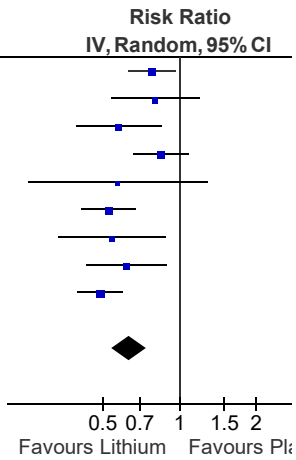
1 Lithium vs Placebo_Bipolar 1_Final

1.1 New episode, any type

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	59	110	76	110	15.6%	0.78 [0.63, 0.96]
Bowden 2000 (2)	28	91	36	94	9.3%	0.80 [0.54, 1.20]
Bowden 2003 (3)	18	44	49	69	9.7%	0.58 [0.39, 0.85]
Calabrese 2003 (4)	56	120	66	119	14.2%	0.84 [0.66, 1.08]
Melia 1970 (5)	4	9	7	9	3.4%	0.57 [0.25, 1.28]
Prien 1973a (6)	43	101	84	104	14.4%	0.53 [0.41, 0.67]
Prien 1973b (7)	9	18	12	13	7.3%	0.54 [0.33, 0.88]
Prien 1984 (8)	18	36	29	36	10.3%	0.62 [0.43, 0.89]
Weisler 2011 (9)	89	364	202	404	16.0%	0.49 [0.40, 0.60]
Total (95% CI)		**893**		**958**	**100.0%**	**0.63 [0.54, 0.74]**
Total events	324		561			

Heterogeneity: Tau² = 0.03; Chi² = 18.74, df = 8 (P = 0.02); I² = 57%

Test for overall effect: Z = 5.52 (P < 0.00001)



Footnotes

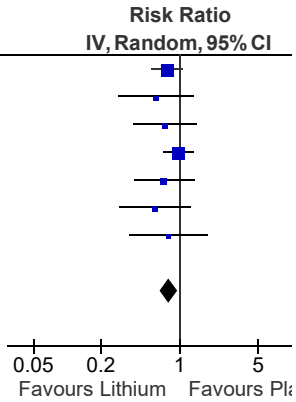
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania, bipolar type I
(3) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(4) Lithium vs placebo, index episode:depression, bipolar type I
(5) Lithium vs placebo, Index episode: not specified, bipolar type not specified
(6) Lithium vs placebo, index episode: mania, bipolar type not specified
(7) Lithium vs placebo, Index episode: depression, bipolar type not specified
(8) Imipramine + lithium vs imipramine, index episode: depression or mania, bipolar type not specified
(9) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.2 New episode, depression

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	39	110	50	110	32.3%	0.78 [0.56, 1.08]
Bowden 2000 (2)	9	91	15	94	5.7%	0.62 [0.29, 1.34]
Bowden 2003 (3)	10	44	21	69	8.0%	0.75 [0.39, 1.43]
Calabrese 2003 (4)	46	120	47	119	33.7%	0.97 [0.71, 1.33]
Fieve 1976 (5)	9	24	15	29	8.7%	0.72 [0.39, 1.35]
Prien 1973a (6)	10	101	17	104	6.4%	0.61 [0.29, 1.26]
Prien 1984 (7)	8	36	10	36	5.2%	0.80 [0.36, 1.79]
Total (95% CI)		**526**		**561**	**100.0%**	**0.81 [0.67, 0.97]**
Total events	131		175			

Heterogeneity: Tau² = 0.00; Chi² = 2.54, df = 6 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)



Footnotes

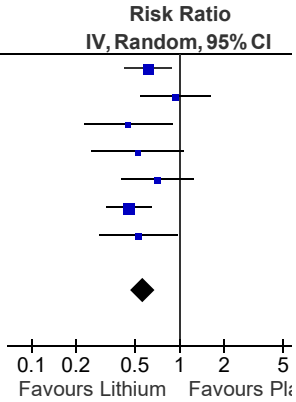
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania, bipolar type I
(3) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(4) Lithium vs placebo, index episode:depression, bipolar type I
(5) Lilthium va placebo, index episode: not specified, bipolar I and II
(6) Lithium vs placebo, index episode: mania, bipolar type not specified
(7) Imipramine + lithium vs imipramine, index episode: depression or mania, bipolar type not specified

Risk of bias legend

1.3 New episode, mania

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	30	110	49	110	25.6%	0.61 [0.42, 0.89]
Bowden 2000 (2)	19	91	21	94	11.6%	0.93 [0.54, 1.62]
Bowden 2003 (3)	8	44	28	69	7.4%	0.45 [0.23, 0.89]
Calabrese 2003 (4)	10	120	19	119	6.7%	0.52 [0.25, 1.07]
Fieve 1976 (5)	10	24	17	29	11.0%	0.71 [0.40, 1.25]
Prien 1973a (6)	28	101	63	104	28.4%	0.46 [0.32, 0.65]
Prien 1984 (7)	10	36	19	36	9.4%	0.53 [0.29, 0.97]
Total (95% CI)		**526**		**561**	**100.0%**	**0.57 [0.48, 0.69]**
Total events	115		216			

Heterogeneity: Tau² = 0.00; Chi² = 5.93, df = 6 (P = 0.43); I² = 0%
Test for overall effect: Z = 5.82 (P < 0.00001)



Footnotes

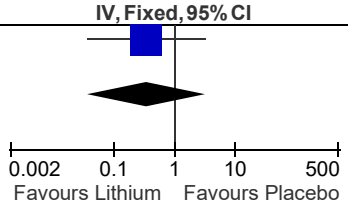
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania, bipolar type I
(3) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(4) Lithium vs placebo, index episode:depression, bipolar type I
(5) Lilthium va placebo, index episode: not specified, bipolar I and II
(6) Lithium vs placebo, index episode: mania, bipolar type not specified
(7) Imipramine + lithium vs imipramine, index episode: depression or mania, bipolar type not specified

Risk of bias legend

1.4 New episode, mixed

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Prien 1973a (1)	1	101	3	104	100.0%	0.34 [0.04, 3.25]
Total (95% CI)		**101**		**104**	**100.0%**	**0.34 [0.04, 3.25]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)



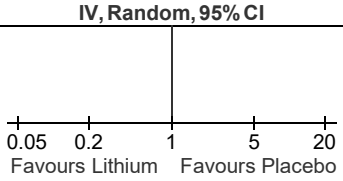
Footnotes
(1) Lithium vs placebo, index episode: mania, bipolar type not specified

Risk of bias legend

1.5 New episode, hypomania

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

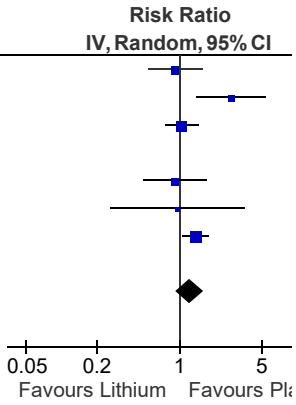


Risk of bias legend

1.6 Withdrawal, any cause

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	21	110	23	110	16.1%	0.91 [0.54, 1.55]
Bowden 2003 (2)	18	46	10	70	11.6%	2.74 [1.39, 5.39]
Calabrese 2003 (3)	45	121	43	121	25.3%	1.05 [0.75, 1.46]
Fieve 1976 (4)	2	24	1	29		Not estimable
Prien 1973a (5)	16	101	18	104	13.3%	0.92 [0.49, 1.69]
Prien 1973b (6)	4	18	3	13	3.9%	0.96 [0.26, 3.59]
Weisler 2011 (7)	99	364	80	404	29.8%	1.37 [1.06, 1.78]
Total (95% CI)		**760**		**822**	**100.0%**	**1.22 [0.93, 1.60]**
Total events	203		177			

