10 200 Favours quetiapine Favours placebo

#### Change in weight (kg)

	Que	tiapir	ie	Pla	iceb	0		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
SUPPES2009	0.46	6	310	-1.95	5.1	313	100.0%	0.43 [0.27, 0.59]	-
Total (95% CI)			310			313	100.0%	0.43 [0.27, 0.59]	•
Heterogeneity: Not ap Test for overall effect:			0.0000	1)					-1 -0.5 0 0.5 1 Favours quetiapine Favours placebo

#### Number of suicides



#### Number of deaths



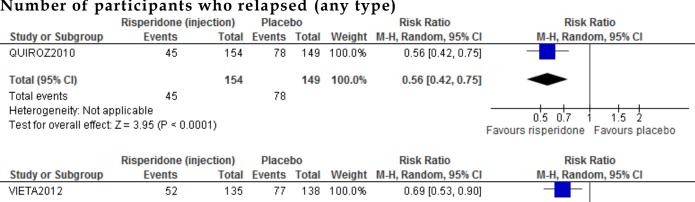
### 1.3.8 Outcomes for quetiapine compared with valproate

#### Number of participants discontinuing (for any reason)



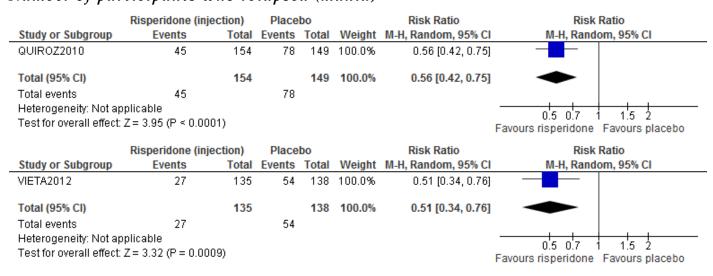
## 1.3.9 Outcomes for risperidone long-acting injectable compared with placebo injection

Number of participants who relapsed (any type)

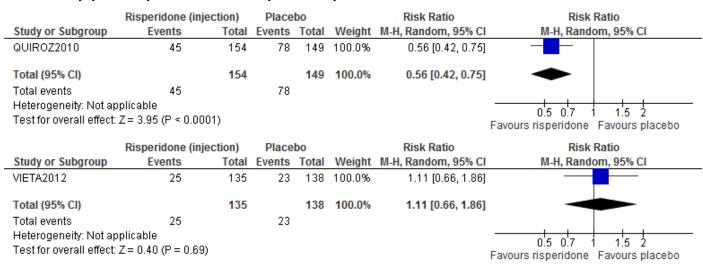


Total (95% CI) 135 138 100.0% 0.69 [0.53, 0.90] Total events 52 77 Heterogeneity: Not applicable 0.5 0.7 1.5 Test for overall effect: Z = 2.80 (P = 0.005) Favours risperidone Favours placebo

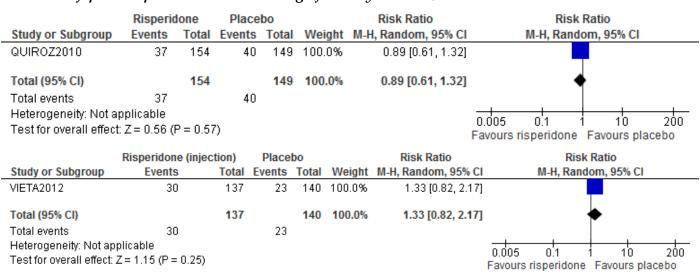
#### Number of participants who relapsed (mania)



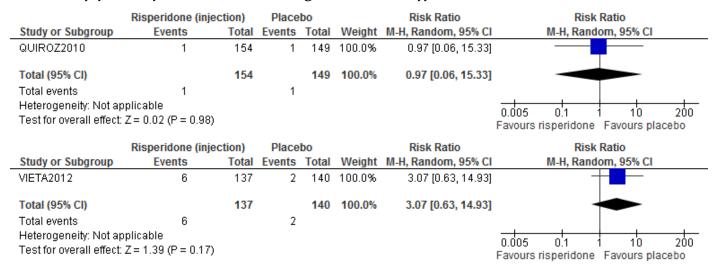
#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)



