APPENDIX 21: PHARMACOLOGICAL INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF BIPOLAR DISORDER – FOREST PLOTS

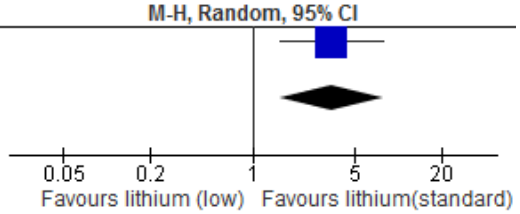
Lithium

Outcomes for low dose of lithium compared with standard dose

Number of participants who relapsed[1] (any type)

Study or Subgroup	Lithium (low) Events	Lithium (low) Total	Lithium (standard) Events	Lithium (standard) Total	Weight	Risk Ratio M-H, Random, 95% CI
GELENBERG1989	21	47	6	47	100.0%	3.50 [1.55, 7.89]
Total (95% CI)		**47**		**47**	**100.0%**	**3.50 [1.55, 7.89]**
Total events	21		6			

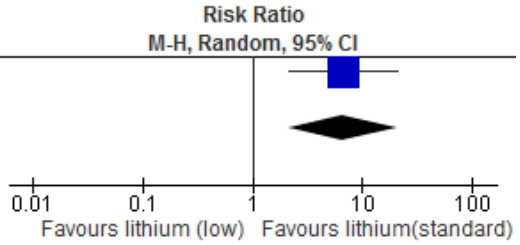
Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.003)



Number of participants who relapsed (mania)

Study or Subgroup	Lithium (low) Events	Lithium (low) Total	Lithium (standard) Events	Lithium (standard) Total	Weight	Risk Ratio M-H, Random, 95% CI
GELENBERG1989	20	47	3	47	100.0%	6.67 [2.12, 20.93]
Total (95% CI)		**47**		**47**	**100.0%**	**6.67 [2.12, 20.93]**
Total events	20		3			

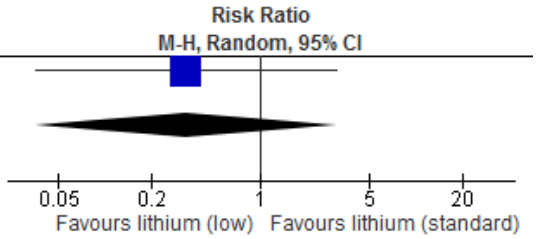
Heterogeneity: Not applicable
Test for overall effect: Z = 3.25 (P = 0.001)



Number of participants who relapsed(depression)

Study or Subgroup	Lithium (low) Events	Lithium (low) Total	Lithium (standard) Events	Lithium (standard) Total	Weight	Risk Ratio M-H, Random, 95% CI
GELENBERG1989	1	47	3	47	100.0%	0.33 [0.04, 3.09]
Total (95% CI)		**47**		**47**	**100.0%**	**0.33 [0.04, 3.09]**
Total events	1		3			

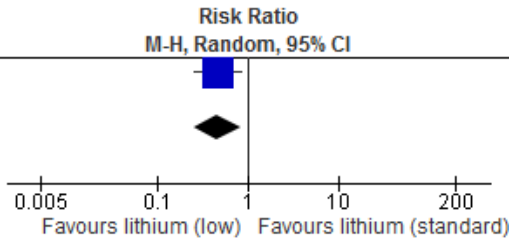
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)



Number of participants discontinuing(for any reason)

Study or Subgroup	Lithium (low) Events	Lithium (low) Total	Lithium (standard) Events	Lithium (standard) Total	Weight	Risk Ratio M-H, Random, 95% CI
GELENBERG1989	11	47	24	47	100.0%	0.46 [0.25, 0.83]
Total (95% CI)		**47**		**47**	**100.0%**	**0.46 [0.25, 0.83]**
Total events	11		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.60 (P = 0.009)



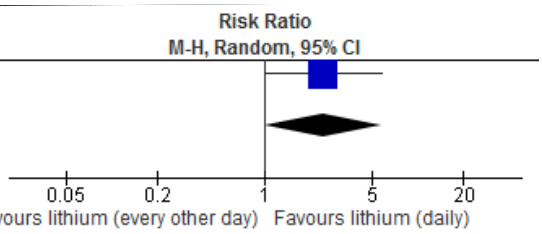
Outcomes for lithium every other day compared with lithium daily

Number of participants who relapsed (any type)

[1] The definition of relapse differs between studies. Please refer to Table 1 below for a full definition.

Study or Subgroup	Lithium (every other day) Events	Total	Lithium (daily) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
JENSEN1995	12	25	5	25	100.0%	2.40 [0.99, 5.81]
Total (95% CI)		**25**		**25**	**100.0%**	**2.40 [0.99, 5.81]**
Total events	12		5			

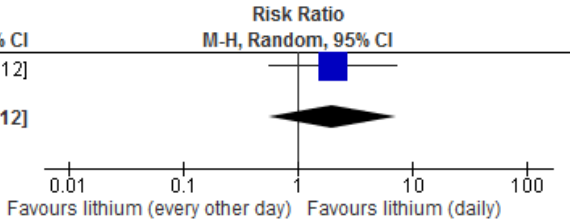
Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)



Number of participants who relapsed (mania)

Study or Subgroup	Lithium (every other day) Events	Total	Lithium (daily) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
JENSEN1995	6	25	3	25	100.0%	2.00 [0.56, 7.12]
Total (95% CI)		**25**		**25**	**100.0%**	**2.00 [0.56, 7.12]**
Total events	6		3			

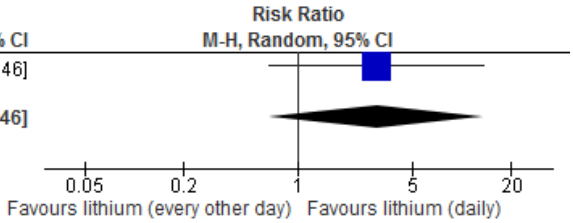
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)



Number of participants who relapsed (depression)

Study or Subgroup	Lithium (every other day) Events	Total	Lithium (daily) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
JENSEN1995	6	25	2	25	100.0%	3.00 [0.67, 13.46]
Total (95% CI)		**25**		**25**	**100.0%**	**3.00 [0.67, 13.46]**
Total events	6		2			

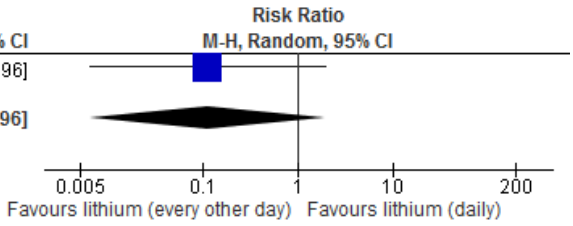
Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)



Number of participants discontinuing (for any reason)

Study or Subgroup	Lithium (every other day) Events	Total	Lithium (daily) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
JENSEN1995	0	25	4	25	100.0%	0.11 [0.01, 1.96]
Total (95% CI)		**25**		**25**	**100.0%**	**0.11 [0.01, 1.96]**
Total events	0		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)

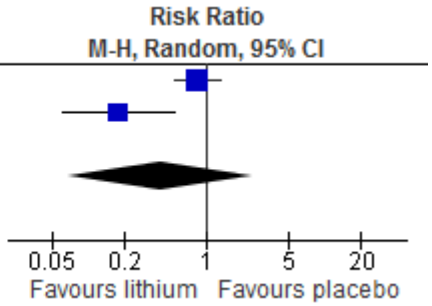


Outcomes for lithium compared with placebo

Number of participants who relapsed (any type)

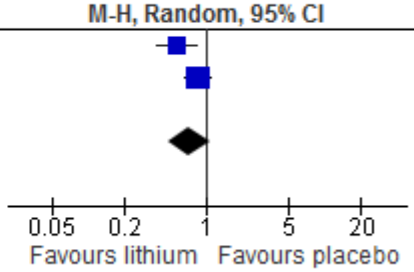
Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
DUNNER1976	10	16	18	24	53.9%	0.83 [0.53, 1.30]
STALLONE1973	3	25	18	27	46.1%	0.18 [0.06, 0.54]
Total (95% CI)		**41**		**51**	**100.0%**	**0.41 [0.07, 2.43]**
Total events	13		36			

Heterogeneity: Tau² = 1.47; Chi² = 9.11, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.98 (P = 0.33)



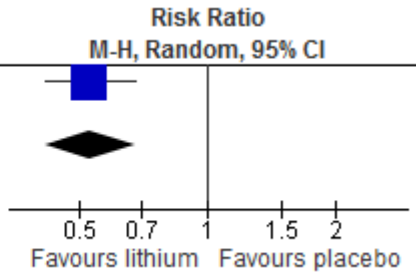
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	18	46	49	70	43.3%	0.56 [0.38, 0.83]
CALABRESE2003	56	121	66	121	56.7%	0.85 [0.66, 1.09]
Total (95% CI)		**167**		**191**	**100.0%**	**0.71 [0.47, 1.06]**
Total events	74		115			

Heterogeneity: Tau² = 0.06; Chi² = 3.10, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 1.66 (P = 0.10)



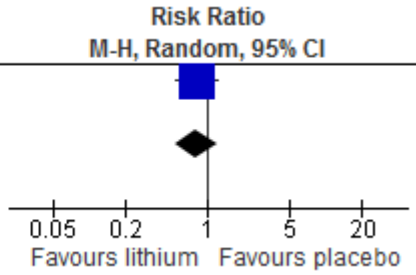
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973	43	101	84	104	100.0%	0.53 [0.41, 0.67]
Total (95% CI)		**101**		**104**	**100.0%**	**0.53 [0.41, 0.67]**
Total events	43		84			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.12 (P < 0.00001)



Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

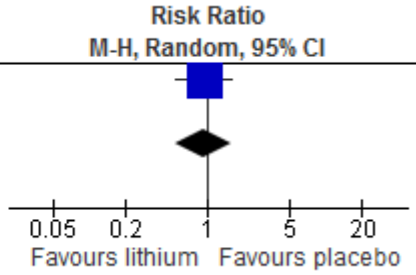
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)



Number of participants who relapsed (mania)

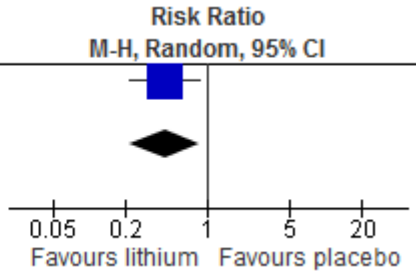
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	19	91	21	94	100.0%	0.93 [0.54, 1.62]
Total (95% CI)		**91**		**94**	**100.0%**	**0.93 [0.54, 1.62]**
Total events	19		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



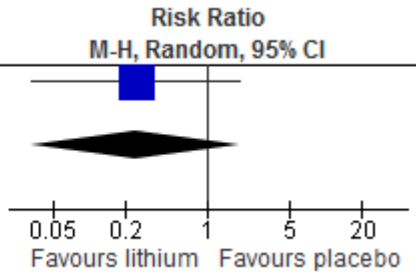
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	8	46	28	70	100.0%	0.43 [0.22, 0.87]
Total (95% CI)		**46**		**70**	**100.0%**	**0.43 [0.22, 0.87]**
Total events	8		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.36 (P = 0.02)



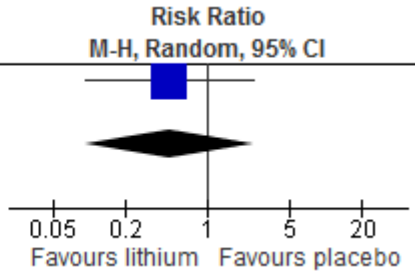
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
DUNNER1976	1	16	6	24	100.0%	0.25 [0.03, 1.89]
Total (95% CI)		**16**		**24**	**100.0%**	**0.25 [0.03, 1.89]**
Total events	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)



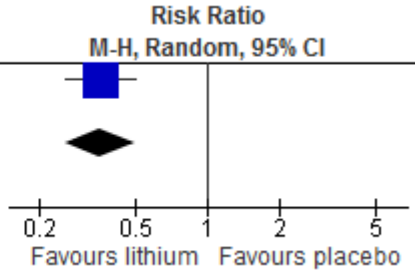
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973B	2	18	3	13	100.0%	0.48 [0.09, 2.48]
Total (95% CI)		**18**		**13**	**100.0%**	**0.48 [0.09, 2.48]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)



Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

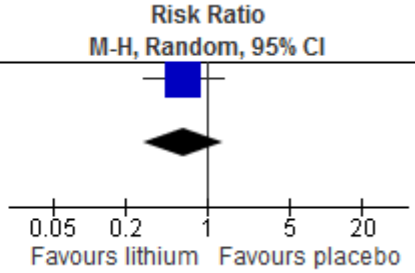
Heterogeneity: Not applicable
Test for overall effect: Z = 5.92 (P < 0.00001)



Number of participants who relapsed (depression)

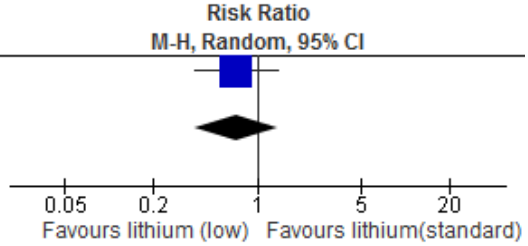
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	9	91	15	94	100.0%	0.62 [0.29, 1.34]
Total (95% CI)		**91**		**94**	**100.0%**	**0.62 [0.29, 1.34]**
Total events	9		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)



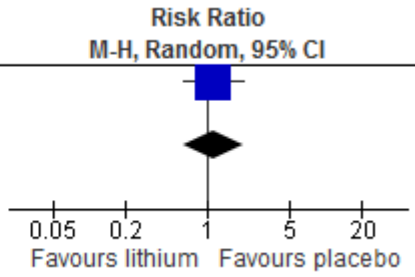
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	10	46	21	70	100.0%	0.72 [0.38, 1.39]
Total (95% CI)		**46**		**70**	**100.0%**	**0.72 [0.38, 1.39]**
Total events	10		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.33)