Heterogeneity: Tau² = 0.05; Chi² = 9.20, df = 5 (P = 0.10); I² = 46%
Test for overall effect: Z = 1.40 (P = 0.16)



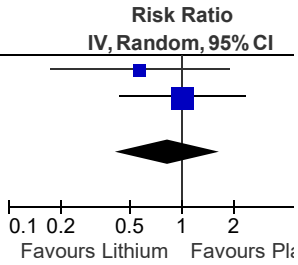
Footnotes
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(3) Lithium vs placebo, index episode:depression, bipolar type I
(4) Index episode: not specified
(5) Lithium vs placebo, index episode: mania, bipolar type not specified
(6) Lithium vs placebo, Index episode: depression, bipolar type not specified
(7) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.7 Serious adverse events (SAE)

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	4	110	7	110	33.1%	0.57 [0.17, 1.90]
Weisler 2011 (2)	10	364	11	404	66.9%	1.01 [0.43, 2.35]
Total (95% CI)		**474**		**514**	**100.0%**	**0.84 [0.42, 1.67]**
Total events	14		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)



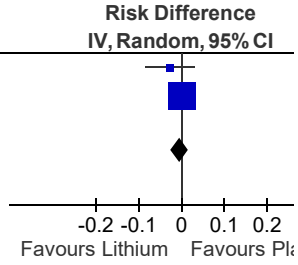
Footnotes
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Index episode: mania/depression/mixed

Risk of bias legend

1.8 Serious adverse events (SAE) risk diff

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	4	110	7	110	13.9%	-0.03 [-0.08, 0.03]
Weisler 2011 (2)	10	364	11	404	86.1%	0.00 [-0.02, 0.02]
Total (95% CI)		**474**		**514**	**100.0%**	**-0.00 [-0.03, 0.02]**
Total events	14		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)



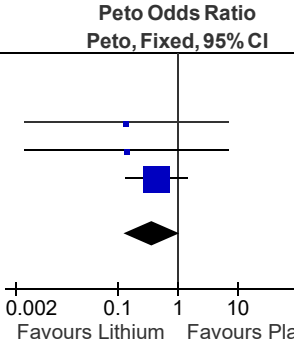
Footnotes
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.9 Suicidal behaviour

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	0	110	0	110		Not estimable
Bowden 2003 (2)	0	44	0	69		Not estimable
Calabrese 2003 (3)	0	120	1	121	7.8%	0.14 [0.00, 6.88]
Prien 1973a (4)	0	101	1	104	7.8%	0.14 [0.00, 7.02]
Weisler 2011 (5)	3	364	8	404	84.4%	0.44 [0.13, 1.45]
Total (95% CI)		**739**		**808**	**100.0%**	**0.37 [0.12, 1.10]**
Total events	3		10			

Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)



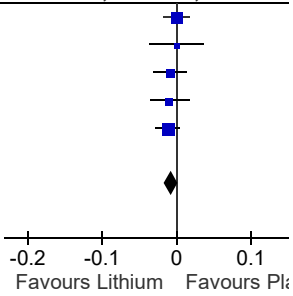
Footnotes
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(3) Lithium vs placebo, index episode:depression, bipolar type I
(4) Lithium vs placebo, index episode: mania, bipolar type not specified
(5) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.10 Suicidal behaviour, risk diff

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	0	110	0	110	29.2%	0.00 [-0.02, 0.02]
Bowden 2003 (2)	0	44	0	69	6.8%	0.00 [-0.04, 0.04]
Calabrese 2003 (3)	0	120	1	121	17.6%	-0.01 [-0.03, 0.01]
Prien 1973a (4)	0	101	1	104	13.0%	-0.01 [-0.04, 0.02]
Weisler 2011 (5)	3	364	8	404	33.4%	-0.01 [-0.03, 0.00]
Total (95% CI)		**739**		**808**	**100.0%**	**-0.01 [-0.02, 0.00]**
Total events	3		10			

Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)



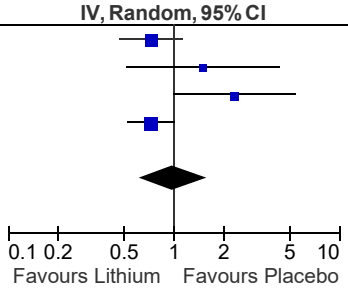
Footnotes
(1) Valproate + lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(3) Lithium vs placebo, index episode:depression, bipolar type I
(4) Lithium vs placebo, index episode: mania, bipolar type not specified
(5) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.11 Sedation

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bowden 2000 (1)	24	94	33	94	32.1%	0.73 [0.47, 1.13]
Bowden 2003 (2)	6	46	6	69	13.3%	1.50 [0.52, 4.37]
Calabrese 2003 (3)	16	120	7	121	17.9%	2.30 [0.98, 5.40]
Weisler 2011 (4)	52	418	69	404	36.6%	0.73 [0.52, 1.02]
Total (95% CI)		**678**		**688**	**100.0%**	**0.99 [0.62, 1.57]**
Total events	98		115			

Heterogeneity: Tau² = 0.12; Chi² = 7.64, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 0.06 (P = 0.95)



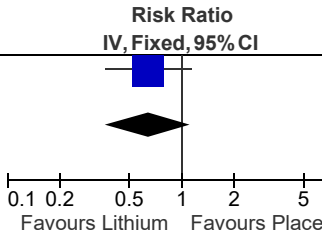
Footnotes
(1) Lithium vs placebo, index episode: mania, bipolar type I
(2) Lithium vs placebo, index episode: mania/hypomania, bipolar type I, somnolence
(3) Lithium vs placebo, index episode:depression, bipolar type I
(4) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.12 Psychiatric hospitalization

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	16	110	25	110	100.0%	0.64 [0.36, 1.13]
Total (95% CI)		**110**		**110**	**100.0%**	**0.64 [0.36, 1.13]**
Total events	16		25			

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



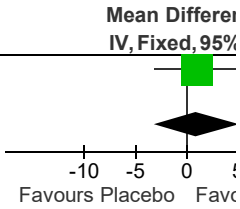
Footnotes
(1) Lithuim + valproate vs valproate, index episode: mania, bipolar II

Risk of bias legend

1.13 Global functioning

Study or Subgroup	Lithium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BALANCEinvestigatorsandcollaborators 2010 (1)	79.3	15.3	110	78.3	16.2	110	100.0%	1.00 [-3.16, 5.16]
Total (95% CI)			**110**			**110**	**100.0%**	**1.00 [-3.16, 5.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)



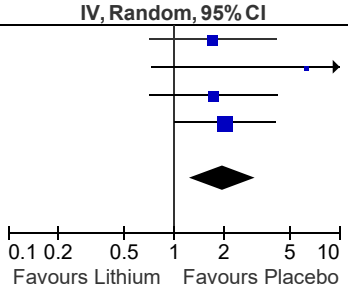
Footnotes
(1) Lithuim + valproate vs valproate, index episode: mania, bipolar II

Risk of bias legend

1.14 Weigt gain, over 7%

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bowden 2000 (1)	12	94	7	94	26.8%	1.71 [0.71, 4.16]
Bowden 2003 (2)	4	44	1	69	4.5%	6.27 [0.72, 54.31]
Calabrese 2003 (3)	12	120	7	121	26.2%	1.73 [0.70, 4.24]
Weisler 2011 (4)	23	418	11	404	42.4%	2.02 [1.00, 4.09]
Total (95% CI)		**676**		**688**	**100.0%**	**1.95 [1.23, 3.09]**
Total events	51		26			

Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



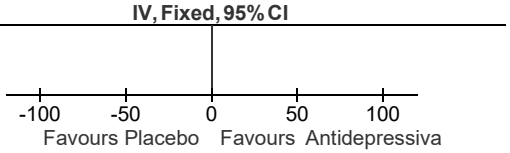
Footnotes
(1) Lithium vs placebo, index episode: mania, bipolar type I
(2) Lithium vs placebo, index episode: mania/hypomania, bipolar type I
(3) Lithium vs placebo, index episode:depression, bipolar type I
(4) Lithium vs placebo, index episode: mania/depression/mixed, bipolar type I

Risk of bias legend

1.16 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable



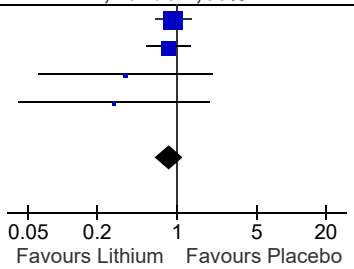
Risk of bias legend

2 Lithium vs Placebo_Bipolar 2_Final

2.1 New episode, any type

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Amsterdam 2010 (1)	17	26	19	27	56.1%	0.93 [0.64, 1.35]
Dunner 1976 (2)	10	16	18	24	39.3%	0.83 [0.53, 1.30]
Kane 1982 (3)	1	4	5	7	2.5%	0.35 [0.06, 2.04]
Kane 1982 (4)	1	6	3	5	2.1%	0.28 [0.04, 1.91]
Total (95% CI)		**52**		**63**	**100.0%**	**0.85 [0.64, 1.12]**
Total events	29		45			

Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)



Footnotes

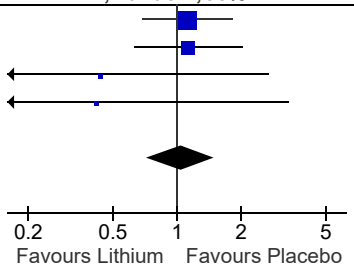
(1) Lithium vs placebo, index episode: depression, bipolar type II
(2) Lithium vs placebo, index episode: not specified, bipolar type not specified
(3) Lithium vs placebo, Index episode: not specified, bipolar type II
(4) Lithium + imipramine vs imipramine + placebo, Index episode: not specified,...

Risk of bias legend

2.2 New episode, depression

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Amsterdam 2010 (1)	15	26	14	27	54.9%	1.11 [0.68, 1.82]
Dunner 1976 (2)	9	16	12	24	38.1%	1.13 [0.62, 2.03]
Kane 1982 (3)	1	4	4	7	4.0%	0.44 [0.07, 2.69]
Kane 1982 (4)	1	6	2	5	3.0%	0.42 [0.05, 3.36]
Total (95% CI)		**52**		**63**	**100.0%**	**1.04 [0.73, 1.50]**
Total events	26		32			

Heterogeneity: Tau² = 0.00; Chi² = 1.75, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



Footnotes

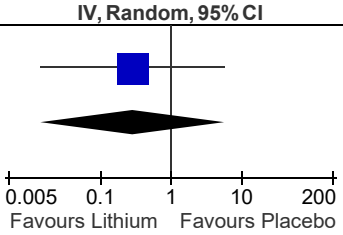
(1) Lithium vs placebo, index episode: depression, bipolar type II
(2) Lithium vs placebo, index episode: not specified, bipolar type not specified
(3) Lithium vs placebo, Index episode: not specified, bipolar type II
(4) Lithium + imipramine vs imipramine + placebo, Index episode: not specified,...

Risk of bias legend

2.3 New episode, mania

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Kane 1982 (1)	0	4	0	7		Not estimable
Kane 1982 (2)	0	6	1	5	100.0%	0.29 [0.01, 5.79]
Total (95% CI)		**10**		**12**	**100.0%**	**0.29 [0.01, 5.79]**
Total events	0		1			

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



Footnotes

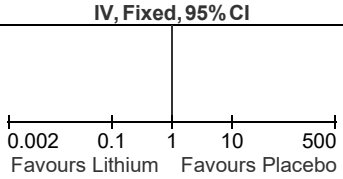
(1) Lithium vs placebo, Index episode: not specified, bipolar type II
(2) Lithium + imipramine vs imipramine + placebo, Index episode: not specified,...

Risk of bias legend

2.4 New episode, mixed

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

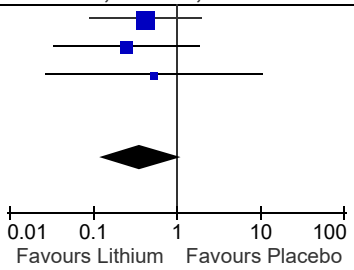


Risk of bias legend

2.5 New episode, hypomania

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Amsterdam 2010 (1)	2	26	5	27	53.9%	0.42 [0.09, 1.95]	
Dunner 1976 (2)	1	16	6	24	31.7%	0.25 [0.03, 1.89]	
Kane 1982 (3)	0	4	1	7	14.4%	0.53 [0.03, 10.70]	
Kane 1982 (4)	0	6	0	5		Not estimable	
Total (95% CI)		**52**		**63**	**100.0%**	**0.37 [0.12, 1.14]**	
Total events	3		12				

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)



Footnotes

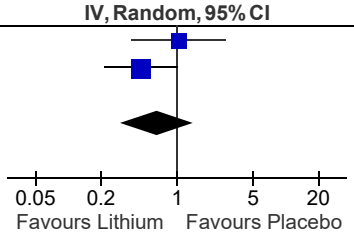
(1) Lithium vs placebo, index episode: depression, bipolar type II
(2) Lithium vs placebo, index episode: not specified, bipolar type not specified
(3) Lithium vs placebo, Index episode: not specified, bipolar type II
(4) Lithium + imipramine vs imipramine + placebo, Index episode: not specified,...

Risk of bias legend

2.6 Withdrawal, any cause

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Amsterdam 2010 (1)	6	26	6	27	42.1%	1.04 [0.38, 2.81]	
Dunner 1976 (2)	5	16	16	24	57.9%	0.47 [0.21, 1.02]	
Total (95% CI)		**42**		**51**	**100.0%**	**0.66 [0.30, 1.42]**	
Total events	11		22				

Heterogeneity: Tau² = 0.11; Chi² = 1.52, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 1.08 (P = 0.28)



Footnotes

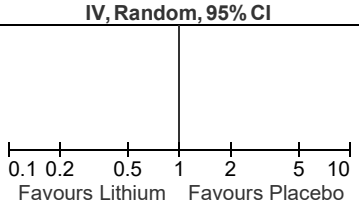
(1) Lithium vs placebo, index episode: depression, bipolar type II
(2) Lithium vs placebo, index episode: not specified, bipolar type not specified

Risk of bias legend

2.7 Serious adverse events (SAE)

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Amsterdam 2010 (1)	0	26	0	27		Not estimable		
Total (95% CI)		**26**		**27**		**Not estimable**		
Total events	0		0					

Heterogeneity: Not applicable
Test for overall effect: Not applicable



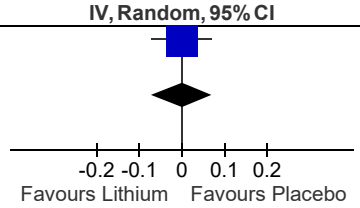
Footnotes
(1) Lithium vs placebo, index episode: depression, bipolar type II

Risk of bias legend

2.8 Serious adverse events (SAE) risk diff

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Amsterdam 2010 (1)	0	26	0	27	100.0%	0.00 [-0.07, 0.07]		
Total (95% CI)		**26**		**27**	**100.0%**	**0.00 [-0.07, 0.07]**		
Total events	0		0					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



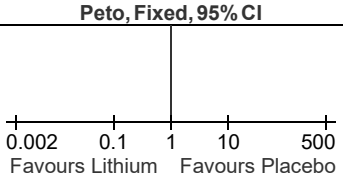
Footnotes
(1) Lithium vs placebo, index episode: depression, bipolar type II