#### Number of participants discontinuing due to side effects

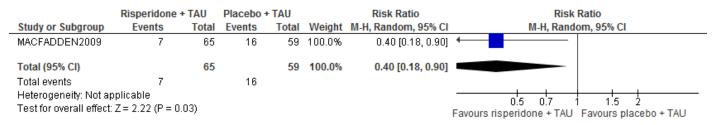


## 1.3.10 Outcomes for risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual)

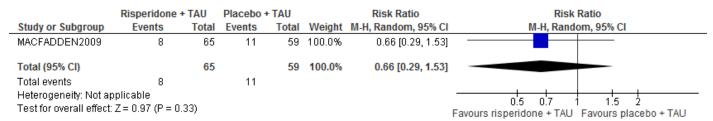
#### Number of participants who relapsed (any type)



#### Number of participants who relapsed (mania)



### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)

	Risperidone	Risperidone + TAU		J		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
B0B02011B	9	25	6	25	100.0%	1.50 [0.63, 3.59]	-	
Total (95% CI)		25		25	100.0%	1.50 [0.63, 3.59]	<b>*</b>	
Total events	9		6					
Heterogeneity: Not ap Test for overall effect:	•	.36)				Favo	0.005 0.1 1 10 2 ours risperidone + TAU Favours TAU	200

#### Number of participants discontinuing due to side effects

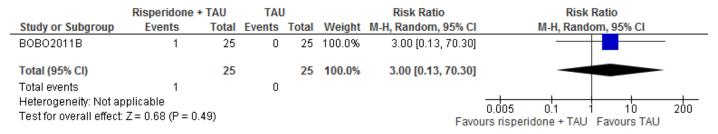


## 1.3.11Outcomes for risperidone long-acting injectable and treatment as usual compared with treatment as usual alone

#### Number of participants discontinuing (for any reason)



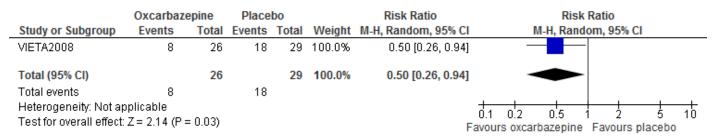
#### Number of participants discontinuing due to side effects



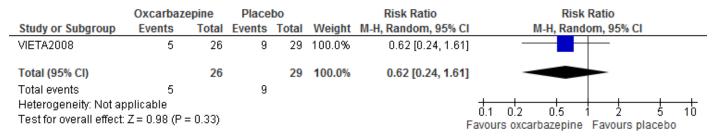
#### 1.4 ANTICONVULSANTS

# 1.4.1 Outcomes for oxcarbazepine compared with placebo (all participants were taking lithium)

#### Number of participants who relapsed (any type)



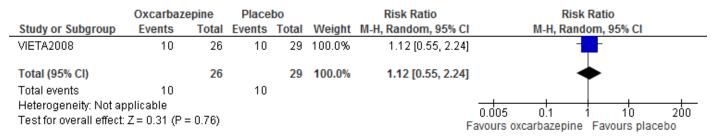
#### Number of participants who relapsed (mania)



#### Number of participants who relapsed (depression)

	Oxcarbaze	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
VIETA2008	3	26	9	29	100.0%	0.37 [0.11, 1.23]	
Total (95% CI)		26		29	100.0%	0.37 [0.11, 1.23]	
Total events	3		9				
Heterogeneity: Not ap	oplicable						01 02 05 1 2 5 10
Test for overall effect:	Z=1.62 (P=	0.10)				F	avours oxcarbazepine Favours placebo

### Number of participants discontinuing (for any reason)



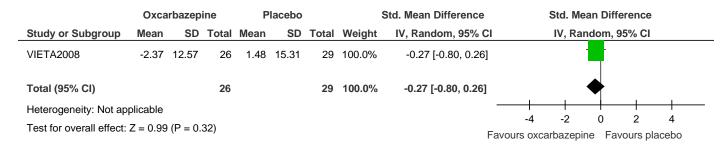
#### Number of participants discontinuing due to side effects

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
VIETA2008	3	26	2	29	100.0%	1.67 [0.30, 9.24]	
Total (95% CI)		26		29	100.0%	1.67 [0.30, 9.24]	•
Total events	3		2				
Heterogeneity: Not ap Test for overall effect	•	= 0.56)					0.005 0.1 1 10 200  Favours oxcarbazepine Favours placebo