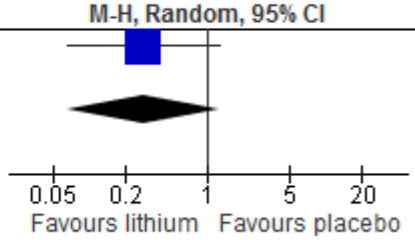
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
DUNNER1976	9	16	12	24	100.0%	1.13 [0.62, 2.03]
Total (95% CI)		**16**		**24**	**100.0%**	**1.13 [0.62, 2.03]**
Total events	9		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)



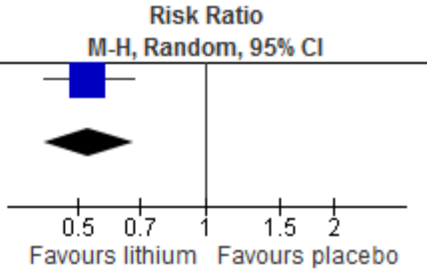
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973B	2	18	5	13	100.0%	0.29 [0.07, 1.26]
Total (95% CI)		**18**		**13**	**100.0%**	**0.29 [0.07, 1.26]**
Total events	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)



Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

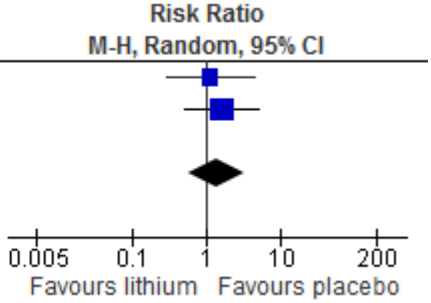
Heterogeneity: Not applicable
Test for overall effect: Z = 5.12 (P < 0.00001)



Number of participants discontinuing (for any reason)

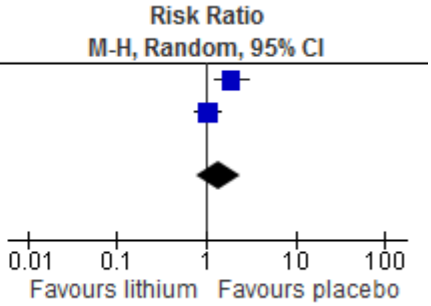
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
DUNNER1976	3	16	4	24	41.5%	1.13 [0.29, 4.37]
STALLONE1973	6	25	4	27	58.5%	1.62 [0.52, 5.08]
Total (95% CI)		**41**		**51**	**100.0%**	**1.39 [0.58, 3.34]**
Total events	9		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)



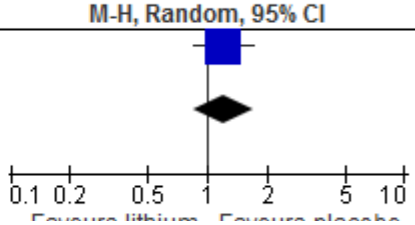
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	26	46	21	70	47.0%	1.88 [1.22, 2.92]
CALABRESE2003	45	121	43	121	53.0%	1.05 [0.75, 1.46]
Total (95% CI)		**167**		**191**	**100.0%**	**1.38 [0.78, 2.45]**
Total events	71		64			

Heterogeneity: Tau² = 0.13; Chi² = 4.39, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 1.09 (P = 0.27)



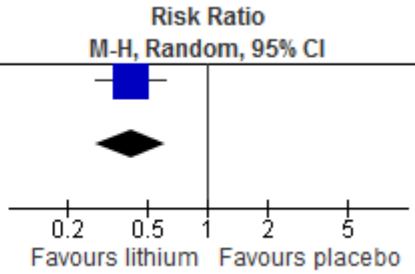
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	41	91	35	94	100.0%	1.21 [0.86, 1.71]
Total (95% CI)		**91**		**94**	**100.0%**	**1.21 [0.86, 1.71]**
Total events	41		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



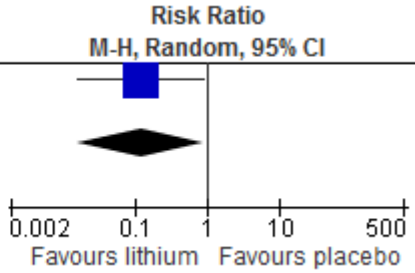
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973	23	101	57	104	100.0%	0.42 [0.28, 0.62]
Total (95% CI)		**101**		**104**	**100.0%**	**0.42 [0.28, 0.62]**
Total events	23		57			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.31 (P < 0.0001)



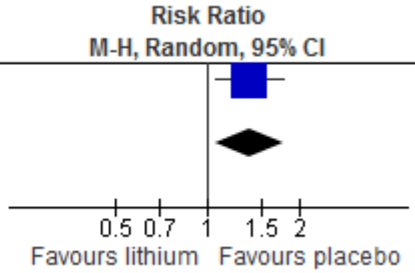
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973B	1	18	6	13	100.0%	0.12 [0.02, 0.88]
Total (95% CI)		**18**		**13**	**100.0%**	**0.12 [0.02, 0.88]**
Total events	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.08 (P = 0.04)



Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

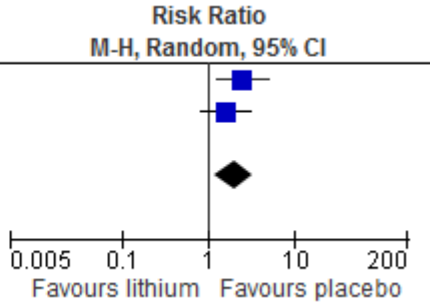
Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)



Number of participants discontinuing due to side effects

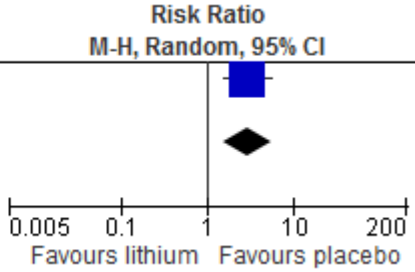
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	16	46	10	70	48.6%	2.43 [1.21, 4.89]
CALABRESE2003	19	121	12	121	51.4%	1.58 [0.80, 3.12]
Total (95% CI)		**167**		**191**	**100.0%**	**1.95 [1.20, 3.17]**
Total events	35		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)



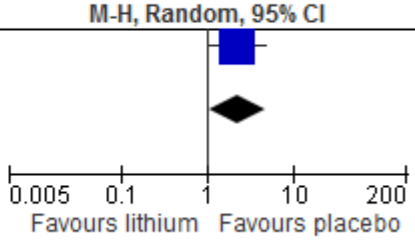
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	31	91	11	94	100.0%	2.91 [1.56, 5.44]
Total (95% CI)		**91**		**94**	**100.0%**	**2.91 [1.56, 5.44]**
Total events	31		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.35 (P = 0.0008)



Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

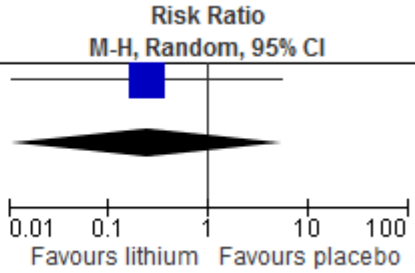
Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)



Number of suicides

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

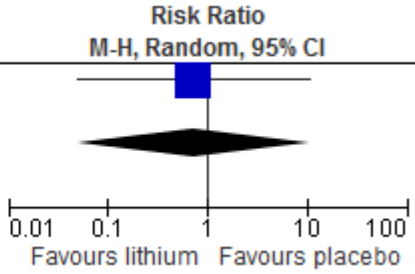
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



Number of deaths

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973B	1	18	1	13	100.0%	0.72 [0.05, 10.52]
Total (95% CI)		**18**		**13**	**100.0%**	**0.72 [0.05, 10.52]**
Total events	1		1			

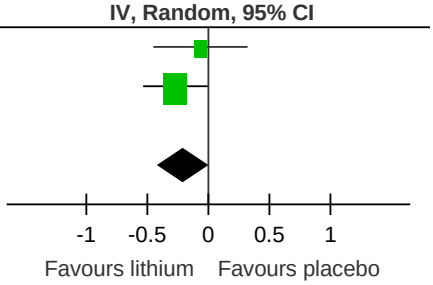
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



*Psychosocial functioning (Global assessment scale)**

Study or Subgroup	Lithium Mean	Lithium SD	Lithium Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference 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: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)



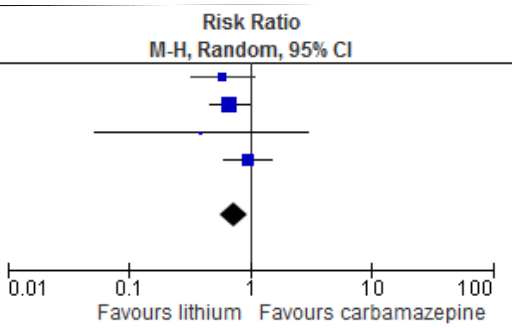
*Scores have been reversed so that higher change scores indicate a worsening of functioning

Outcomes for lithium compared with carbamazepine

Number of participants who relapsed (any type)

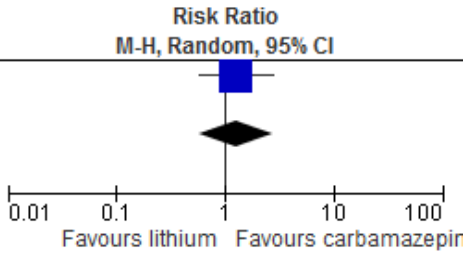
Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
HARTONG2003	11	44	21	50	18.8%	0.60 [0.32, 1.09]
KLEINDIENST2000a	23	58	33	56	46.6%	0.67 [0.46, 0.99]
KLEINDIENST2000b	1	9	4	14	1.7%	0.39 [0.05, 2.95]
WOLF1997	25	84	26	84	33.0%	0.96 [0.61, 1.52]
Total (95% CI)		**195**		**204**	**100.0%**	**0.73 [0.56, 0.95]**
Total events	60		84			

Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)



Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
COXHEAD1992	8	16	6	15	100.0%	1.25 [0.57, 2.75]
Total (95% CI)		**16**		**15**	**100.0%**	**1.25 [0.57, 2.75]**
Total events	8		6			

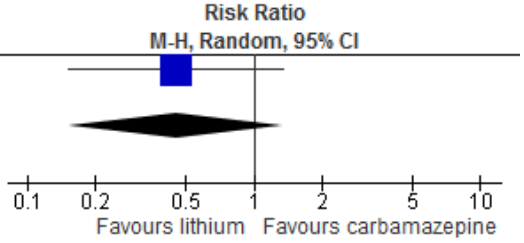
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)



Number of participants who relapsed(mania)

Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
HARTONG2003	4	44	10	50	100.0%	0.45 [0.15, 1.35]
Total (95% CI)		**44**		**50**	**100.0%**	**0.45 [0.15, 1.35]**
Total events	4		10			

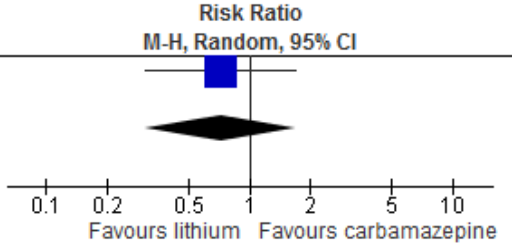
Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)



Number of participants who relapsed (depression)

Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio 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			

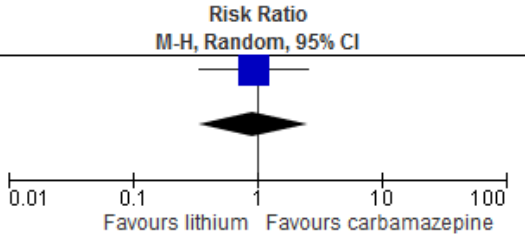
Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)



Number of participants who were hospitalised

Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
COXHEAD1992	5	16	5	15	100.0%	0.94 [0.34, 2.60]
Total (95% CI)		**16**		**15**	**100.0%**	**0.94 [0.34, 2.60]**
Total events	5		5			

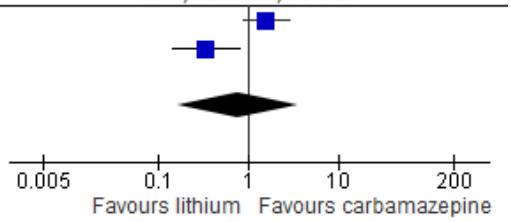
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)



Number of participants discontinuing(for any reason)

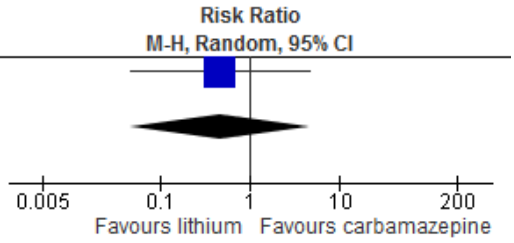
Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
HARTONG2003	18	44	13	50	52.2%	1.57 [0.87, 2.83]
WOLF1997	6	84	18	84	47.8%	0.33 [0.14, 0.80]
Total (95% CI)		**128**		**134**	**100.0%**	**0.75 [0.16, 3.54]**
Total events	24		31			

Heterogeneity: Tau² = 1.11; Chi² = 8.73, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.36 (P = 0.72)



Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
COXHEAD1992	1	16	2	15	100.0%	0.47 [0.05, 4.65]
Total (95% CI)		**16**		**15**	**100.0%**	**0.47 [0.05, 4.65]**
Total events	1		2			

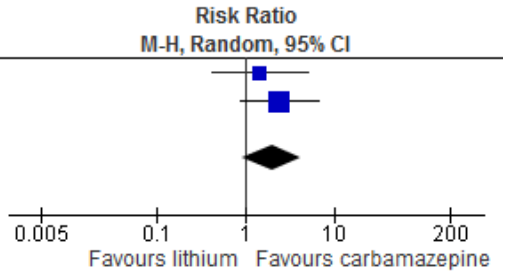
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)