Risk of bias legend

2.9 Suicidal behaviour

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					

Heterogeneity: Not applicable
Test for overall effect: Not applicable

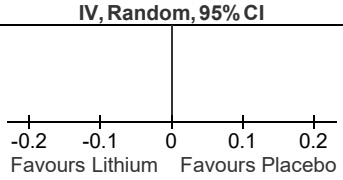


Risk of bias legend

2.10 Suicidal behaviour, risk diff

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					

Heterogeneity: Not applicable
Test for overall effect: Not applicable

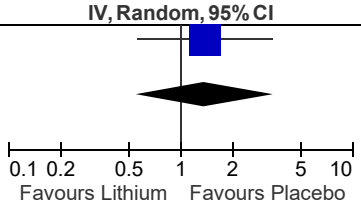


Risk of bias legend

2.11 Sedation

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Amsterdam 2010 (1)	8	26	6	27	100.0%	1.38 [0.56, 3.44]
Total (95% CI)		**26**		**27**	**100.0%**	**1.38 [0.56, 3.44]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)



Risk of Bias

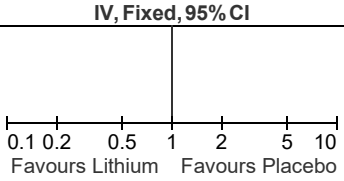
Footnotes
(1) Lithium vs placebo, index episode: depression, bipolar type II

Risk of bias legend

2.12 Psychiatric hospitalization

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



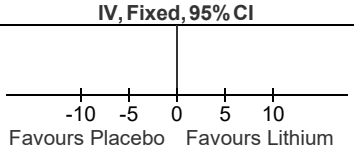
Risk of Bias

Risk of bias legend

2.13 Global functioning

Study or Subgroup	Lithium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable



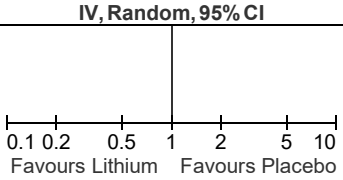
Risk of Bias

Risk of bias legend

2.14 Weigt gain, over 7%

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



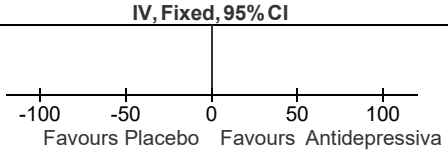
Risk of Bias

Risk of bias legend

2.16 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable



Risk of E

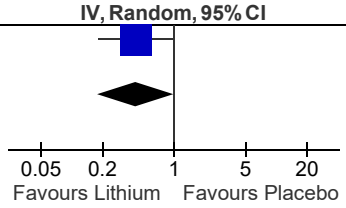
Risk of bias legend

3 Lithium vs Placebo_subgoup type 1 eller 2_Final

3.1 New episode, any type

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Cundall 1972 (1)	3	8	5	5	100.0%	0.42 [0.18, 1.00]
Total (95% CI)		**8**		**5**	**100.0%**	**0.42 [0.18, 1.00]**
Total events	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)



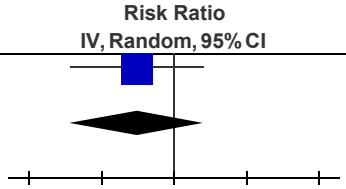
Footnotes
(1) Lithium vs placebo, index episode: not specified, bipolar type not specified

Risk of bias legend

3.2 New episode, depression

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Cundall 1972 (1)	1	8	2	5	100.0%	0.31 [0.04, 2.62]
Total (95% CI)		**8**		**5**	**100.0%**	**0.31 [0.04, 2.62]**
Total events	1		2			

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



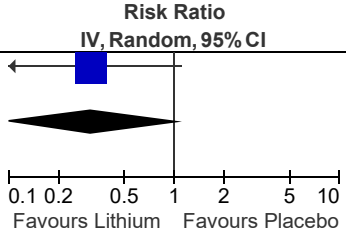
Footnotes
(1) Lithium vs placebo, index episode: not specified, bipolar type not specified

Risk of bias legend

3.3 New episode, mania

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Cundall 1972 (1)	2	8	4	5	100.0%	0.31 [0.09, 1.12]
Total (95% CI)		**8**		**5**	**100.0%**	**0.31 [0.09, 1.12]**
Total events	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.07)



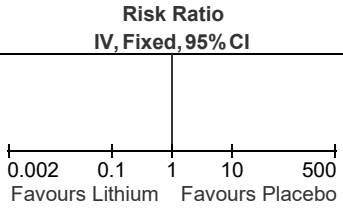
Footnotes
(1) Lithium vs placebo, index episode: not specified, bipolar type not specified

Risk of bias legend

3.4 New episode, mixed

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

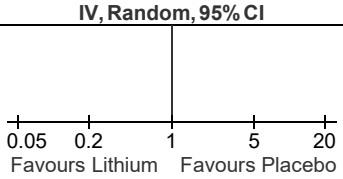


Risk of bias legend

3.5 New episode, hypomania

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

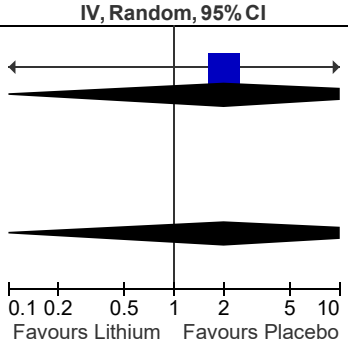


Risk of bias legend

3.6 Withdrawal, any cause

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
3.6.3 Bipolar type not specified							
Cundall 1972 (1)	1	8	0	5	100.0%	2.00 [0.10, 41.37]	
Subtotal (95% CI)		**8**		**5**	**100.0%**	**2.00 [0.10, 41.37]**	
Total events	1		0				
Total (95% CI)		**8**		**5**	**100.0%**	**2.00 [0.10, 41.37]**	
Total events	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Footnotes

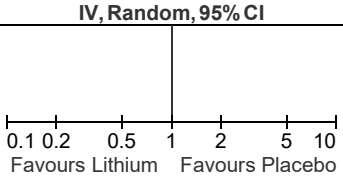
(1) Lithium vs placebo, index episode: not specified, bipolar type not specified

Risk of bias legend

3.7 Serious adverse events (SAE)

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

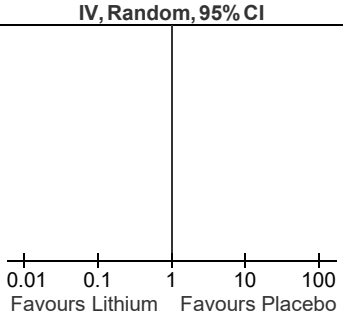


Risk of bias legend

3.9 Suicidal behaviour

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
3.9.3 Bipolar type not specified							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

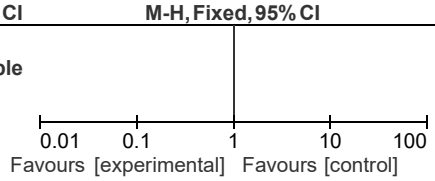
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Risk of bias legend

3.10 Sedation

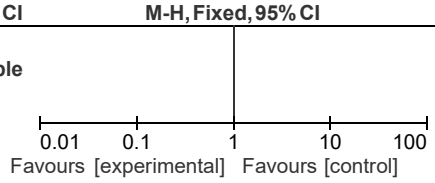
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

3.11 Psychiatric hospitalization

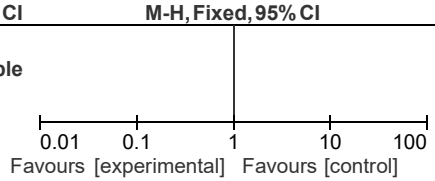
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

3.12 Global functioning

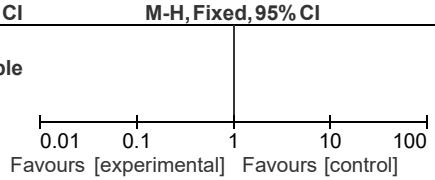
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