#### Change in weight (kg)

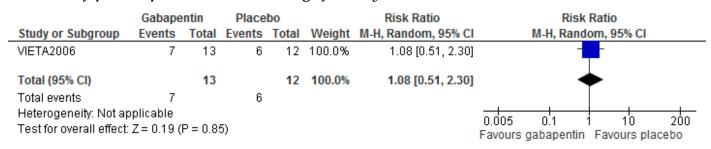


#### Psychosocial functioning (Global Assessment of Functioning)3

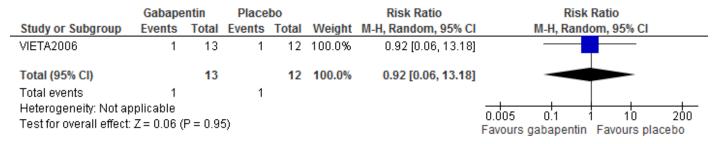


## 1.4.2 Outcomes for gabapentin compared with placebo (all participants were taking lithium, valproate, carbamazepine or combination)

#### Number of participants discontinuing (for any reason)

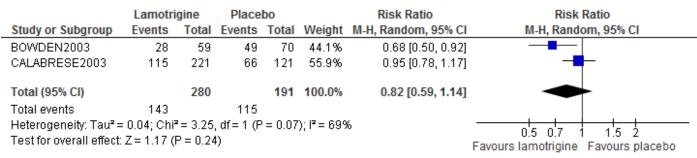


#### Number of participants discontinuing due to side effects



## 1.4.3 Outcomes for lamotrigine compared with placebo

## Number of participants who relapsed (any type)



<sup>&</sup>lt;sup>3</sup> Scores have been reversed so that higher change scores indicate a worsening of functioning.

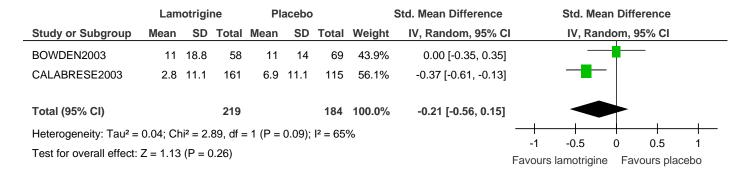
#### Number of participants discontinuing (for any reason)

	Lamotri	gine	Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2003	28	59	21	70	46.3%	1.58 [1.01, 2.47]	-
CALABRESE2003	68	221	43	121	53.7%	0.87 [0.63, 1.18]	•
Total (95% CI)		280		191	100.0%	1.14 [0.64, 2.06]	•
Total events	96		64				
Heterogeneity: Tau² = Test for overall effect:			6	0.005 0.1 1 10 200 Favours lamotrigine Favours placebo			

#### Number of participants discontinuing due to side effects

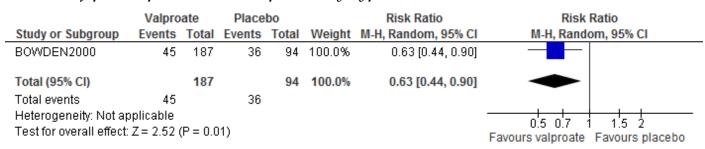
	Lamotri	gine	Placebo		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
BOWDEN2003	6	59	10	70	33.9%	0.71 [0.28, 1.84]	<del></del>	
CALABRESE2003	20	221	12	121	66.1%	0.91 [0.46, 1.80]	<del></del>	
Total (95% CI)		280		191	100.0%	0.84 [0.48, 1.46]	•	
Total events	26		22					
Heterogeneity: Tau <sup>2</sup> =	-		0.005 0.1 1 10 200					
Test for overall effect: Z = 0.62 (P = 0.53)							Favours lamotrigine Favours placebo	

#### Psychosocial functioning (Global Assessment Scale)4



## 1.4.4 Outcomes for valproate compared with placebo

#### Number of participants who relapsed (any type)

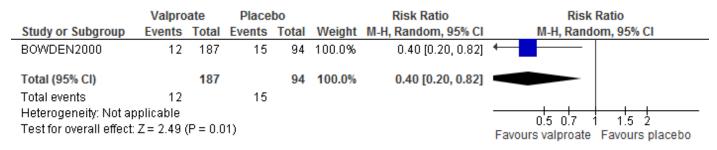


<sup>&</sup>lt;sup>4</sup> Scores have been reversed so that higher change scores indicate a worsening of functioning.