Number of participants discontinuing due to side effects

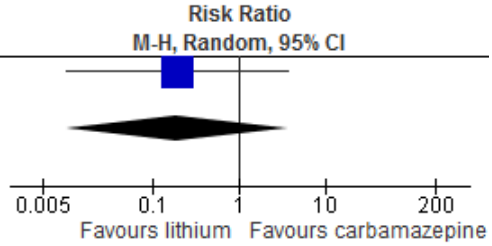
Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
HARTONG2003	5	44	4	50	38.9%	1.42 [0.41, 4.96]
WOLF1997	12	84	5	84	61.1%	2.40 [0.88, 6.51]
Total (95% CI)		**128**		**134**	**100.0%**	**1.96 [0.90, 4.27]**
Total events	17		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)



Study or Subgroup	Lithium Events	Lithium Total	Carbamazepine Events	Carbamazepine Total	Weight	Risk Ratio M-H, Random, 95% CI
COXHEAD1992	0	16	2	15	100.0%	0.19 [0.01, 3.63]
Total (95% CI)		**16**		**15**	**100.0%**	**0.19 [0.01, 3.63]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)

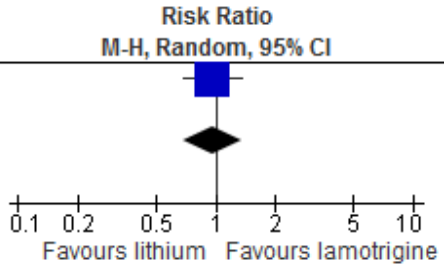


Outcomes for lithium compared with lamotrigine

Number of participants who relapsed (any type)

Study or Subgroup	Lithium Events	Lithium Total	Lamotrigine Events	Lamotrigine Total	Weight	Risk Ratio 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]**
Total events	31		33			

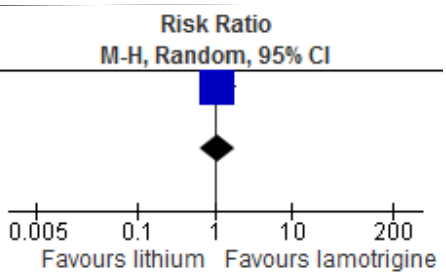
Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)



Number of participants discontinuing(for any reason)

Study or Subgroup	Lithium Events	Lithium Total	Lamotrigine Events	Lamotrigine Total	Weight	Risk Ratio M-H, Random, 95% CI
LICHT2010	19	60	18	62	100.0%	1.09 [0.64, 1.87]
Total (95% CI)		**60**		**62**	**100.0%**	**1.09 [0.64, 1.87]**
Total events	19		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

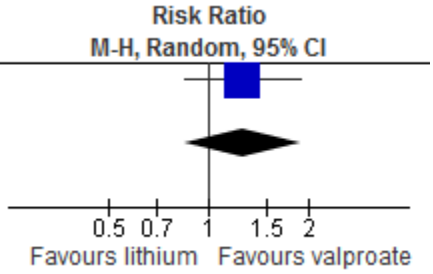


Outcomes for lithium compared with valproate

Number of participants who relapsed(any type)

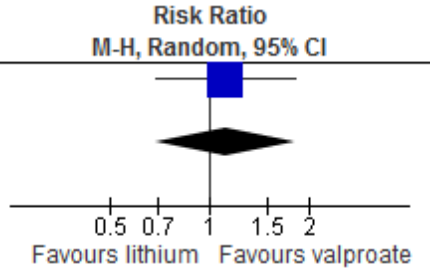
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	28	91	45	187	100.0%	1.28 [0.86, 1.91]
Total (95% CI)		**91**		**187**	**100.0%**	**1.28 [0.86, 1.91]**
Total events	28		45			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)



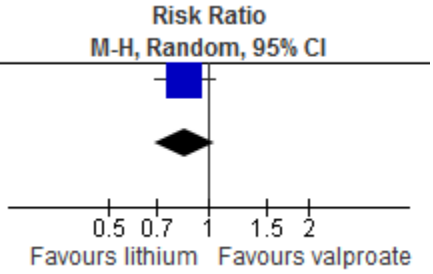
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
CALABRESE2005C	18	32	14	28	100.0%	1.13 [0.70, 1.82]
Total (95% CI)		**32**		**28**	**100.0%**	**1.13 [0.70, 1.82]**
Total events	18		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)



Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
GEDDES2010	64	110	75	110	100.0%	0.85 [0.70, 1.05]
Total (95% CI)		**110**		**110**	**100.0%**	**0.85 [0.70, 1.05]**
Total events	64		75			

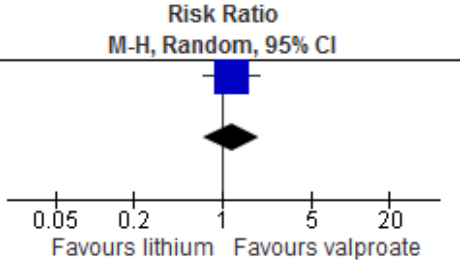
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)



Number of participants who relapsed(mania)

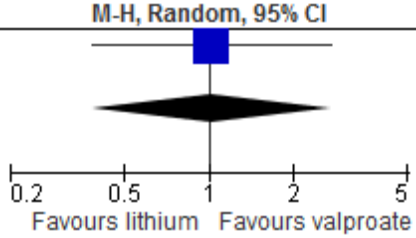
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	19	91	33	187	100.0%	1.18 [0.71, 1.96]
Total (95% CI)		**91**		**187**	**100.0%**	**1.18 [0.71, 1.96]**
Total events	19		33			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)



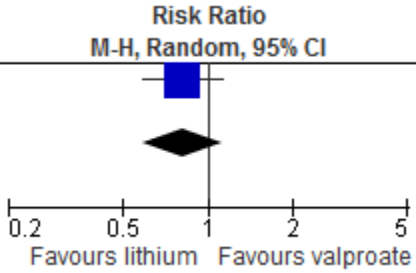
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
CALABRESE2005C	7	32	6	28	100.0%	1.02 [0.39, 2.68]
Total (95% CI)		**32**		**28**	**100.0%**	**1.02 [0.39, 2.68]**
Total events	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)



Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% 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			

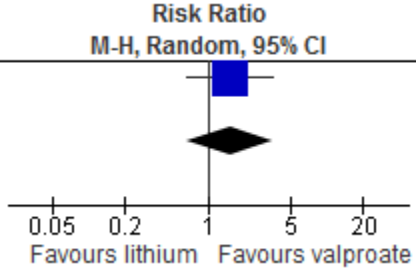
Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)



Number of participants who relapsed (depression)

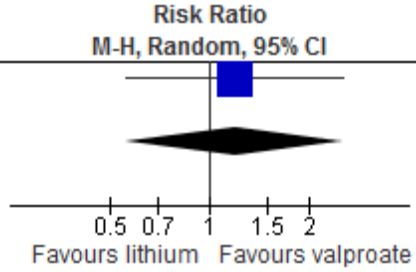
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	9	91	12	187	100.0%	1.54 [0.67, 3.52]
Total (95% CI)		**91**		**187**	**100.0%**	**1.54 [0.67, 3.52]**
Total events	9		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)



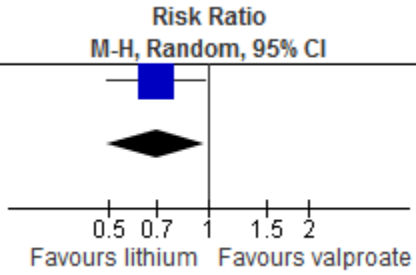
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
CALABRESE2005C	11	32	8	28	100.0%	1.20 [0.56, 2.56]
Total (95% CI)		**32**		**28**	**100.0%**	**1.20 [0.56, 2.56]**
Total events	11		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)



Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
GEDDES2010	35	110	50	110	100.0%	0.70 [0.50, 0.99]
Total (95% CI)		**110**		**110**	**100.0%**	**0.70 [0.50, 0.99]**
Total events	35		50			

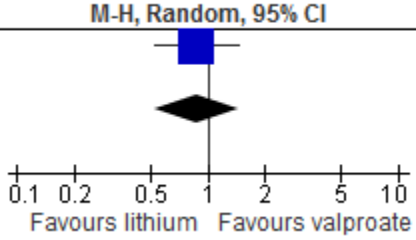
Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)



Number of participants who were hospitalised

Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio 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			

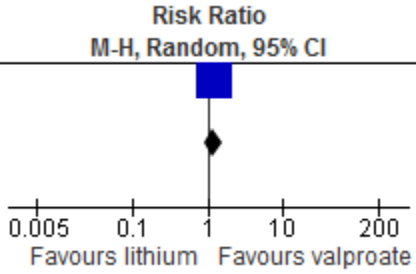
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)



Number of participants discontinuing (for any reason)

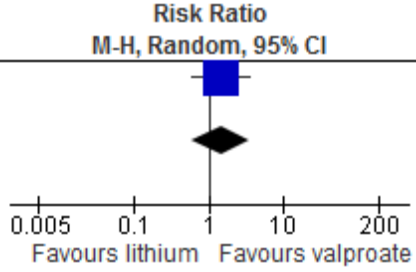
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	41	91	71	187	100.0%	1.19 [0.89, 1.59]
Total (95% CI)		**91**		**187**	**100.0%**	**1.19 [0.89, 1.59]**
Total events	41		71			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)



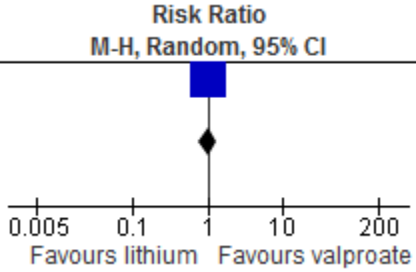
Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
CALABRESE2005C	10	32	6	28	100.0%	1.46 [0.61, 3.50]
Total (95% CI)		**32**		**28**	**100.0%**	**1.46 [0.61, 3.50]**
Total events	10		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio 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			

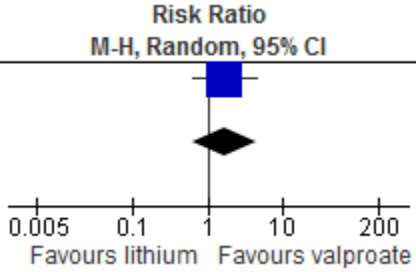
Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)



Number of participants discontinuing due to side effects

Study or Subgroup	Lithium Events	Lithium Total	Valproate Events	Valproate Total	Weight	Risk Ratio 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
Test for overall effect: Z = 1.02 (P = 0.31)

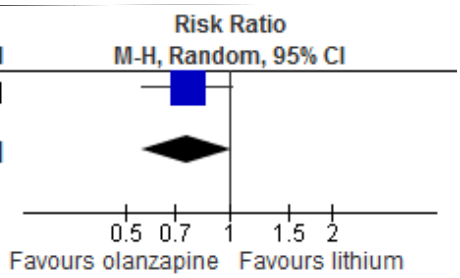


Outcomes for olanzapine compared with lithium

Number of participants who relapsed (any type)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Lithium Events	Lithium Total	Weight	Risk Ratio M-H, Random, 95% CI
TOHEN2005	53	217	69	214	100.0%	0.76 [0.56, 1.03]
Total (95% CI)		**217**		**214**	**100.0%**	**0.76 [0.56, 1.03]**
Total events	53		69			

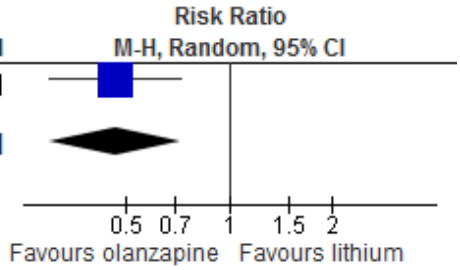
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



Number of participants who relapsed (mania)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Lithium Events	Lithium Total	Weight	Risk Ratio 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			

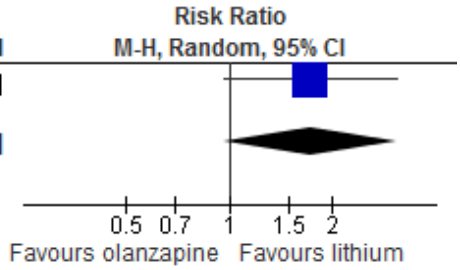
Heterogeneity: Not applicable
Test for overall effect: Z = 3.44 (P = 0.0006)



Number of participants who relapsed (depression)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Lithium Events	Lithium Total	Weight	Risk Ratio 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			

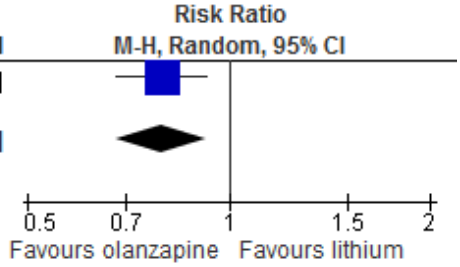
Heterogeneity: Not applicable
Test for overall effect: Z = 1.83 (P = 0.07)



Number of participants discontinuing (for any reason)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Lithium Events	Lithium Total	Weight	Risk Ratio M-H, Random, 95% CI
TOHEN2005	116	217	144	214	100.0%	0.79 [0.68, 0.93]
Total (95% CI)		**217**		**214**	**100.0%**	**0.79 [0.68, 0.93]**
Total events	116		144			

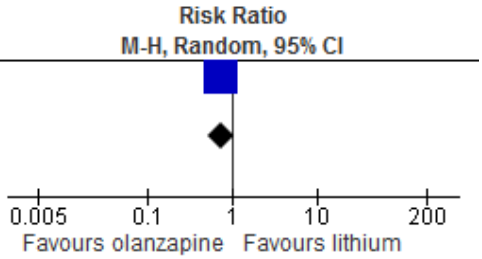
Heterogeneity: Not applicable
Test for overall effect: Z = 2.90 (P = 0.004)



Number of participants discontinuing due to side effects

Study or Subgroup	Olanzapine Events	Olanzapine Total	Lithium Events	Lithium Total	Weight	Risk Ratio M-H, Random, 95% CI
TOHEN2005	41	217	55	214	100.0%	0.74 [0.51, 1.05]
Total (95% CI)		**217**		**214**	**100.0%**	**0.74 [0.51, 1.05]**
Total events	41		55			

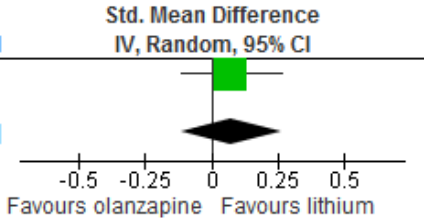
Heterogeneity: Not applicable
Test for overall effect: Z = 1.69 (P = 0.09)