3.13 weight gain, over 7%

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

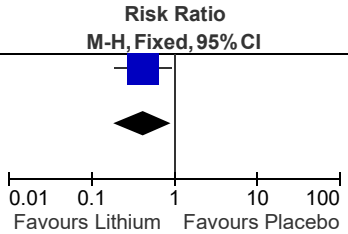


Risk of bias legend

4 Børn og unge_Lithium vs Placebo_Bipolar 1

4.1 New episode any type

Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
Findling 2019 (1)	5	17	10	14	100.0%	0.41 [0.18, 0.92]		
Total (95% CI)		**17**		**14**	**100.0%**	**0.41 [0.18, 0.92]**		
Total events	5		10					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.15 (P = 0.03)								



Footnotes

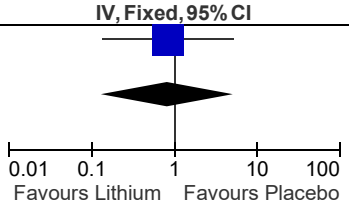
(1) Index episode: mania/mixed, bipolar type I

Risk of bias legend

4.2 Withdrawal, any cause

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Findling 2019 (1)	2	17	2	14	100.0%	0.82 [0.13, 5.12]	
Total (95% CI)		**17**		**14**	**100.0%**	**0.82 [0.13, 5.12]**	
Total events	2		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)



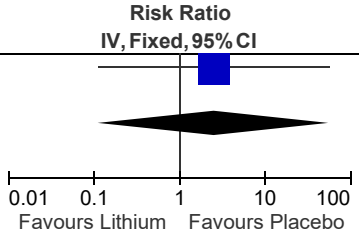
Footnotes
(1) Index episode: mania/mixed, bipolar type I

Risk of bias legend

4.3 Serious adverse events (SAE)

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Findling 2019 (1)	1	17	0	14	100.0%	2.50 [0.11, 56.98]	
Total (95% CI)		**17**		**14**	**100.0%**	**2.50 [0.11, 56.98]**	
Total events	1		0				

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



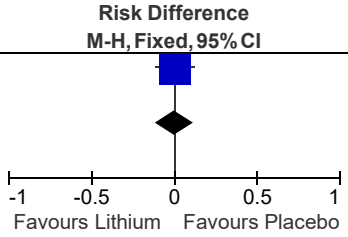
Footnotes
(1) Index episode: mania/mixed, bipolar type I

Risk of bias legend

4.4 Suicidal behaviour

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk of Bias
Findling 2019 (1)	0	17	0	14	100.0%	0.00 [-0.12, 0.12]	
Total (95% CI)		**17**		**14**	**100.0%**	**0.00 [-0.12, 0.12]**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



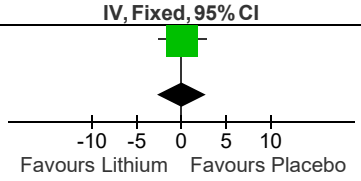
Footnotes
(1) Index episode: mania/mixed, bipolar type I

Risk of bias legend

4.5 Weight gain

Study or Subgroup	Lithium Mean	Lithium SD	Lithium Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias
Findling 2019 (1)	1.8	3.5	17	1.7	4.1	14	100.0%	0.10 [-2.62, 2.82]	
Total (95% CI)			**17**			**14**	**100.0%**	**0.10 [-2.62, 2.82]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)



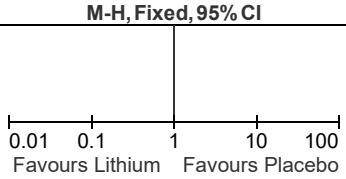
Footnotes
(1) Index episode: mania/mixed, bipolar type I

Risk of bias legend

5 Børn og unge_Lithium vs Placebo_Bipolar 2

5.1 New episode any type

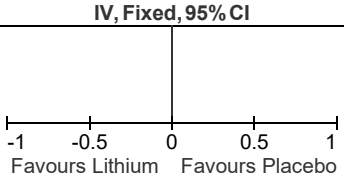
Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

5.2 Withdrawal, any cause

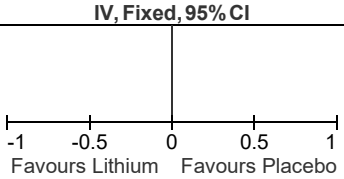
Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI	Risk Difference IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

5.3 Serious adverse events (SAE)

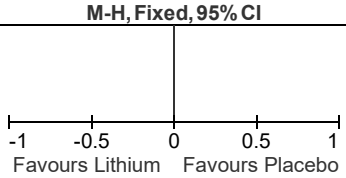
Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI	Risk Difference IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

5.4 Suicidal behaviour

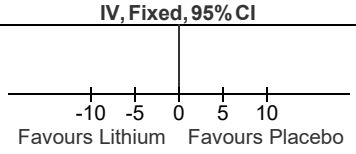
Study or Subgroup	Lithium Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

5.5 Weight gain

Study or Subgroup	Lithium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

6 Antipsychotics vs Placebo_Bipolar 1_Final

6.1 New episode, any type

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
6.1.1 Paliperidon ER							
Berwaerts 2012 (1)	66	146	77	144	8.0%	0.85 [0.67, 1.07]	
Subtotal (95% CI)		**146**		**144**	**8.0%**	**0.85 [0.67, 1.07]**	
Total events	66		77				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.40 (P = 0.16)							
6.1.2 Ziprasidone							
Bowden 2010 (2)	25	127	36	112	5.7%	0.61 [0.39, 0.95]	
Subtotal (95% CI)		**127**		**112**	**5.7%**	**0.61 [0.39, 0.95]**	
Total events	25		36				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.17 (P = 0.03)							
6.1.3 Lurasidone							
Calabrese 2017 (3)	51	246	129	250	7.6%	0.40 [0.31, 0.53]	
Subtotal (95% CI)		**246**		**250**	**7.6%**	**0.40 [0.31, 0.53]**	
Total events	51		129				
Heterogeneity: Not applicable							
Test for overall effect: Z = 6.56 (P < 0.00001)							
6.1.4 Aripiprazole							
Carlson 2012 (4)	40	178	56	173	6.8%	0.69 [0.49, 0.98]	
Keck 2006 (5)	19	77	36	83	5.5%	0.57 [0.36, 0.90]	
Marcus 2011 (6)	25	168	43	169	5.7%	0.58 [0.38, 0.91]	
Woo 2011 (7)	6	40	14	43	2.7%	0.46 [0.20, 1.08]	
Subtotal (95% CI)		**463**		**468**	**20.7%**	**0.61 [0.49, 0.77]**	
Total events	90		149				
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 3 (P = 0.79); I² = 0%							
Test for overall effect: Z = 4.20 (P < 0.0001)							
6.1.5 Quetiapine							
Suppes 2009 (8)	63	310	163	313	7.9%	0.39 [0.31, 0.50]	
Vieta 2008b (9)	62	336	180	367	7.9%	0.38 [0.29, 0.48]	
Weisler 2011 (10)	87	404	202	404	8.3%	0.43 [0.35, 0.53]	
Subtotal (95% CI)		**1050**		**1084**	**24.1%**	**0.40 [0.35, 0.46]**	
Total events	212		545				
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%							
Test for overall effect: Z = 13.33 (P < 0.00001)							
6.1.6 Olanzapine							
Tohen 2004 (11)	15	51	15	48	4.3%	0.94 [0.52, 1.71]	
Tohen 2006 (12)	105	225	109	136	8.7%	0.58 [0.49, 0.69]	
Vieta 2012 (13)	31	130	75	133	6.8%	0.42 [0.30, 0.60]	
Subtotal (95% CI)		**406**		**317**	**19.9%**	**0.57 [0.41, 0.79]**	
Total events	151		199				
Heterogeneity: Tau² = 0.05; Chi² = 5.70, df = 2 (P = 0.06); I² = 65%							
Test for overall effect: Z = 3.34 (P = 0.0008)							
6.1.7 Asenapine							
Szegedi 2018 (14)	11	126	42	126	4.2%	0.26 [0.14, 0.49]	
Subtotal (95% CI)		**126**		**126**	**4.2%**	**0.26 [0.14, 0.49]**	
Total events	11		42				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.26 (P < 0.0001)							
6.1.8 Perphenazine							
Zarate 2004 (15)	5	19	2	18	1.1%	2.37 [0.52, 10.70]	
Subtotal (95% CI)		**19**		**18**	**1.1%**	**2.37 [0.52, 10.70]**	
Total events	5		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.12 (P = 0.26)							
6.1.9 Cariprazine							
McIntyre 2024a (16)	24	143	14	71	4.3%	0.85 [0.47, 1.54]	
McIntyre 2024b (17)	26	145	14	71	4.4%	0.91 [0.51, 1.63]	