#### Number of participants who relapsed (mania)

	Valproate		Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2000	33	187	21	94	100.0%	0.79 [0.49, 1.29]	
Total (95% CI)		187		94	100.0%	0.79 [0.49, 1.29]	-
Total events	33		21				
Heterogeneity: Not applicable							05 07 1 15 2
Test for overall effect: Z = 0.95 (P = 0.34)							Favours valproate Favours placebo

#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)

	Valproate		Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
BOWDEN2000	71	187	35	94	100.0%	1.02 [0.74, 1.40]	
Total (95% CI)		187		94	100.0%	1.02 [0.74, 1.40]	<b>•</b>
Total events	71		35				
Heterogeneity: Not ap	oplicable						0.005 0.1 1 10 200
Test for overall effect: Z = 0.12 (P = 0.90)							Favours valproate Favours placebo

## Number of participants discontinuing due to side effects

	Valpro	ate	Placebo			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
BOWDEN2000	41	187	11	94	100.0%	1.87 [1.01, 3.47]	-	
Total (95% CI)		187		94	100.0%	1.87 [1.01, 3.47]	•	
Total events	41		11					
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20	
Test for overall effect:	Z=1.99	(P = 0.0)	15)				Favours valproate Favours placebo	

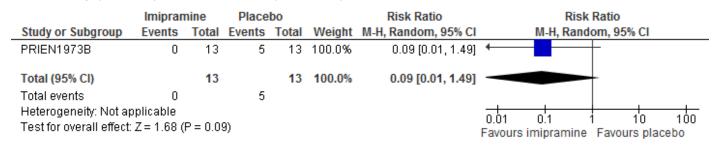
#### 1.5 ANTIDEPRESSANTS

# 1.5.1 Outcomes for imipramine compared with placebo

## Number of participants who relapsed (mania)

	lmipran	nine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRIEN1973B	6	13	3	13	100.0%	2.00 [0.63, 6.34]	
Total (95% CI)		13		13	100.0%	2.00 [0.63, 6.34]	
Total events	6		3				
Heterogeneity: Not ap	plicable						0.2 0.5 1 2 5
Test for overall effect:	Z = 1.18 (	P = 0.2	4)				Favours imipramine Favours placebo

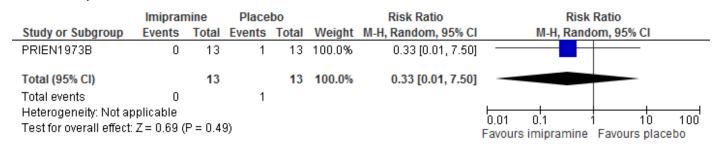
#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)

	lmipran	nine	Place	bo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI	
PRIEN1973B	7	13	6	13	100.0%	1.17 [0.54, 2.53]	-	-	
Total (95% CI)		13		13	100.0%	1.17 [0.54, 2.53]	•	•	
Total events	7		6						
Heterogeneity: Not ap	plicable						0.005 0.1	<del>   </del> 1 10	200
Test for overall effect:	Z = 0.39 (	P = 0.7	0)				Favours imipramine		

#### Number of suicides



#### Number of deaths

	lmipran	nine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRIEN1973B	2	13	1	13	100.0%	2.00 [0.21, 19.44]	
Total (95% CI)		13		13	100.0%	2.00 [0.21, 19.44]	
Total events	2		1				
Heterogeneity: Not ap	plicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.60 (	P = 0.5	5)				Favours imipramine Favours placebo

# 1.5.2 Outcomes for imipramine compared with placebo (all participants were taking lithium)

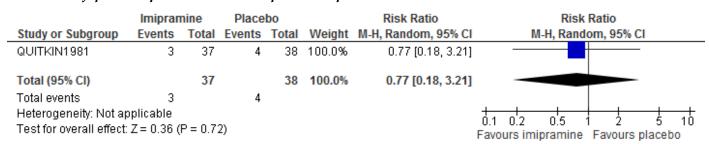
## Number of participants who relapsed (any type)

	lmipran	nine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
QUITKIN1981	12	37	8	38	100.0%	1.54 [0.71, 3.33]	+
Total (95% CI)		37		38	100.0%	1.54 [0.71, 3.33]	
Total events	12		8				
Heterogeneity: Not ap	plicable						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.10 (	P = 0.2	7)				Favours imipramine Favours placebo