Change in weight (kg)

Study or Subgroup	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Lithium Mean	Lithium SD	Lithium Total	Weight	Std. Mean Difference 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 applicable
Test for overall effect: Z = 0.76 (P = 0.44)

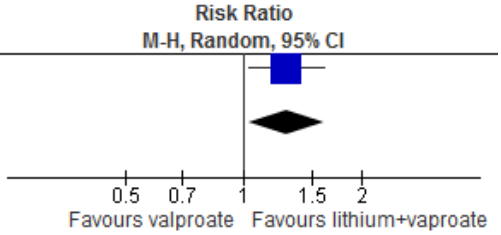


Outcomes for valproatecompared with lithium and valproate combination

Number of participants who relapsed (any type)

Study or Subgroup	Valproate Events	Valproate Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio 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	75		58			

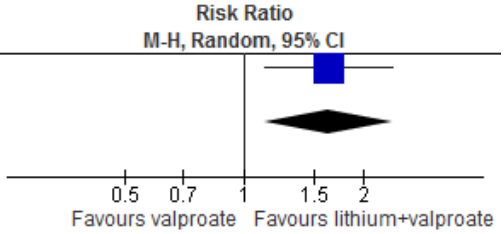
Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (P = 0.02)



Number of participants who relapsed (mania)

Study or Subgroup	Valproate Events	Valproate Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio 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			

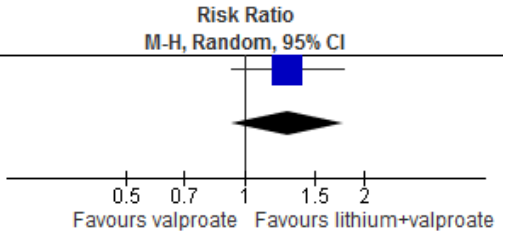
Heterogeneity: Not applicable
Test for overall effect: Z = 2.60 (P = 0.009)



Number of participants who relapsed (depression)

Study or Subgroup	Valproate Events	Valproate Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
GEDDES2010	50	110	39	110	100.0%	1.28 [0.93, 1.77]
Total (95% CI)		**110**		**110**	**100.0%**	**1.28 [0.93, 1.77]**
Total events	50		39			

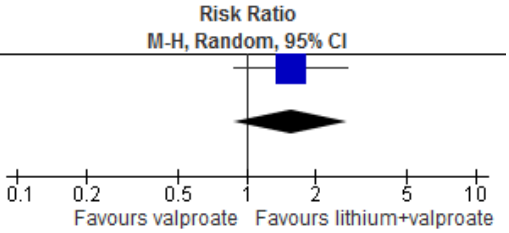
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)



Number of participants who were hospitalised

Study or Subgroup	Valproate Events	Valproate Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio 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			

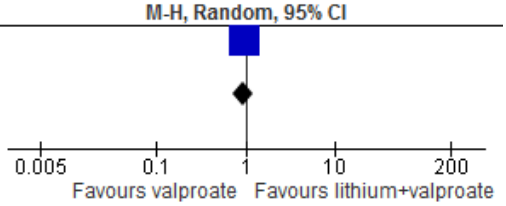
Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)



Number of participants discontinuing (for any reason)

Study or Subgroup	Valproate Events	Valproate Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio M-H, Random, 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			

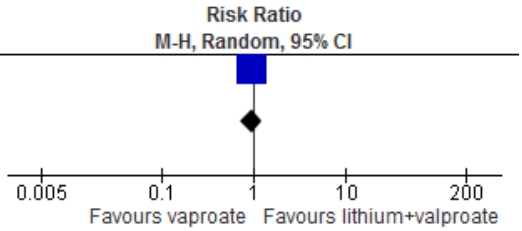
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



Number of participants discontinuing due to side effects

Study or Subgroup	Valproate Events	Valproate Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio M-H, Random, 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 applicable
Test for overall effect: Z = 0.40 (P = 0.69)

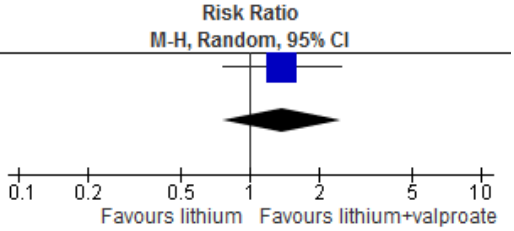


Outcomes for lithium compared with lithium and valproate combination

Number of participants who were hospitalised

Study or Subgroup	Lithium Events	Lithium Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
GEDDES2010	22	110	16	110	100.0%	1.38 [0.76, 2.47]
Total (95% CI)		**110**		**110**	**100.0%**	**1.38 [0.76, 2.47]**
Total events	22		16			

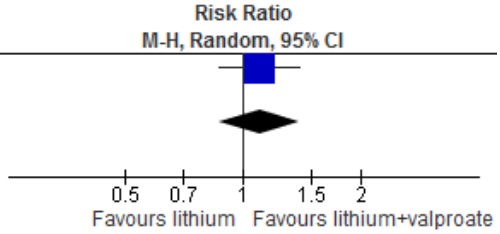
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



Number of participants who relapsed (any type)

Study or Subgroup	Lithium Events	Lithium Total	Lithium + Valproate Events	Lithium + Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
GEDDES2010	64	110	58	110	100.0%	1.10 [0.87, 1.40]
Total (95% CI)		**110**		**110**	**100.0%**	**1.10 [0.87, 1.40]**
Total events	64		58			

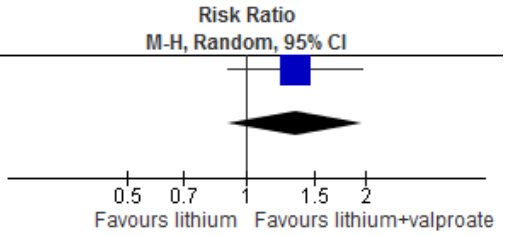
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)



Number of participants who relapsed (mania)

Study or Subgroup	Lithium Events	Lithium Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio 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			

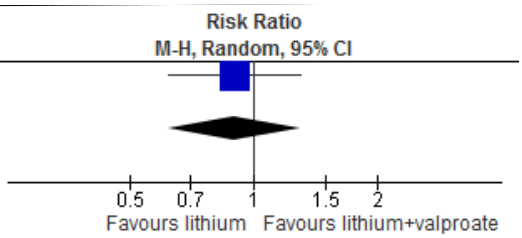
Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)



Number of participants who relapsed (depression)

Study or Subgroup	Lithium Events	Lithium Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio 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			

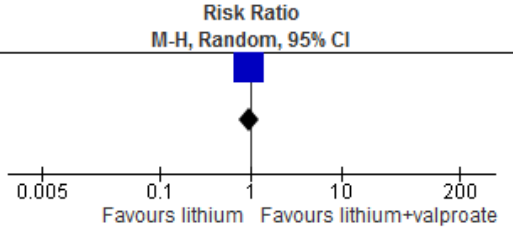
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)



Number of participants discontinuing (for any reason)

Study or Subgroup	Lithium Events	Lithium Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio M-H, Random, 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]**
Total events	54		56			

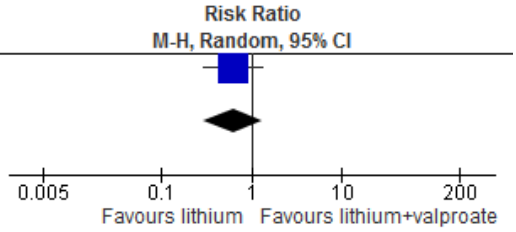
Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)



Number of participants discontinuing due to side effects

Study or Subgroup	Lithium Events	Lithium Total	Lithium + valproate Events	Lithium + valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
GEDDES2010	10	110	16	110	100.0%	0.63 [0.30, 1.32]
Total (95% CI)		**110**		**110**	**100.0%**	**0.63 [0.30, 1.32]**
Total events	10		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.22)



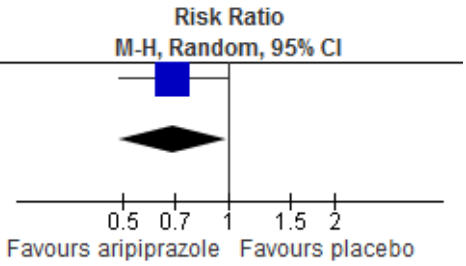
Antipsychotics

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

Number of participants who relapsed (any type)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
CARLSON2012	40	178	56	173	100.0%	0.69 [0.49, 0.98]
Total (95% CI)		**178**		**173**	**100.0%**	**0.69 [0.49, 0.98]**
Total events	40		56			

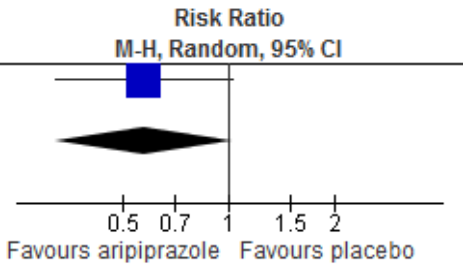
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



Number of participants who relapsed (mania)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

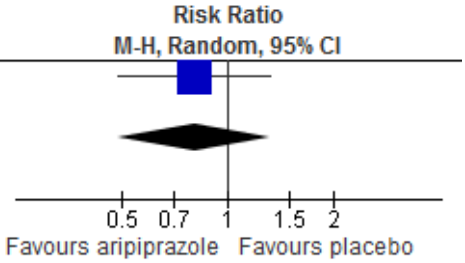
Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)



Number of participants who relapsed (depression)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

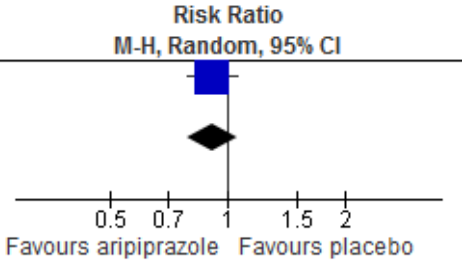
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



Number of participants discontinuing(for any reason)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
CARLSON2012	113	178	120	173	100.0%	0.92 [0.79, 1.06]
Total (95% CI)		**178**		**173**	**100.0%**	**0.92 [0.79, 1.06]**
Total events	113		120			

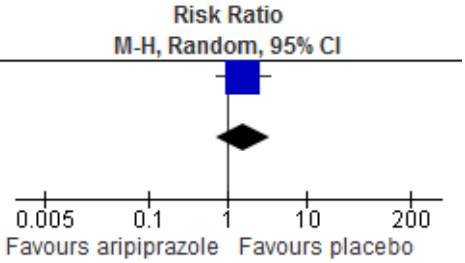
Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.24)



Number of participants discontinuing due to side effects

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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]**
Total events	16		10			

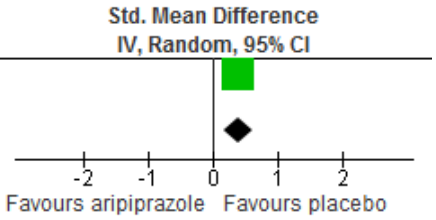
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.26)



Change in weight (kg)

Study or Subgroup	Aripiprazole Mean	Aripiprazole SD	Aripiprazole Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference 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 applicable
Test for overall effect: Z = 3.29 (P = 0.0010)

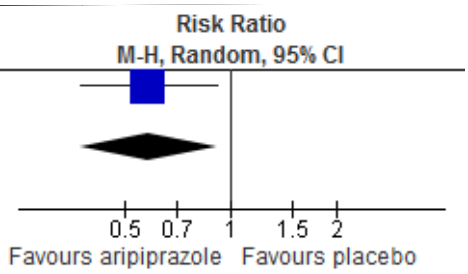


Outcomes for aripiprazole compared with placebo (all participants taking lithium or valproate)

Number of participants who relapsed (any type)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
MARCUS2011	25	168	43	169	100.0%	0.58 [0.38, 0.91]
Total (95% CI)		**168**		**169**	**100.0%**	**0.58 [0.38, 0.91]**
Total events	25		43			

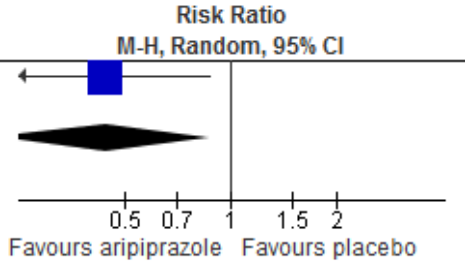
Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)



Number of participants who relapsed (mania/mixed)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
MARCUS2011	11	168	25	169	100.0%	0.44 [0.23, 0.87]
Total (95% CI)		**168**		**169**	**100.0%**	**0.44 [0.23, 0.87]**
Total events	11		25			

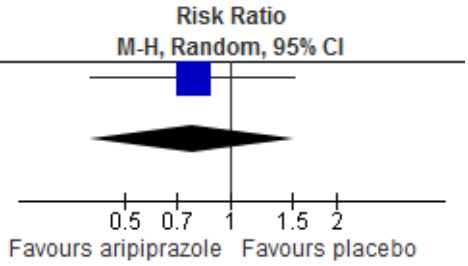
Heterogeneity: Not applicable
Test for overall effect: Z = 2.36 (P = 0.02)



Number of participants who relapsed (depression)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
MARCUS2011	14	168	18	169	100.0%	0.78 [0.40, 1.52]
Total (95% CI)		**168**		**169**	**100.0%**	**0.78 [0.40, 1.52]**
Total events	14		18			

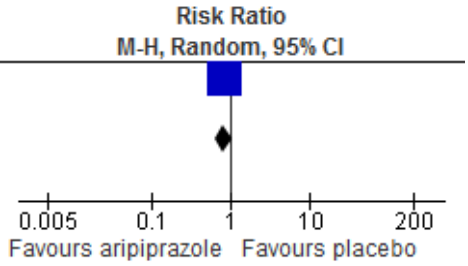
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



Number of participants discontinuing(for any reason)

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
MARCUS2011	65	168	80	169	100.0%	0.82 [0.64, 1.05]
Total (95% CI)		**168**		**169**	**100.0%**	**0.82 [0.64, 1.05]**
Total events	65		80			