Subtotal (95% CI) **288** **142** **8.7%** **0.88 [0.58, 1.34]**

Total events 50 28

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%

Test for overall effect: Z = 0.60 (P = 0.55)

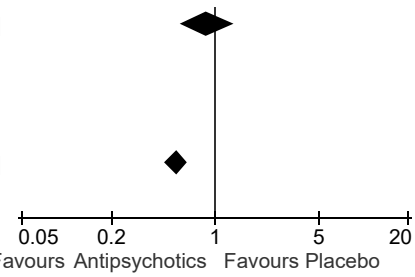
Total (95% CI) **2871** **2661** **100.0%** **0.55 [0.46, 0.65]**

Total events 661 1207

Heterogeneity: Tau² = 0.08; Chi² = 60.33, df = 16 (P < 0.00001); I² = 73%

Test for overall effect: Z = 7.09 (P < 0.00001)

Test for subgroup differences: Chi² = 51.68, df = 8 (P < 0.00001), I² = 84.5%



Risk of bias legend

Footnotes

(1) Paliperidon ER, index episode: mania/mixed, bipolar type I

(2) Ziprasidone i tillæg til lithium/valproate, index episode:mania, bipolar type I

(3) Lurasidon i tillæg til lithium/valproate, index episode:mania/depression, bipolar type I

(4) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed, bipolar type I

(5) Aripiprazole,index episode:mania/mixed, bipolar type I

(6) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed, bipolar type I

(7) Aripiprazole i tillæg til valproat, index episode:mania/mixed, bipolar type I

(8) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity,...

(9) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression, bipolar...

(10) Quetiapin, index episode:mania/mixed/depression, bipolar type I

(11) Olanzapin i tillæg til lithium/valproat, index episode:mania/mixed, bipolar type I

(12) Olanzapin, index episode:mania/mixed, bipolar type I

(13) Olanzapin, index episode:mania/mixed, bipolar type I

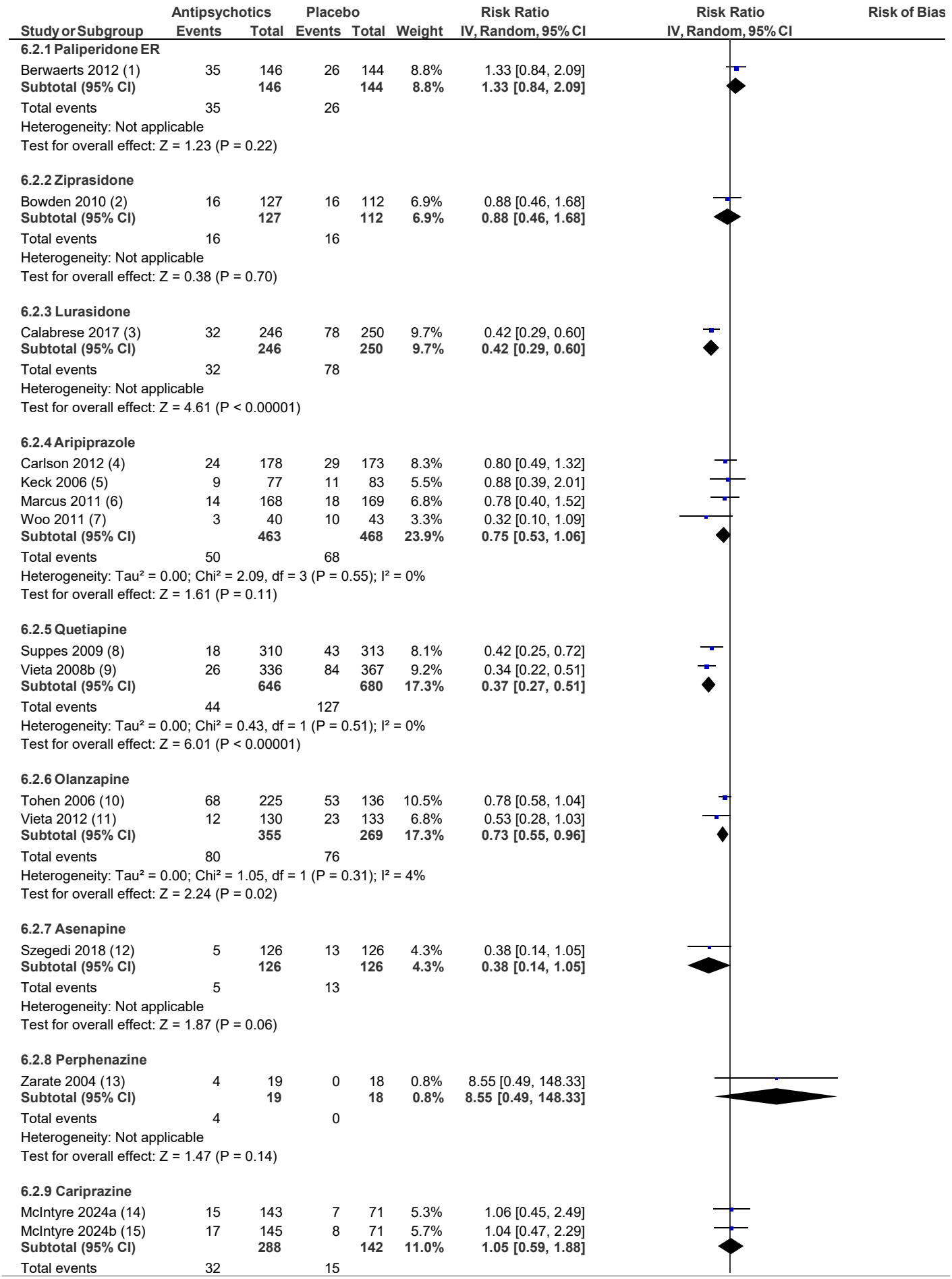
(14) Asenapin, index episode:mania/mixed, bipolar type I

(15) Perphenazine i tillæg til mood stabilizer (lithium/carbamazepine/ valproate), index...