#### Number of participants who relapsed (mania)

	lmipran	nine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
QUITKIN1981	9	37	4	38	100.0%	2.31 [0.78, 6.85]	
Total (95% CI)		37		38	100.0%	2.31 [0.78, 6.85]	
Total events	9		4				
Heterogeneity: Not ap	-						01 02 05 1 2 5 10
Test for overall effect:	Z = 1.51 (	P = 0.13	3)				Favours imipramine Favours placebo

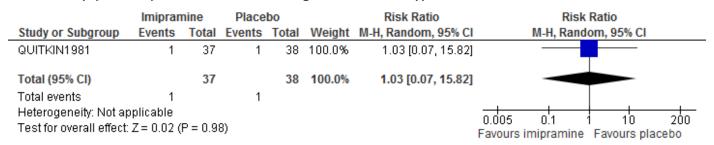
#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)

	lmiprar	nine	Place	bo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 95% CI	
QUITKIN1981	25	37	30	38	100.0%	0.86 [0.65, 1.13]			
Total (95% CI)		37		38	100.0%	0.86 [0.65, 1.13]	•	•	
Total events	25		30						
Heterogeneity: Not ap	plicable						0.005 0.1 1	10	200
Test for overall effect:	Z = 1.10 (	P = 0.2	7)				Favours imipramine		

#### Number of participants discontinuing due to side effects

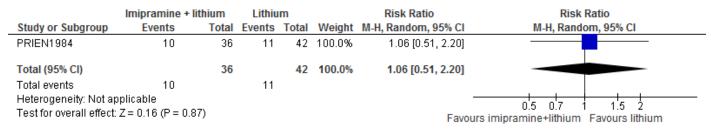


# 1.5.3 Outcomes for imipramine and lithium combination compared with lithium

## Number of participants who relapsed (any type)

	Imipramine + I	ithium	Lithiu	m		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
PRIEN1984	29	36	23	42	100.0%	1.47 [1.07, 2.02]		
Total (95% CI)		36		42	100.0%	1.47 [1.07, 2.02]		-
Total events	29		23					
Heterogeneity: Not ap Test for overall effect:		12)				Favo	0.5 0.7 urs imipramine+lithium	1.5 2 Favours lithium

### Number of participants who relapsed (mania)



# Number of participants who relapsed (depression)

	lmipramine + li	ithium	Lithiu	m		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRIEN1984	8	36	12	42	100.0%	0.78 [0.36, 1.69]	
Total (95% CI)		36		42	100.0%	0.78 [0.36, 1.69]	
Total events	8		12				
Heterogeneity: Not ap Test for overall effect	•	3)				Favo	0.5 0.7 1 1.5 2 urs imipramine+lithium Favours lithium

## Number of participants discontinuing (for any reason)



# 1.6 DEFINITIONS OF RELAPSE IN STUDIES OF LONG-TERM MANAGEMENT

Comparison	N	K	Relapse (any)*	Definition†	Discontinuation (for any reason)*	Length of follow-up‡	References
Pharmacological interventions						_	
Lithium							
Lithium (standard dose) compared with lithium (low dose)	94	1	RR = 3.50 [1.55, 7.89]	Research diagnostic criteria or DSM-III criteria for mania or depression	RR = 0.46 [0.25, 0.83]	52	GELENBERG1989
Lithium daily compared with lithium every other day)	50	1	RR = 2.40 [0.99, 5.81]	Manic or depressive relapse was defined as the DSM-III-R criteria for mania or major depression and a BRMaS score ≥ 10 or a BRMeS score ≥ 10, respectively	RR = 0.11 [0.01, 1.96]	56	JENSEN1995
Lithium compared with placebo (participants were euthymic at study entry)	92	2	RR = 0.41 [0.07, 2.43]	Extra medication required to treat symptoms	RR = 1.39 [0.58, 5.08]	121, 69	STALLONE1972, DUNNER1976
Lithium compared with placebo (participants received open-label lamotrigine – alone or in combination with other psychotropic drugs – for 8-16 weeks and were randomised once euthymic)	358	2	RR = 0.71 [0.47, 1.06]	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.38 [0.78, 2.45]	72, 76	CALABRESE2003, BOWDEN2003
Lithium compared with placebo (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)	185	1	RR = 0.80 [0.54, 1.20]	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.21 [0.86, 1.71]	52	BOWDEN2000