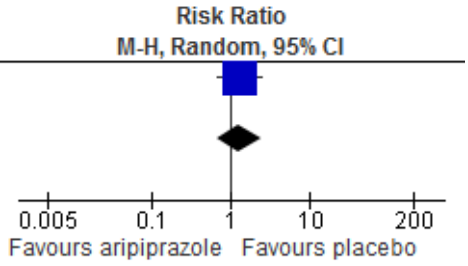
Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)



Number of participants discontinuing due to side effects

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
MARCUS2011	19	168	15	169	100.0%	1.27 [0.67, 2.42]
Total (95% CI)		**168**		**169**	**100.0%**	**1.27 [0.67, 2.42]**
Total events	19		15			

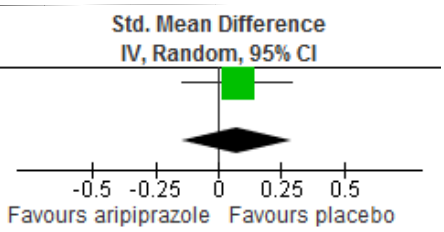
Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)



Change in weight (kg)

Study or Subgroup	Aripiprazole Mean	Aripiprazole SD	Aripiprazole Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference 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]**

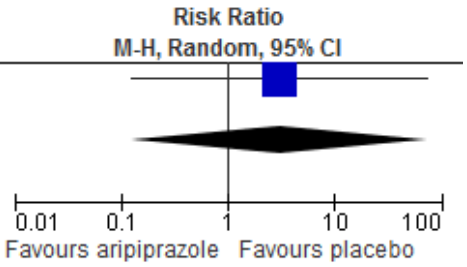
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



Number of suicides

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
MARCUS2011	1	168	0	169	100.0%	3.02 [0.12, 73.55]
Total (95% CI)		**168**		**169**	**100.0%**	**3.02 [0.12, 73.55]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

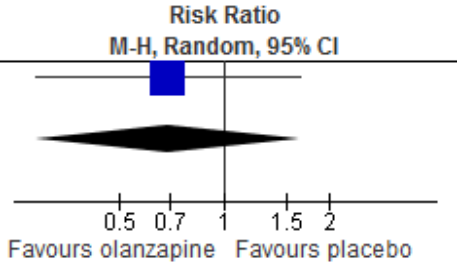


Outcomes for olanzapine compared with placebo (all participants taking lithium or valproate)

Number of participants who relapsed (mania)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TOHEN2004	6	30	11	38	100.0%	0.69 [0.29, 1.65]
Total (95% CI)		**30**		**38**	**100.0%**	**0.69 [0.29, 1.65]**
Total events	6		11			

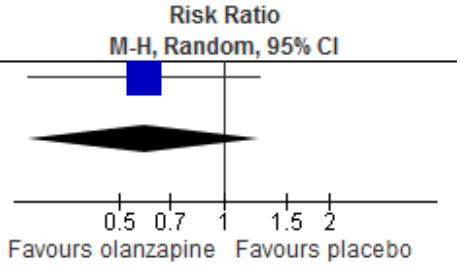
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



Number of participants who relapsed (depression)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

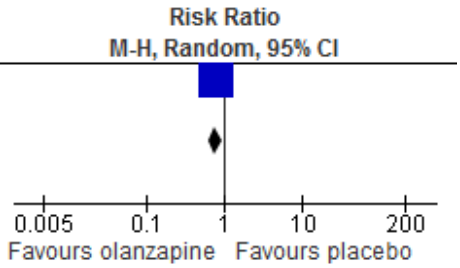
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



Number of participants discontinuing(for any reason)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

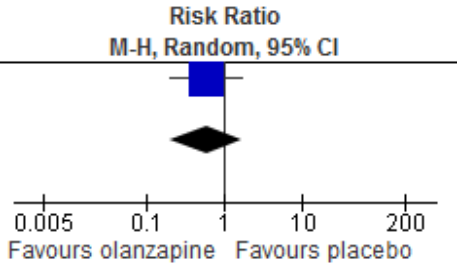
Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)



Number of participants discontinuing due to side effects

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TOHEN2004	5	51	8	48	100.0%	0.59 [0.21, 1.67]
Total (95% CI)		**51**		**48**	**100.0%**	**0.59 [0.21, 1.67]**
Total events	5		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

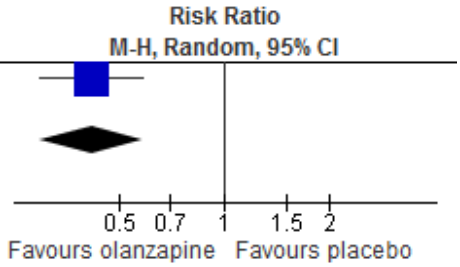


Outcomes for olanzapine compared with placebo

Number of participants who relapsed (any type)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

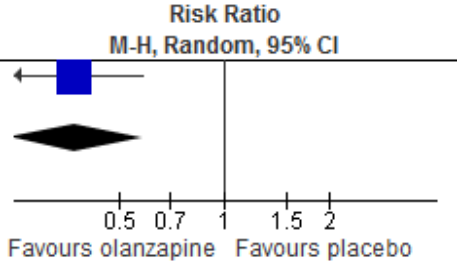
Heterogeneity: Not applicable
Test for overall effect: Z = 5.05 (P < 0.00001)



Number of participants who relapsed (mania)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	20	137	54	138	100.0%	0.37 [0.24, 0.59]
Total (95% CI)		**137**		**138**	**100.0%**	**0.37 [0.24, 0.59]**
Total events	20		54			

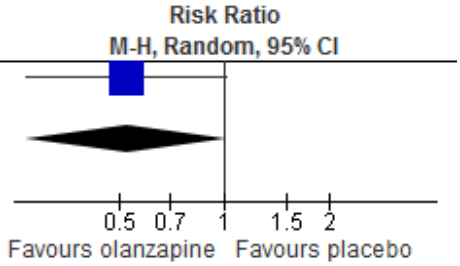
Heterogeneity: Not applicable
Test for overall effect: Z = 4.24 (P < 0.0001)



Number of participants who relapsed (depression)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	12	137	23	138	100.0%	0.53 [0.27, 1.01]
Total (95% CI)		**137**		**138**	**100.0%**	**0.53 [0.27, 1.01]**
Total events	12		23			

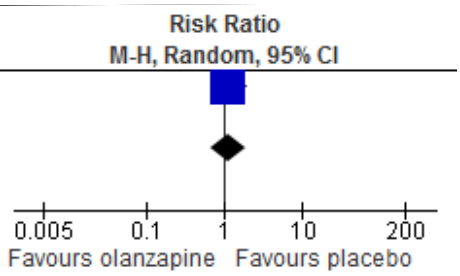
Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)



Number of participants discontinuing(for any reason)

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	25	138	23	140	100.0%	1.10 [0.66, 1.85]
Total (95% CI)		**138**		**140**	**100.0%**	**1.10 [0.66, 1.85]**
Total events	25		23			

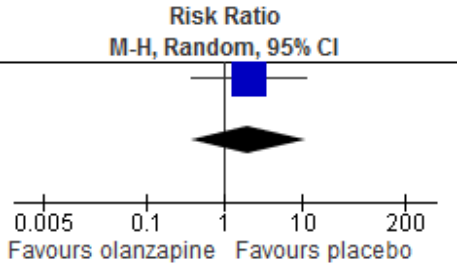
Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)



Number of participants discontinuing due to side effects

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 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 applicable
Test for overall effect: Z = 0.82 (P = 0.41)

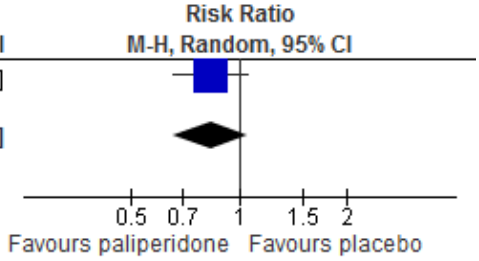


Outcomes for paliperidone compared with placebo

Number of participants who relapsed (any type)

Study or Subgroup	Paliperidone Events	Paliperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

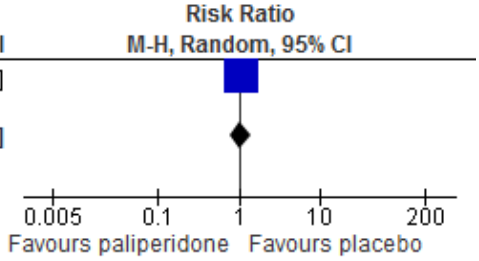
Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)



Number of participants discontinuing(for any reason)

Study or Subgroup	Paliperidone Events	Paliperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 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			

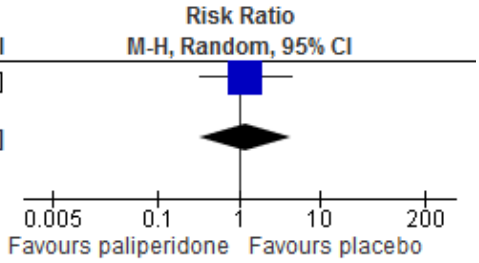
Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)



Number of participants discontinuing due to side effects

Study or Subgroup	Paliperidone Events	Paliperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BERWAERTS2012	5	152	4	148	100.0%	1.22 [0.33, 4.44]
Total (95% CI)		**152**		**148**	**100.0%**	**1.22 [0.33, 4.44]**
Total events	5		4			

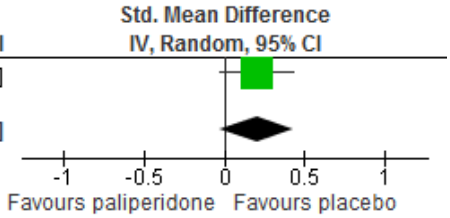
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)



Change in weight (kg)

Study or Subgroup	Paliperidone Mean	Paliperidone SD	Paliperidone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference 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 applicable
Test for overall effect: Z = 1.74 (P = 0.08)

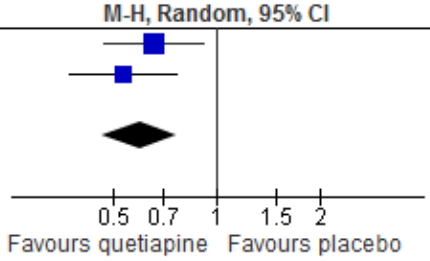


Outcomes for quetiapine compared with placebo

Number of participants who relapsed (any type)

Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
YOUNG2012 (300mg)	37	141	59	147	53.6%	0.65 [0.47, 0.92]
YOUNG2012 (600mg)	32	150	59	147	46.4%	0.53 [0.37, 0.77]
Total (95% CI)		**291**		**294**	**100.0%**	**0.59 [0.46, 0.76]**
Total events	69		118			

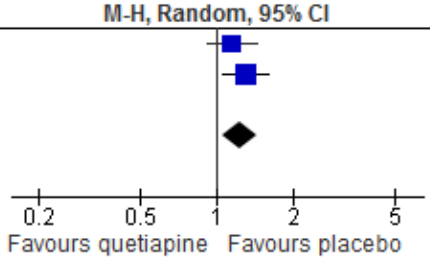
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 4.10 (P < 0.0001)



Number of participants discontinuing(for any reason)

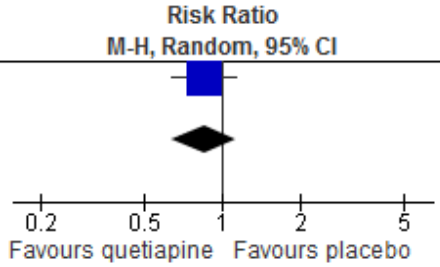
Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
YOUNG2012 (300mg)	77	141	70	147	46.4%	1.15 [0.91, 1.44]
YOUNG2012 (600mg)	93	150	70	147	53.6%	1.30 [1.05, 1.61]
Total (95% CI)		**291**		**294**	**100.0%**	**1.23 [1.05, 1.43]**
Total events	170		140			

Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)



Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
WEISLER2011	68	404	80	404	100.0%	0.85 [0.63, 1.14]
Total (95% CI)		**404**		**404**	**100.0%**	**0.85 [0.63, 1.14]**
Total events	68		80			

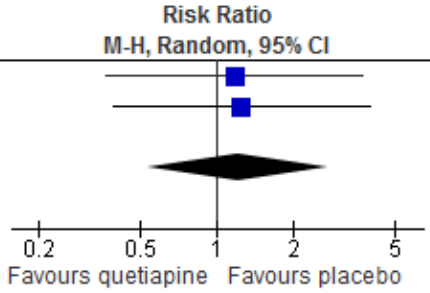
Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)



Number of participants discontinuing due to side effects

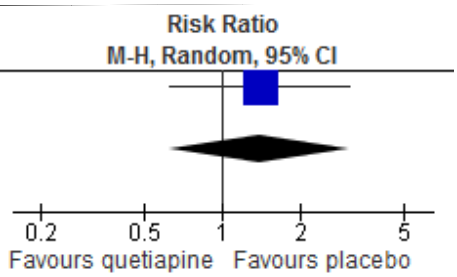
Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
YOUNG2012 (600mg)	6	150	5	147	50.0%	1.18 [0.37, 3.77]
YOUNG2012 (300mg)	6	141	5	147	50.0%	1.25 [0.39, 4.01]
Total (95% CI)		**291**		**294**	**100.0%**	**1.21 [0.53, 2.76]**
Total events	12		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)



Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
WEISLER2011	14	404	10	404	100.0%	1.40 [0.63, 3.11]
Total (95% CI)		**404**		**404**	**100.0%**	**1.40 [0.63, 3.11]**
Total events	14		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)

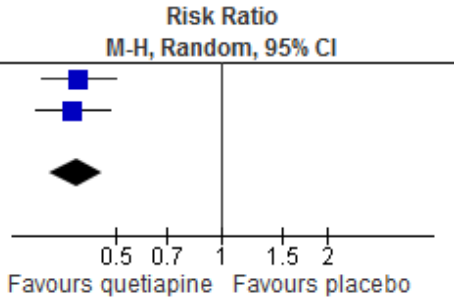


Outcomes for quetiapine compared with placebo (all participants were taking lithium or valproate)