(16) cariprazine 1.5 mg/day; outcome relapse

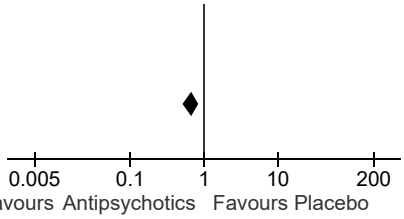
(17) cariprazine 3mg/day; outcome: relapse

6.2 New episode, depression



Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)

Total (95% CI) **2416** **2209** **100.0%** **0.67 [0.51, 0.87]**
Total events 298 419
Heterogeneity: Tau² = 0.15; Chi² = 39.46, df = 14 (P = 0.0003); I² = 65%
Test for overall effect: Z = 3.04 (P = 0.002)
Test for subgroup differences: Chi² = 35.74, df = 8 (P < 0.0001), I² = 77.6%

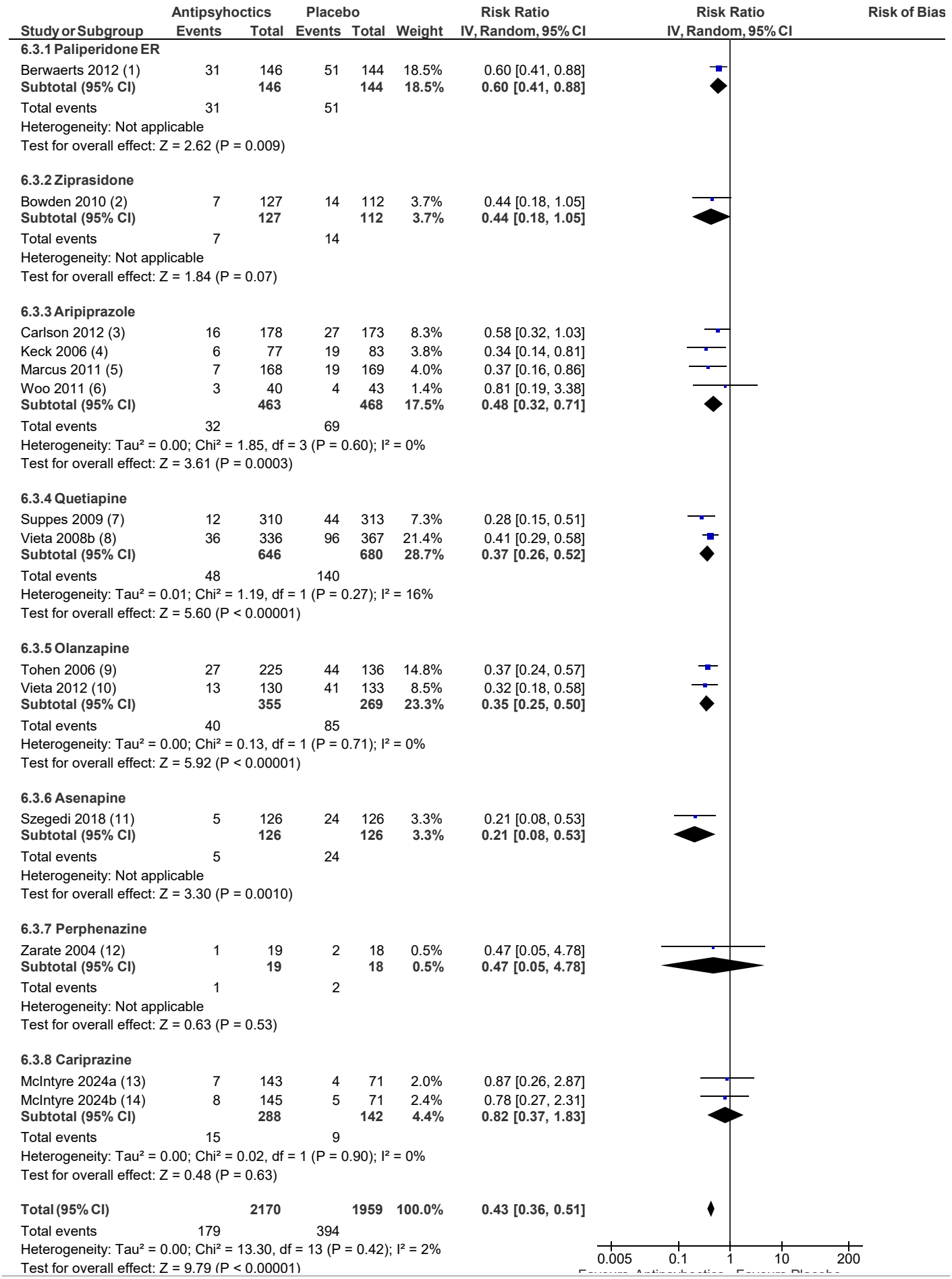


Risk of bias legend

Footnotes

(1) Paliperidon ER, index episode: mania/mixed
(2) Ziprasidone i tillæg til lithium/valproate, index episode:mania
(3) Lurasidon i tillæg til lithium/valproate, index episode:mania/depression
(4) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed
(5) Aripiprazole,index episode:mania/mixed
(6) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(7) Aripiprazole i tillæg til valproat, index episode:mania/mixed
(8) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(9) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression
(10) Olanzapin, index episode:mania/mixed
(11) Olanzapin, index episode:mania/mixed
(12) Asenapin, index episode:mania/mixed
(13) Perphenazine i tillæg til mood stabilizer (lithium/carbamazepine/ valproate), index...
(14) 1,6 mg/day: outcome relapse
(15) 3 mg/day: outcome relapse

6.3 New episode, mania



Favours Antipsychotics Favours Placebo

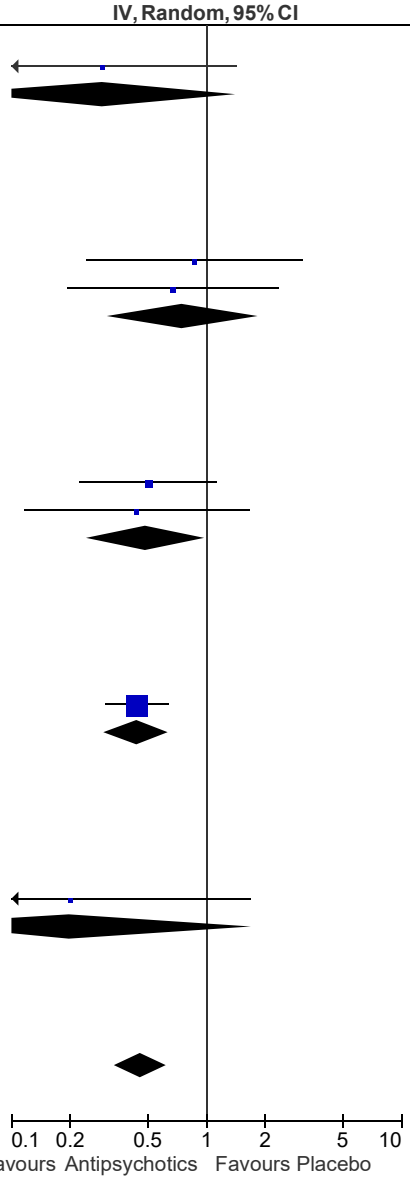
Test for subgroup differences: Chi² = 10.05, df = 7 (P = 0.19), I² = 30.4%

Footnotes

(1) Paliperidon ER, index episode: mania/mixed
(2) Ziprasidone i tillæg til lithium/valproate, index episode:mania
(3) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed
(4) Aripiprazole,index episode:mania/mixed
(5) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(6) Aripiprazole i tillæg til valproat, index episode:mania/mixed
(7) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(8) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression
(9) Olanzapin, index episode:mania/mixed
(10) Olanzapin, index episode:mania/mixed
(11) Asenapin, index episode:mania/mixed
(12) Perphenazine i tillæg til mood stabilizer (lithium/carbamazepine/ valproate), index...
(13) 1,5 mg/day
(14) 3 mg/day