Comparison	N	K	Relapse (any)*	Definition+	Discontinuation (for any reason)*	Length of follow-up‡	References
Lithium compared with placebo (following remission of an acute manic episode and prior to discharge patients were stabilised on maintenance doses of lithium)	205	1	RR = 0.53 [0.41, 0.67]	Manic or depressive attack requiring hospitalisation or supplementary drugs	RR = 0.42 [0.28, 0.62]	104	PRIEN1973
Lithium compared with placebo (following remission from a depressive episode, patients were stabilised on lithium or imipramine)	31	1	NR	Manic or depressive attack requiring hospitalisation or supplementary drugs	RR = 0.12 [0.02, 0.88]	104	PRIEN1973B
Lithium compared with placebo (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)	768 8	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.37 [1.06, 1.78]	104	WEISLER2011
Lithium compared with carbamazepine (participants were euthymic and were ready to start prophylactic treatment)	399	3	RR = 0.73 [0.56, 0.95]	Recurrence of an affective episode	RR = 0.75 [ 0.16, 3.54] K = 2; N = 262	52, 104, 130	WOLF1997, HARTONG2003, KLEINDIENST2000
Lithium compared with carbamazepine (participants were euthymic and all on stable doses of lithium)	31	1	RR = 1.25 [0.57, 2.75]	Not defined	RR = 0.47 [0.05, 4.56]	52	COXHEAD1992
Lithium compared with quetiapine (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)	768⁵	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania;	RR = 1.62 [1.23, 2.13]	104	WEISLER2011

Comparison	N	K	Relapse (any)*	Definition†	Discontinuation (for any reason)*	Length of follow- up‡	References
				a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania			
Lithium compared with valproate (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)	278	1	RR = 1.28 [0.86, 1.91]	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.19 [0.89, 1.59]	52	BOWDEN2000
Lithium compared with valproate (participants were randomised when euthymic and after 6 months of active treatment with lithium and valproate)	60	1	RR = 1.13 [0.70, 1.82]	Patients who met criteria for mania (a total YMRS score ≥ 20 for up to 8 weeks) or depression (a 24-item Hamilton depression scale score ≥ 20 for 8 weeks) were considered to have relapsed	RR = 1.46 [0.61, 3.50]	80	CALABRESE2005C
Lithium compared with valproate (participants were randomised whilst euthymic and after 4-8 weeks of active treatment with lithium and valproate)	220β	1	RR = 0.85 [0.70, 1.05]	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 1.02 [0.78, 1.34]	104	GEDDES2010
Lithium compared to lithium and valproate combination	220β	1	RR = 1.10 [0.87, 1.40]	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 0.96 [0.74, 1.26]	104	GEDDES2010
Valproate compared to lithium and valproate combination	220β	1	RR = 1.29 [1.04, 1.61]	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 0.95 [0.72, 1.24]	104	GEDDES2010
Olanzapine compared with lithium	431	1	RR = 0.76 [0.56, 1.03]	DSM-IV criteria for a depressive, manic or mixed episode	RR = 0.79 [0.68, 0.93]	52	TOHEN2005