Number of participants who relapsed (any type)

Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SUPPES2009	63	310	163	313	50.6%	0.39 [0.31, 0.50]
VIETA2008B	62	336	180	367	49.4%	0.38 [0.29, 0.48]
Total (95% CI)		**646**		**680**	**100.0%**	**0.38 [0.32, 0.46]**
Total events	125		343			

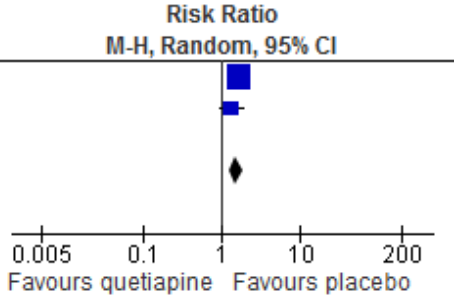
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 10.80 (P < 0.00001)



Number of participants discontinuing(for any reason)

Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
SUPPES2009	137	310	84	313	67.3%	1.65 [1.32, 2.06]
VIETA2008B	60	336	50	367	32.7%	1.31 [0.93, 1.85]
Total (95% CI)		**646**		**680**	**100.0%**	**1.53 [1.24, 1.89]**
Total events	197		134			

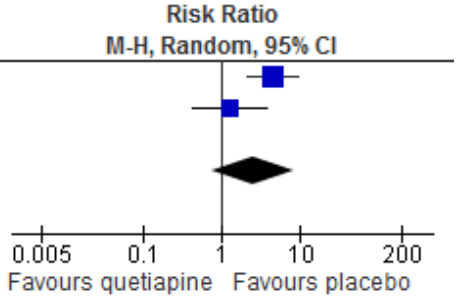
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 3.94 (P < 0.0001)



Number of participants discontinuing due to side effects

Study or Subgroup	Quetiapine Events	Quetiapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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]
Total (95% CI)		**646**		**680**	**100.0%**	**2.53 [0.75, 8.53]**
Total events	42		14			

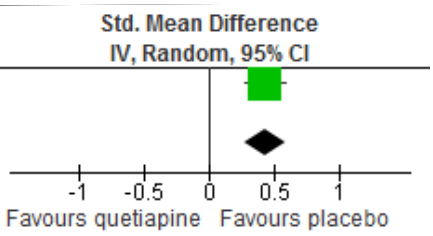
Heterogeneity: Tau² = 0.55; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.49 (P = 0.14)



Change in weight (kg)

Study or Subgroup	Quetiapine Mean	Quetiapine SD	Quetiapine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference 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]**

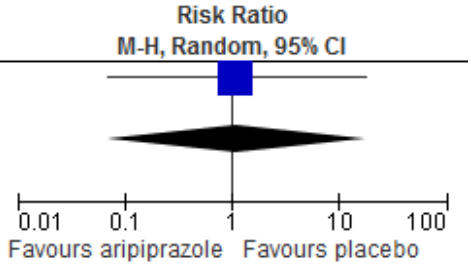
Heterogeneity: Not applicable
Test for overall effect: Z = 5.33 (P < 0.00001)



Number of suicides

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2008B	1	336	1	367	100.0%	1.09 [0.07, 17.39]
Total (95% CI)		**336**		**367**	**100.0%**	**1.09 [0.07, 17.39]**
Total events	1		1			

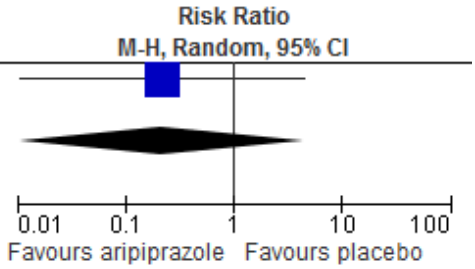
Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)



Number of deaths

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2008B	0	336	2	367	100.0%	0.22 [0.01, 4.53]
Total (95% CI)		**336**		**367**	**100.0%**	**0.22 [0.01, 4.53]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

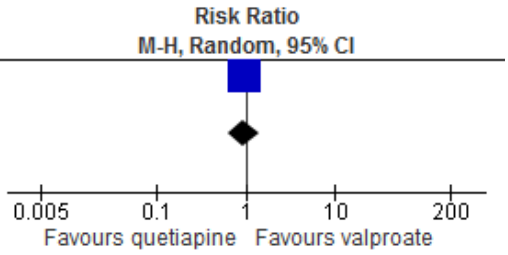


Outcomes for quetiapine compared with valproate

Number of participants discontinuing(for any reason)

Study or Subgroup	Quetiapine Events	Quetiapine Total	Valproate Events	Valproate Total	Weight	Risk Ratio M-H, Random, 95% CI
LANGOSCH2008	15	21	12	16	100.0%	0.95 [0.64, 1.41]
Total (95% CI)		**21**		**16**	**100.0%**	**0.95 [0.64, 1.41]**
Total events	15		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)

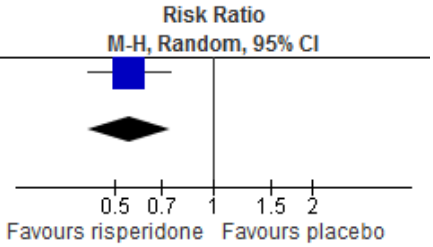


Outcomes for risperidone long-acting injectable compared with placebo injection

Number of participants who relapsed (any type)

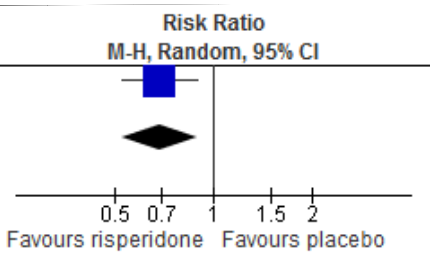
Study or Subgroup	Risperidone (injection) Events	Risperidone (injection) Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
QUIROZ2010	45	154	78	149	100.0%	0.56 [0.42, 0.75]
Total (95% CI)		**154**		**149**	**100.0%**	**0.56 [0.42, 0.75]**
Total events	45		78			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.95 (P < 0.0001)



Study or Subgroup	Risperidone (injection) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	52	135	77	138	100.0%	0.69 [0.53, 0.90]
Total (95% CI)		**135**		**138**	**100.0%**	**0.69 [0.53, 0.90]**
Total events	52		77			

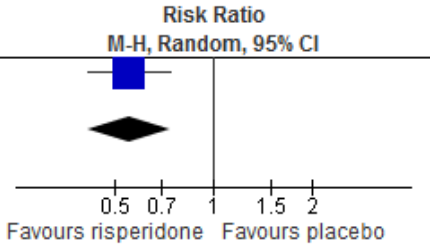
Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.005)



Number of participants who relapsed (mania)

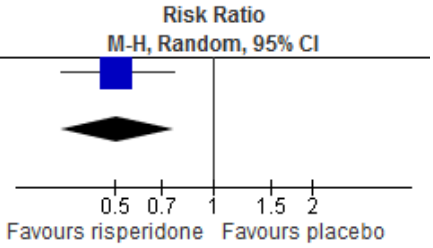
Study or Subgroup	Risperidone (injection) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
QUIROZ2010	45	154	78	149	100.0%	0.56 [0.42, 0.75]
Total (95% CI)		**154**		**149**	**100.0%**	**0.56 [0.42, 0.75]**
Total events	45		78			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.95 (P < 0.0001)



Study or Subgroup	Risperidone (injection) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	27	135	54	138	100.0%	0.51 [0.34, 0.76]
Total (95% CI)		**135**		**138**	**100.0%**	**0.51 [0.34, 0.76]**
Total events	27		54			

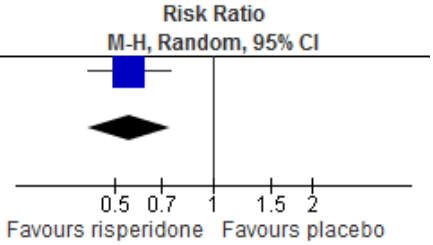
Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)



Number of participants who relapsed (depression)

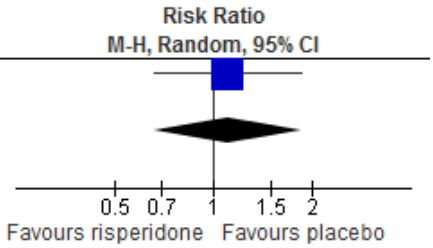
Study or Subgroup	Risperidone (injection) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
QUIROZ2010	45	154	78	149	100.0%	0.56 [0.42, 0.75]
Total (95% CI)		**154**		**149**	**100.0%**	**0.56 [0.42, 0.75]**
Total events	45		78			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.95 (P < 0.0001)



Study or Subgroup	Risperidone (injection) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	25	135	23	138	100.0%	1.11 [0.66, 1.86]
Total (95% CI)		**135**		**138**	**100.0%**	**1.11 [0.66, 1.86]**
Total events	25		23			

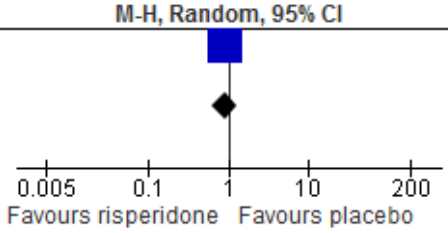
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



Number of participants discontinuing(for any reason)

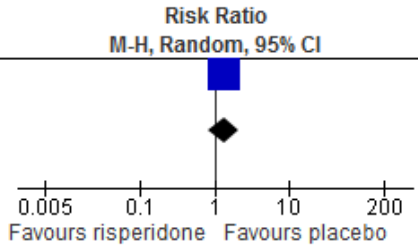
Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
QUIROZ2010	37	154	40	149	100.0%	0.89 [0.61, 1.32]
Total (95% CI)		**154**		**149**	**100.0%**	**0.89 [0.61, 1.32]**
Total events	37		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)



Study or Subgroup	Risperidone (injection) Events	Risperidone (injection) Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	30	137	23	140	100.0%	1.33 [0.82, 2.17]
Total (95% CI)		**137**		**140**	**100.0%**	**1.33 [0.82, 2.17]**
Total events	30		23			

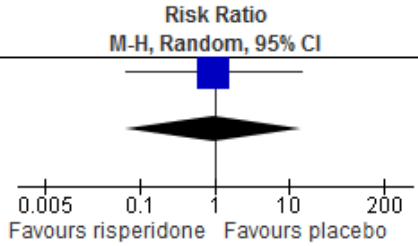
Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)



Number of participants discontinuing due to side effects

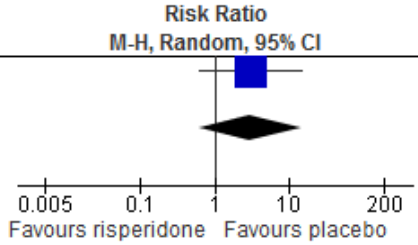
Study or Subgroup	Risperidone (injection) Events	Risperidone (injection) Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
QUIROZ2010	1	154	1	149	100.0%	0.97 [0.06, 15.33]
Total (95% CI)		**154**		**149**	**100.0%**	**0.97 [0.06, 15.33]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)



Study or Subgroup	Risperidone (injection) Events	Risperidone (injection) Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2012	6	137	2	140	100.0%	3.07 [0.63, 14.93]
Total (95% CI)		**137**		**140**	**100.0%**	**3.07 [0.63, 14.93]**
Total events	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.17)

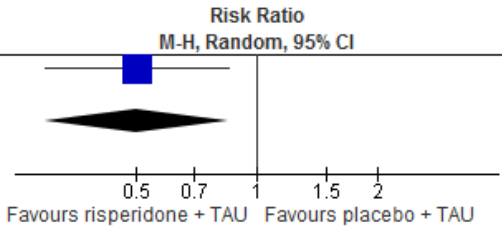


Outcomes for risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual)

Number of participants who relapsed (any type)

Study or Subgroup	Risperidone + TAU Events	Risperidone + TAU Total	Placebo + TAU Events	Placebo + TAU Total	Weight	Risk Ratio M-H, Random, 95% CI
MACFADDEN2009	15	65	27	59	100.0%	0.50 [0.30, 0.85]
Total (95% CI)		**65**		**59**	**100.0%**	**0.50 [0.30, 0.85]**
Total events	15		27			

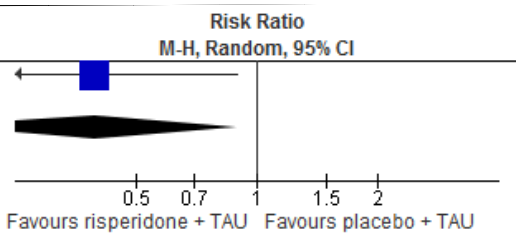
Heterogeneity: Not applicable
Test for overall effect: Z = 2.56 (P = 0.01)



Number of participants who relapsed (mania)

Study or Subgroup	Risperidone + TAU Events	Total	Placebo + TAU Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
MACFADDEN2009	7	65	16	59	100.0%	0.40 [0.18, 0.90]
Total (95% CI)		**65**		**59**	**100.0%**	**0.40 [0.18, 0.90]**
Total events	7		16			

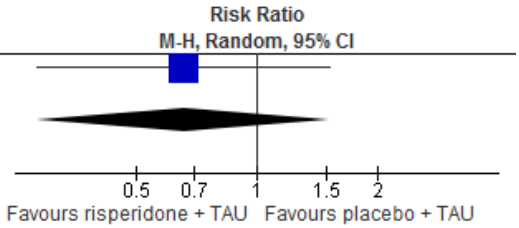
Heterogeneity: Not applicable
Test for overall effect: Z = 2.22 (P = 0.03)



Number of participants who relapsed (depression)

Study or Subgroup	Risperidone + TAU Events	Total	Placebo + TAU Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
MACFADDEN2009	8	65	11	59	100.0%	0.66 [0.29, 1.53]
Total (95% CI)		**65**		**59**	**100.0%**	**0.66 [0.29, 1.53]**
Total events	8		11			

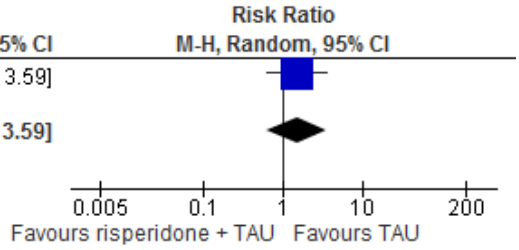
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)