Antipsychotics							
Aripiprazole compared with placebo (all participants taking lamotrigine)	351	1	RR = 0.69 [0.49, 0.98]	One or more of the following events: hospitalisation for a manic or mixed episode; a serious adverse event or worsening disease during the study; or discontinuation due to a lack of efficacy (as determined by the investigator). For the latter two criteria, patients also needed to have a YMRS total score $\geq$ 14 and a MADRS total score $\geq$ 16 for a relapse to a manic episode; a YMRS total score $\geq$ 14 and a MADRS total score $\geq$ 16 for a relapse to a mixed episode; and a YMRS total score $\leq$ 14 and a MADRS total score $\geq$ 16 for a relapse to a depressive episode	RR = 0.92 [0.79, 1.06]	52	CARLSON2012
Aripiprazole compared with placebo (all participants taking lithium or valproate)	337	1	RR = 0.58 [0.38, 0.91]	One or more of the following: hospitalisation for a manic, mixed or depressive episode; a serious adverse event of worsening disease accompanied by a YMRS total score ≥ 16 and/or a MADRS total score ≥ 16; discontinuation due to lack of efficacy, as determined by the investigator, accompanied by a YMRS total score ≥ 16 and/or a MADRS total score ≥ 16	RR = 0.82 [0.64, 1.05]	52	MARCUS2011
Olanzapine compared with placebo (all participants taking lithium or valproate)	68	1	RR = 0.66 [0.38, 1.15]	YMRS total score ≥ 15, symptomatic relapse of depression defined as an HRSD-21 total score ≥ 15	RR = 0.77 [0.62, 0.94]	78	TOHEN2004
Olanzapine compared with placebo	278	1	RR = 0.42 [0.30, 0.59]	(1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (3) hospitalisation for any bipolar mood episode; (4) had YMRS score ≥ 12, MADRS score ≥ 12, or CGI-S scale score ≥ 4 at any visit	RR = 1.10 [0.66, 1.85]	78	VIETA2012

Paliperidone compared with placebo	300	1	RR = 0.83 [0.66, 1.06]	(1) YMRS ≥ 15 and CGI-BP-S for mania ≥ 4; YMRS ≥ 15, MADRS ≥ 16 and CGI-BP-S for depression ≥ 4; voluntary or involuntary hospitalisation for any mood symptoms; therapeutic intervention to prevent or treat an impending mood episode; another therapeutic measure; any other clinically relevant event suggestive of a recurrent mood episode	RR = 1.05 [0.78, 1.42]	129	BERWAERTS2012
Quetiapine compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with quetiapine)	585	1	RR = 0.59 [0.49, 0.76]	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.23 [1.05, 1.43]	52	YOUNG2012
Quetiapine compared with placebo (participants were randomised when euthymic after 4-24 weeks of active treatment with quetiapine)	808 <sup>8</sup>	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 20; or discontinuation due to depression and/or mania or hypomania	RR = 0.85 [0.63, 1.14]	104	WEISLER2011
Quetiapine compared with placebo (all participants were taking lithium or valproate)	1,326	2	RR = 0.38 [0.29, 0.48]	Initiation of any medication to treat mixed, manic, or depressive symptoms, including an antipsychotic, antidepressant, or mood-stabilising agent other than lithium or divalproex or an anxiolytic other than lorazepam; psychiatric hospitalisation; YMRS or MADRS total scores ≥ 20 at two consecutive assessments; or discontinuation from the study because of a mood event (as determined by the investigator)	RR = 1.53 [1.24, 1.89]	104	SUPPES2009, VIETA2008B

Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with risperidone)	273	1	RR = 0.69 [0.53, 0.90]	(1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (3) hospitalisation for any bipolar mood episode; (4) had YMRS score ≥ 12, MADRS score ≥ 12, or CGI-S scale score ≥ 4 at any visit	RR = 1.33 [0.82, 2.17]	78	VIETA2012
Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 3 weeks of active treatment with oral risperidone and 26 weeks of risperidone long-acting injectable)	303	1	RR = 0.63 [0.51, 0.77]	(1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (3) hospitalisation for any bipolar mood episode; (4) had YMRS score ≥ 12, MADRS score ≥ 12, or CGI-S scale score ≥ 4 at any visit	RR = 0.89 [0.61, 1.32]	104	QUIROZ2010
Risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual and were euthymic as randomisation following 16 weeks of active treatment with risperidone long-acting injectable)	124	1	RR = 0.50 [0.30, 0.85]	DSM-IV-TR criteria for an acute mood episode in the setting of adequate compliance with oral TAU.  Additionally, at least one of the following three conditions was satisfied: (i) clinical worsening, with the addition of a new mood stabiliser, antidepressant or antipsychotic or a > 20% dose increase of existing oral TAU medication, and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score ≥ 4 or CGI-BP-C score ≥ 6 or GAF score decreased by > 10 points from baseline; (ii) hospitalisation for worsening of manic or depressive symptoms and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score ≥ 4 or CGI-BP-C score ≥ 6 or GAF score decreased by > 10 points from baseline; (iii) hospitalisation for worsening of manic or depressive symptoms and having significant suicidal ideation	RR = 1.27 [0.61, 2.64]	52	MACFADDEN2009