Number of participants discontinuing(for any reason)

Study or Subgroup	Risperidone + TAU Events	Total	TAU Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BOBO2011B	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]**
Total events	9		6			

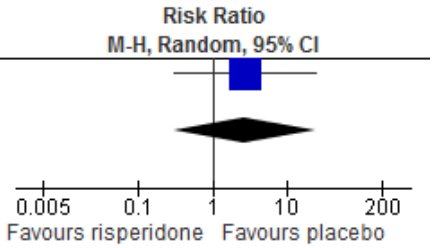
Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)



Number of participants discontinuing due to side effects

Study or Subgroup	Risperidone (injection) Events	Total	Pacebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
MACFADDEN2009	3	65	1	59	100.0%	2.72 [0.29, 25.47]
Total (95% CI)		**65**		**59**	**100.0%**	**2.72 [0.29, 25.47]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)

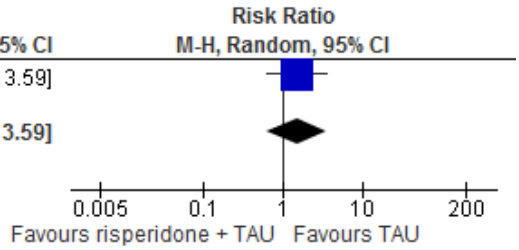


Outcomes for risperidone long-acting injectable and treatment as usual compared with treatment as usual alone

Number of participants discontinuing(for any reason)

Study or Subgroup	Risperidone + TAU Events	Total	TAU Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BOBO2011B	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]**
Total events	9		6			

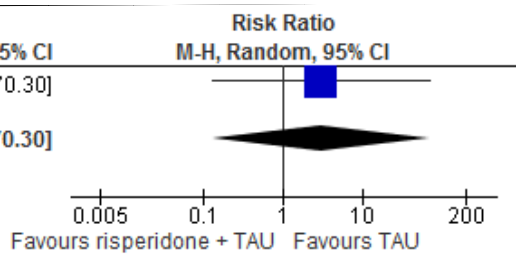
Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)



Number of participants discontinuing due to side effects

Study or Subgroup	Risperidone + TAU Events	Risperidone + TAU Total	TAU Events	TAU Total	Weight	Risk Ratio M-H, Random, 95% CI
BOBO2011B	1	25	0	25	100.0%	3.00 [0.13, 70.30]
Total (95% CI)		**25**		**25**	**100.0%**	**3.00 [0.13, 70.30]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)



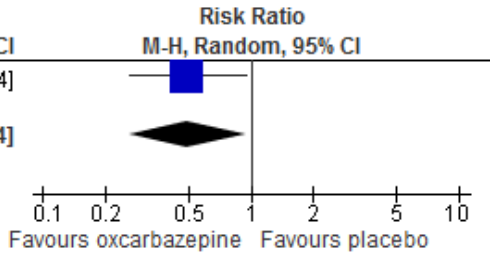
Anticonvulsants

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

Number of participants who relapsed (any type)

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2008	8	26	18	29	100.0%	0.50 [0.26, 0.94]
Total (95% CI)		**26**		**29**	**100.0%**	**0.50 [0.26, 0.94]**
Total events	8		18			

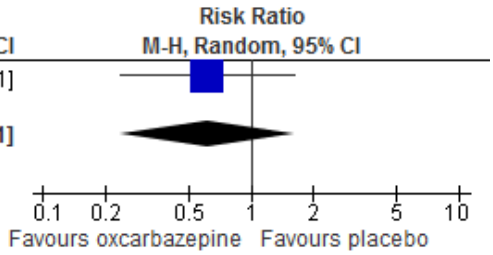
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)



Number of participants who relapsed (mania)

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2008	5	26	9	29	100.0%	0.62 [0.24, 1.61]
Total (95% CI)		**26**		**29**	**100.0%**	**0.62 [0.24, 1.61]**
Total events	5		9			

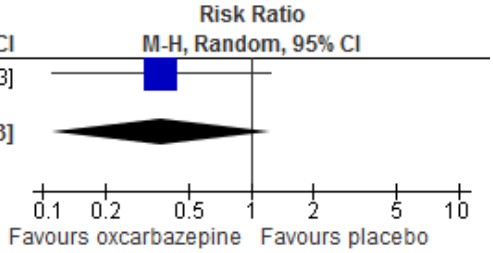
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



Number of participants who relapsed (depression)

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

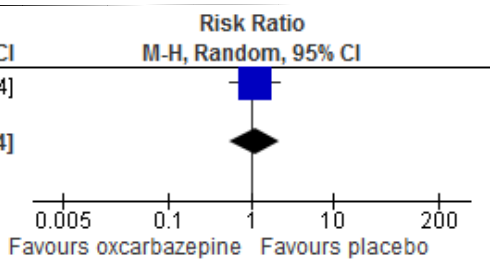
Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.10)



Number of participants discontinuing(for any reason)

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2008	10	26	10	29	100.0%	1.12 [0.55, 2.24]
Total (95% CI)		**26**		**29**	**100.0%**	**1.12 [0.55, 2.24]**
Total events	10		10			

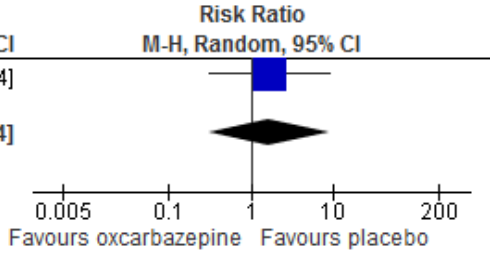
Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)



Number of participants discontinuing due to side effects

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

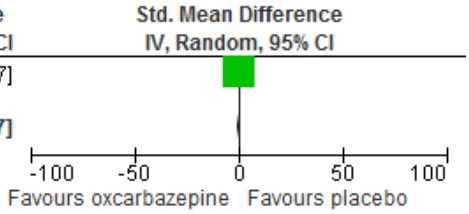
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)



Change in weight (kg)

Study or Subgroup	Oxcarbazepine Mean	Oxcarbazepine SD	Oxcarbazepine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
VIETA2008	-0.14	1.49	26	0.14	1.95	29	100.0%	-0.16 [-0.69, 0.37]
Total (95% CI)			**26**			**29**	**100.0%**	**-0.16 [-0.69, 0.37]**

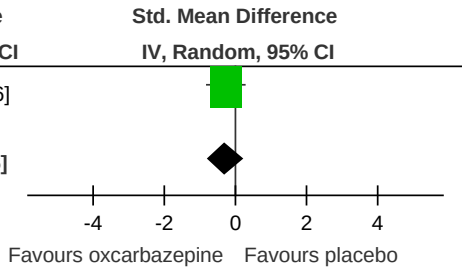
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



*Psychosocial functioning (Global assessment of functioning)**

Study or Subgroup	Oxcarbazepine Mean	Oxcarbazepine SD	Oxcarbazepine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
VIETA2008	-2.37	12.57	26	1.48	15.31	29	100.0%	-0.27 [-0.80, 0.26]
Total (95% CI)			**26**			**29**	**100.0%**	**-0.27 [-0.80, 0.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)



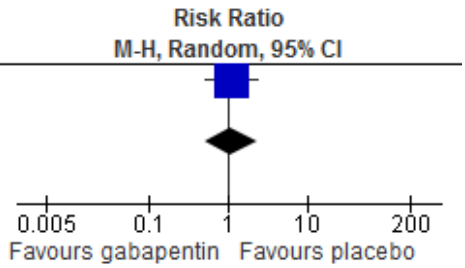
*Scores have been reversed so that higher change scores indicate a worsening of functioning

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

Number of participants discontinuing(for any reason)

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2006	7	13	6	12	100.0%	1.08 [0.51, 2.30]
Total (95% CI)		**13**		**12**	**100.0%**	**1.08 [0.51, 2.30]**
Total events	7		6			

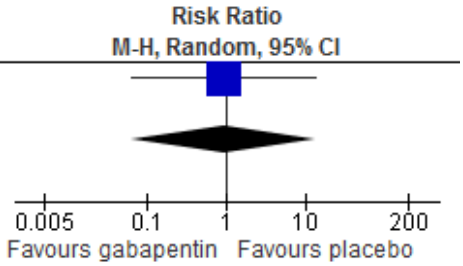
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)



Number of participants discontinuing due to side effects

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
VIETA2006	1	13	1	12	100.0%	0.92 [0.06, 13.18]
Total (95% CI)		**13**		**12**	**100.0%**	**0.92 [0.06, 13.18]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)

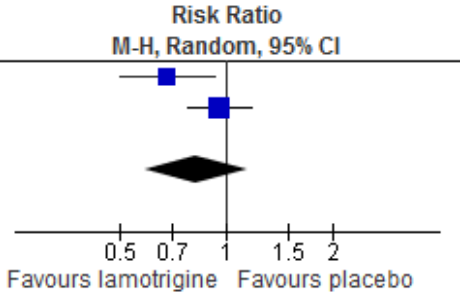


Outcomes for lamotrigine compared with placebo

Number of participants who relapsed (any type)

Study or Subgroup	Lamotrigine Events	Lamotrigine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	28	59	49	70	44.1%	0.68 [0.50, 0.92]
CALABRESE2003	115	221	66	121	55.9%	0.95 [0.78, 1.17]
Total (95% CI)		**280**		**191**	**100.0%**	**0.82 [0.59, 1.14]**
Total events	143		115			

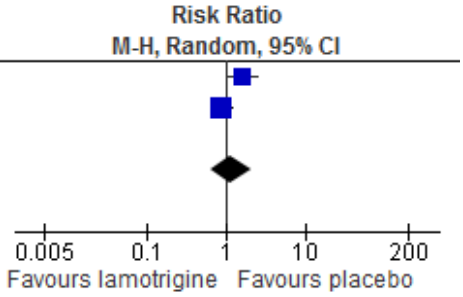
Heterogeneity: Tau² = 0.04; Chi² = 3.25, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 1.17 (P = 0.24)



Number of participants discontinuing(for any reason)

Study or Subgroup	Lamotrigine Events	Lamotrigine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

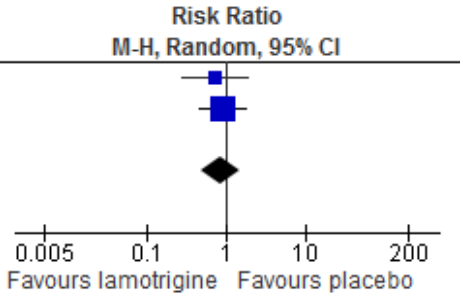
Heterogeneity: Tau² = 0.14; Chi² = 4.70, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.45 (P = 0.65)



Number of participants discontinuing due to side effects

Study or Subgroup	Lamotrigine Events	Lamotrigine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2003	6	59	10	70	33.9%	0.71 [0.28, 1.84]
CALABRESE2003	20	221	12	121	66.1%	0.91 [0.46, 1.80]
Total (95% CI)		**280**		**191**	**100.0%**	**0.84 [0.48, 1.46]**
Total events	26		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)

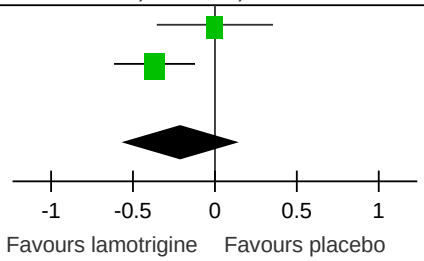


*Psychosocial functioning (Global assessment scale)**

Study or Subgroup	Lamotrigine Mean	Lamotrigine SD	Lamotrigine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
BOWDEN2003	11	18.8	58	11	14	69	43.9%	0.00 [-0.35, 0.35]
CALABRESE2003	2.8	11.1	161	6.9	11.1	115	56.1%	-0.37 [-0.61, -0.13]
Total (95% CI)			**219**			**184**	**100.0%**	**-0.21 [-0.56, 0.15]**

Heterogeneity: Tau² = 0.04; Chi² = 2.89, df = 1 (P = 0.09); I² = 65%

Test for overall effect: Z = 1.13 (P = 0.26)



*Scores have been reversed so that higher change scores indicate a worsening of functioning

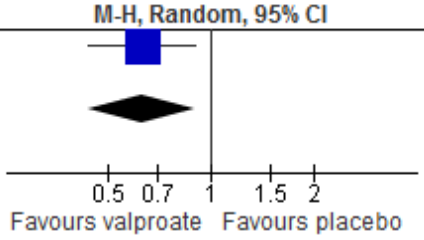
Outcomes for valproate compared with placebo

Number of participants who relapsed (any type)

Study or Subgroup	Valproate Events	Valproate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	45	187	36	94	100.0%	0.63 [0.44, 0.90]
Total (95% CI)		**187**		**94**	**100.0%**	**0.63 [0.44, 0.90]**
Total events	45		36			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.52 (P = 0.01)

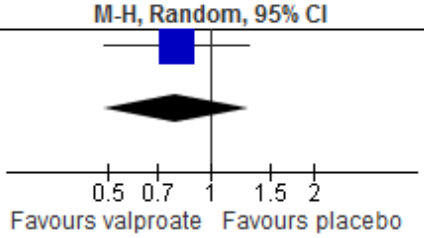


Number of participants who relapsed (mania)

Study or Subgroup	Valproate Events	Valproate Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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

Test for overall effect: Z = 0.95 (P = 0.34)

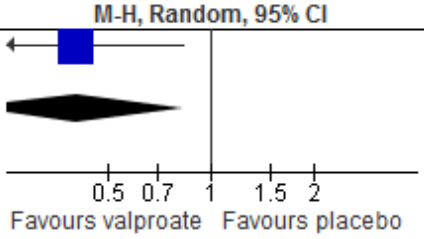


Number of participants who relapsed (depression)

Study or Subgroup	Valproate Events	Valproate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BOWDEN2000	12	187	15	94	100.0%	0.40 [0.20, 0.82]
Total (95% CI)		**187**		**94**	**100.0%**	**0.40 [0.20, 0.82]**
Total events	12		15			

Heterogeneity: Not applicable

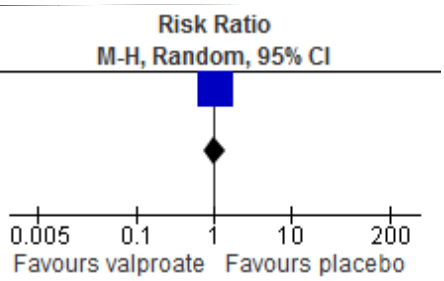
Test for overall effect: Z = 2.49 (P = 0.01)



Number of participants discontinuing(for any reason)

Study or Subgroup	Valproate Events	Valproate Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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]**
Total events	71		35			

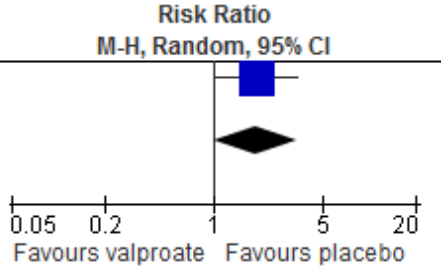
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)



Number of participants discontinuing due to side effects

Study or Subgroup	Valproate Events	Valproate Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 1.99 (P = 0.05)



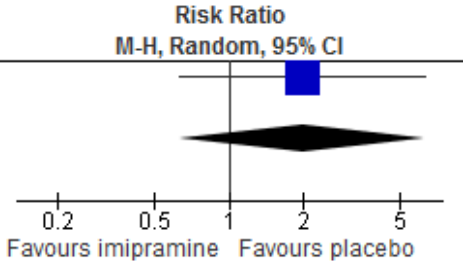
Antidepressants

Outcomes for imipramine compared with placebo

Number of participants who relapsed (mania)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

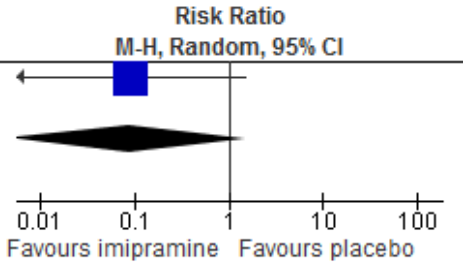
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)



Number of participants who relapsed (depression)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973B	0	13	5	13	100.0%	0.09 [0.01, 1.49]
Total (95% CI)		**13**		**13**	**100.0%**	**0.09 [0.01, 1.49]**
Total events	0		5			

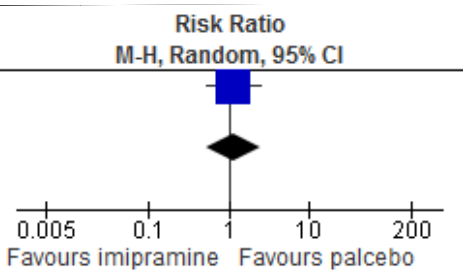
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)



Number of participants discontinuing(for any reason)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 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			

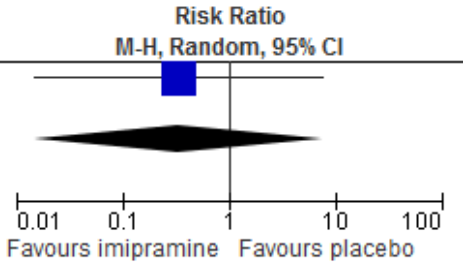
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)



Number of suicides

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1973B	0	13	1	13	100.0%	0.33 [0.01, 7.50]
Total (95% CI)		**13**		**13**	**100.0%**	**0.33 [0.01, 7.50]**
Total events	0		1			

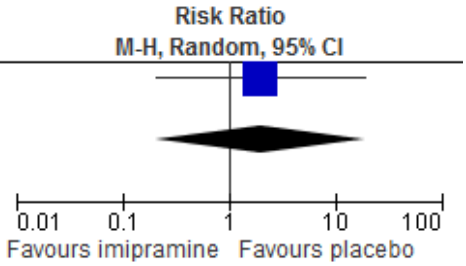
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



Number of deaths

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.60 (P = 0.55)

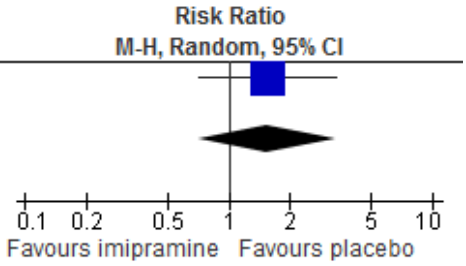


Outcomes for imipramine compared with placebo (all participants were taking lithium)

Number of participants who relapsed (any type)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

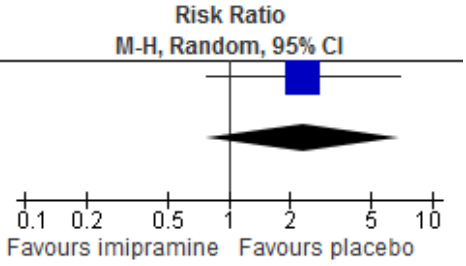
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



Number of participants who relapsed (mania)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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			

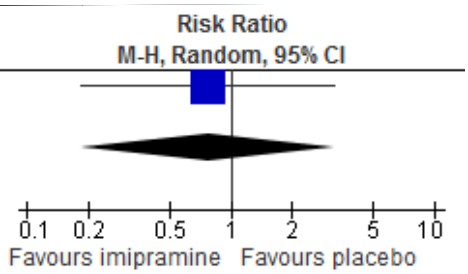
Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)



Number of participants who relapsed (depression)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
QUITKIN1981	3	37	4	38	100.0%	0.77 [0.18, 3.21]
Total (95% CI)		**37**		**38**	**100.0%**	**0.77 [0.18, 3.21]**
Total events	3		4			

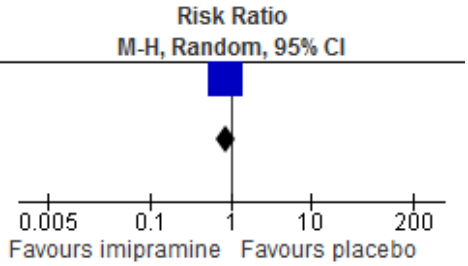
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



Number of participants discontinuing(for any reason)

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 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			

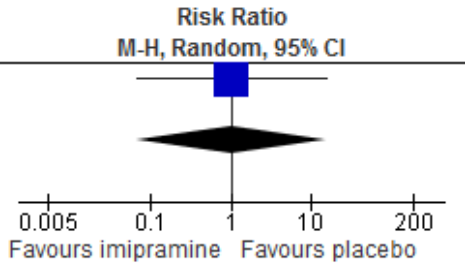
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



Number of participants discontinuing due to side effects

Study or Subgroup	Imipramine Events	Imipramine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
QUITKIN1981	1	37	1	38	100.0%	1.03 [0.07, 15.82]
Total (95% CI)		**37**		**38**	**100.0%**	**1.03 [0.07, 15.82]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)

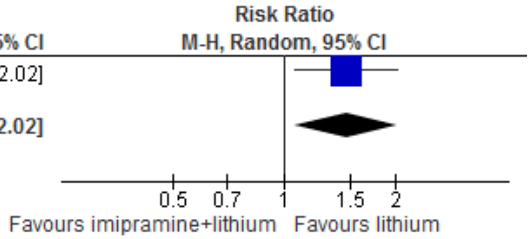


Outcomes for imipramine and lithium combination compared with lithium

Number of participants who relapsed (any type)

Study or Subgroup	Imipramine + lithium Events	Imipramine + lithium Total	Lithium Events	Lithium Total	Weight	Risk Ratio M-H, Random, 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			

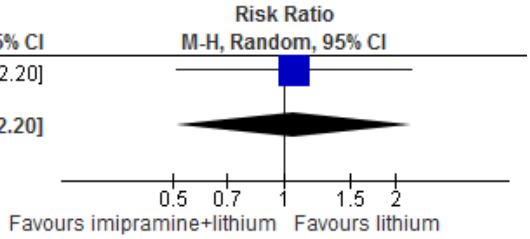
Heterogeneity: Not applicable
Test for overall effect: Z = 2.38 (P = 0.02)



Number of participants who relapsed (mania)

Study or Subgroup	Imipramine + lithium Events	Imipramine + lithium Total	Lithium Events	Lithium Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1984	10	36	11	42	100.0%	1.06 [0.51, 2.20]
Total (95% CI)		**36**		**42**	**100.0%**	**1.06 [0.51, 2.20]**
Total events	10		11			

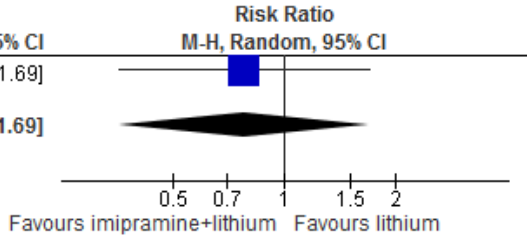
Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)



Number of participants who relapsed (depression)

Study or Subgroup	Imipramine + lithium Events	Total	Lithium Events	Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.63 (P = 0.53)



Number of participants discontinuing(for any reason)

Study or Subgroup	Imipramine + lithium Events	Total	Lithium Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIEN1984	2	36	0	42	100.0%	5.81 [0.29, 117.23]
Total (95% CI)		**36**		**42**	**100.0%**	**5.81 [0.29, 117.23]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)

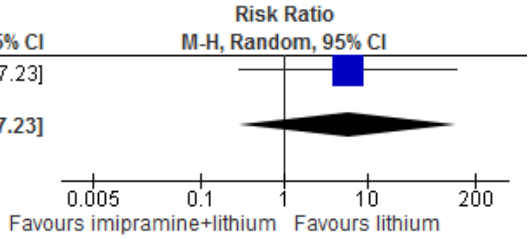


Table 1.

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	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 stabilizers, 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 hospitalization. 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-upΔ	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 δ	1	NR	*One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilizing 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

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
Lithium compared with quetiapine (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)	768δ	1	NR	*One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilizing agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania*	RR= 1.62 [1.23, 2.13]	104	WEISLER2011
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 hospitalization. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms*	RR= 1.19 [0.89, 1.59]	52	BOWDEN2000
Lithium compared with valproate (participants were randomised when euthymic and after 6 months of active treatment with lithium and valproate)	60	1	RR= 1.13 [0.70, 1.82]	Patients who met criteria for mania (a total Young Mania Rating Scale score ≥20 for up to 8 weeks) or depression (a 24-item Hamilton depression scale score ≥20 for 8 weeks) were considered to have relapsed.	RR= 1.46 [0.61, 3.50]	80	CALABRESE2005C
Lithium compared with valproate (participants were randomised whilst euthymic and after 4-8 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

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
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: hospitalization for a manic or mixed episode; a serious adverse event or worsening disease during the study; or discontinuation due to a lack of efficacy (as determined by the investigator). For the latter two criteria, patients also needed to have a YMRS total score ≥14 and a MADRS total score ≤16 for a relapse to a manic episode; a YMRS total score ≥14 and a MADRS total score ≥16 for a relapse to a mixed episode; and a YMRS total score ≤14 and a MADRS total score ≥16 for a relapse to a depressive episode*	RR = 0.92 [0.79, 1.06]	52	CARLSON2012
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: hospitalization 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

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
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 stabilizer, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalization 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 hospitalization 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 stabilizing 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

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
Quetiapine compared with placebo (participants were randomised when euthymic after 4-24 weeks of active treatment with quetiapine)	808δ	1	NR	*One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilizing 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-stabilizing agent other than lithium or divalproex or an anxiolytic other than lorazepam; psychiatric hospitalization; 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 stabilizer, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalization 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

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
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 stabilizer, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalization 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 stabilizer, 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) hospitalization 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) hospitalization for worsening of manic or depressive symptoms and having significant suicidal ideation*	RR= 1.27 [0.61, 2.64]	52	MACFADDEN2009

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
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 hospitalization; emergency department visit; or referral for respite care, partial hospitalization, 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 stabilizers, or benzodiazepines (exceeding doses of rescue medication)*	RR = 1.14 [0.64, 2.06]	76, 78	CALABRESE2003, BOWDEN2003

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References
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 hospitalization. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms*	RR = 1.02 [0.74, 1.40]	52	BOWDEN2000
Antidepressants							
Imipramine compared with placebo (all participants were taking lithium)	75	1	RR = 1.54 [0.71, 3.33]	Research diagnostic criteria for mania or major depressive disorder	RR = 0.86 [0.65, 1.13]	129	QUITKIN1981
Imipramine compared with placebo	26	1	RR = 0.75 [0.36, 1.55]	*Manic or depressive attack requiring hospitalization or supplementary drugs (i.e., psychopharmacologic agents other than the patient's assigned treatment)*	RR = 1.17 [0.54, 2.53]	104	PRIEN1973b
Imipramine and lithium combination compared with lithium	78[μ]	1	RR = 0.68 [0.49, 0.93]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	RR[∂] = 5.81 [0.29, 117.23]	104	PRIEN1984
Imipramine and lithium combination compared with imipramine	72[μ]	1	RR = 0.62 [0.43, 0.89]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	RR[∂] = 5.81 [0.29, 117.23]	104	PRIEN1984
Imipramine compared with lithium	78[μ]	1	RR = 1.47 [1.07, 2.02]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	There was no discontinuation in either group.	104	PRIEN1984
Antidepressants compared with placebo	70	1	NR	NR	NR	52	GHAEMI2010

Comparison	N	K	Relapse (any)†	Definition‡	Discontinuation (for any reason)†	Length of follow-upΔ	References

†A relative risk (RR) of less than 1 favours the first treatment named
‡Definitions of relapse which do not meet the GDG's definition have been *italicised*
ΔLength of follow-up reported in number of weeks
[β]GEDDES2010 is a three-arm trial including lithium, valproate and the combination of lithium and valproate. The overall number of participants is 330. All three comparisons have been included in this table so the number of participants has been double-counted.
[δ]WEISLER2011 is a three-arm trial including lithium, quetiapine and placebo. The overall number of participants is 1,172. All three comparisons have been included in this table so the number of participants has been double-counted.
[μ]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.
[∂] Discontinuation due to side effects. No other reasons for discontinuation were reported.