Risperidone long-acting injectable in addition to treatment as usual compared with treatment as usual (all participants were rapid cycler's and not in an acute episode at randomisation)	50	1	NR	Occurrence of any of the following at any study visit: (1) a YMRS score >14 or a MADRS score >15; (2) 20% or greater increase in YMRS or MADRS scores from the previous study visit for patients with a MADRS score ≥ 10 or a YMRS score ≥ 8 at the current study visit; (3) urgent care visit/referral (psychiatric hospitalisation; emergency department visit; or referral for respite care, partial hospitalisation, or intensive outpatient treatment) due to worsening mood symptoms; (4) a CGI-S score ≥ 4; (5) syndromal relapse (DSM-IV-TR criteria for manic, hypomanic, major depressive, or mixed episode met); (6) withdrawal from the study due to inefficacy; and (7) necessary clinical medication adjustments	RR = 1.50 [0.63, 3.59]	52	BOBO2011b
Anticonvulsants							
Oxcarbazepine compared with placebo	55	1	RR = 0.50 [0.26, 0.94]	DSM-IV-TR criteria for a manic, hypomanic, mixed or depressive episode or scoring ≥ 12 in the YMRS or ≥ 20 in the MADRS	RR = 1.12 [0.55, 2.24]	52	VIETA2008
Gabapentin compared with placebo	25	1	NR	NR	RR = 1.08 [0.51, 2.30]	52	VIETA2006
Lamotrigine compared with placebo	471	2	RR = 0.82 [0.59, 1.14]	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.14 [0.64, 2.06]	76, 78	CALABRESE2003, BOWDEN2003
Valproate compared with placebo	281	1	RR = 0.63 [0.44, 0.90]	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.02 [0.74, 1.40]	52	BOWDEN2000
Antidepressants				I.			

Imipramine compared with placebo (all participants were taking lithium)	75	1	RR = 1.54 [0.71, 3.33]	Research diagnostic criteria for mania or major depressive disorder	RR = 0.86 [0.65, 1.13]	129	QUITKIN1981
Imipramine compared with placebo	26	1	RR = 0.75 [0.36, 1.55]	Manic or depressive attack requiring hospitalisation or supplementary drugs (that is, psychopharmacologic agents other than the patient's assigned treatment)	RR = 1.17 [0.54, 2.53]	104	PRIEN1973b
Imipramine and lithium combination compared with lithium	78μ	1	RR = 0.68 [0.49, 0.93]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less	$RR^{\theta} = 5.81$ [0.29, 117.23]	104	PRIEN1984
Imipramine and lithium combination compared with imipramine	72 <sup>μ</sup>	1	RR = 0.62 [0.43, 0.89]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less	$RR^{\partial} = 5.81$ [0.29, 117.23]	104	PRIEN1984
Imipramine compared with lithium	78μ	1	RR = 1.47 [1.07, 2.02]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less	There was no discontinuation in either group.	104	PRIEN1984
Antidepressants compared with placebo	70	1	NR	NR	NR	52	GHAEMI2010

<sup>\*</sup> A relative risk (RR) of less than 1 favours the first treatment named.

<sup>†</sup> Definitions of relapse which do not meet the GDG's definition have been italicised.

<sup>‡</sup> Length of follow-up reported in number of weeks.

βGEDDES2010 is a three-arm trial including lithium, valproate and the combination of lithium and valproate. The overall number of participants is 330. All three comparisons have been included in this table so the number of participants has been double-counted.

δWEISLER2011 is a three-arm trial including lithium, quetiapine and placebo. The overall number of participants is 1,172. All three comparisons have been included in this table so the number of participants has been double-counted.

<sup>&</sup>lt;sup>µ</sup>PRIEN1984 is a three-arm trial including imipramine, lithium and the combination of imipramine and lithium. The overall number of participants is 114. All three comparisons have been included in this table so the number of participants has been double-counted.

 $<sup>\</sup>partial$  Discontinuation due to side effects. No other reasons for discontinuation were reported.