Risk of bias legend

6.4 New episode, mixed



Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
6.4.1 Ziprasidone							
Bowden 2010 (1)	2	127	6	112	3.6%	0.29 [0.06, 1.43]	
Subtotal (95% CI)		**127**		**112**	**3.6%**	**0.29 [0.06, 1.43]**	
Total events	2		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
6.4.2 Aripiprazole							
Keck 2006 (2)	4	77	5	83	5.6%	0.86 [0.24, 3.09]	
Marcus 2011 (3)	4	168	6	169	5.9%	0.67 [0.19, 2.33]	
Subtotal (95% CI)		**245**		**252**	**11.4%**	**0.76 [0.31, 1.85]**	
Total events	8		11				
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%							
Test for overall effect: Z = 0.61 (P = 0.54)							
6.4.3 Olanzapine							
Tohen 2006 (4)	10	225	12	136	13.8%	0.50 [0.22, 1.13]	
Vieta 2012 (5)	3	130	7	133	5.1%	0.44 [0.12, 1.66]	
Subtotal (95% CI)		**355**		**269**	**19.0%**	**0.49 [0.24, 0.97]**	
Total events	13		19				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%							
Test for overall effect: Z = 2.05 (P = 0.04)							
6.4.4 Quetiapine							
Suppes 2009 (6)	33	310	76	313	64.0%	0.44 [0.30, 0.64]	
Subtotal (95% CI)		**310**		**313**	**64.0%**	**0.44 [0.30, 0.64]**	
Total events	33		76				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.28 (P < 0.0001)							
6.4.5 Asenapine							
Szegedi 2018 (7)	1	126	5	126	2.0%	0.20 [0.02, 1.69]	
Subtotal (95% CI)		**126**		**126**	**2.0%**	**0.20 [0.02, 1.69]**	
Total events	1		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Total (95% CI)		**1163**		**1072**	**100.0%**	**0.46 [0.34, 0.62]**	
Total events	57		117				
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 6 (P = 0.89); I² = 0%							
Test for overall effect: Z = 5.02 (P < 0.00001)							
Test for subgroup differences: Chi² = 2.18, df = 4 (P = 0.70), I² = 0%							

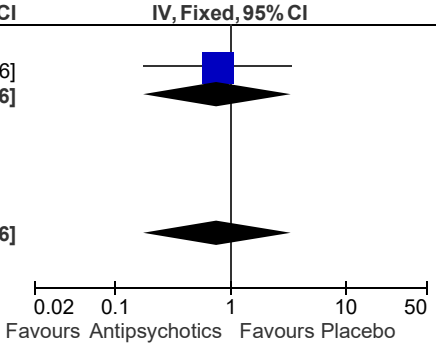
Risk of bias legend

Footnotes

(1) Ziprasidone i tillæg til lithium/valproate, index episode:mania
(2) Aripiprazole,index episode:mania/mixed
(3) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(4) Olanzapin, index episode:mania/mixed
(5) Olanzapin, index episode:mania/mixed
(6) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(7) Asenapin, index episode:mania/mixed

6.5 New episode, hypomania

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
6.5.1 Olanzapine								
Vieta 2012 (1)	3	130	4	133	100.0%	0.77 [0.18, 3.36]		
Subtotal (95% CI)		**130**		**133**	**100.0%**	**0.77 [0.18, 3.36]**		
Total events	3		4					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								
Total (95% CI)		**130**		**133**	**100.0%**	**0.77 [0.18, 3.36]**		
Total events	3		4					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								
Test for subgroup differences: Not applicable								

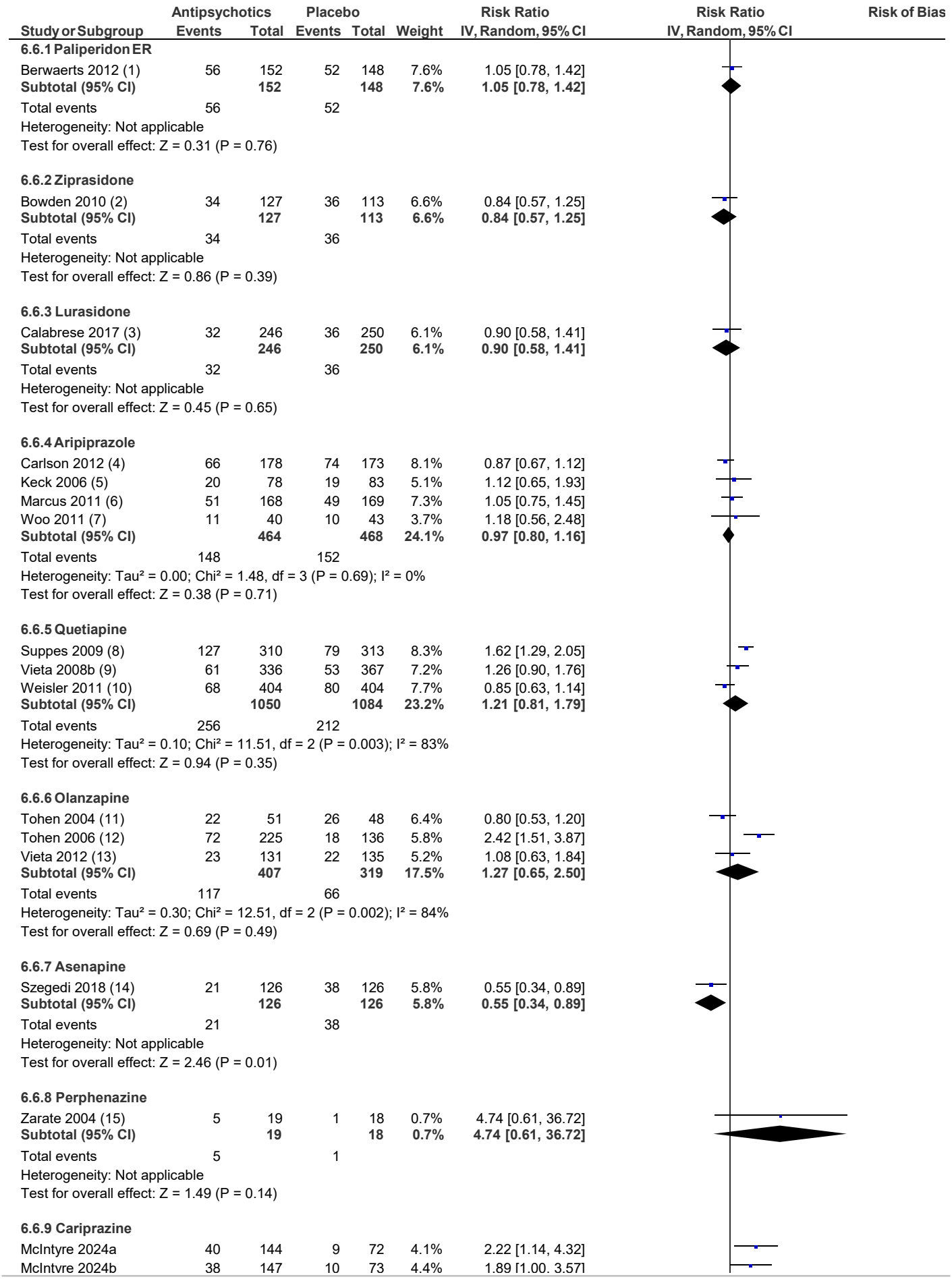


Footnotes

(1) Olanzapin, index episode:mania/mixed

Risk of bias legend

6.6 Withdrawal, any cause

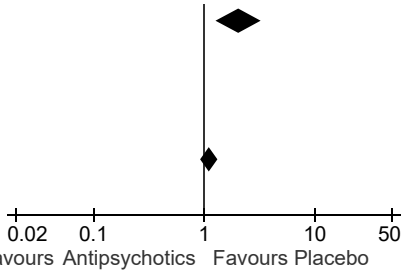


Subtotal (95% CI)	**291**	**145**	**8.5%**	**2.04 [1.29, 3.23]**	
Total events	78	19			

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.04 (P = 0.002)

Total (95% CI)	**2882**	**2671**	**100.0%**	**1.12 [0.93, 1.34]**	
Total events	747	612			

Heterogeneity: Tau² = 0.09; Chi² = 50.70, df = 16 (P < 0.0001); I² = 68%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Chi² = 20.03, df = 8 (P = 0.01), I² = 60.1%

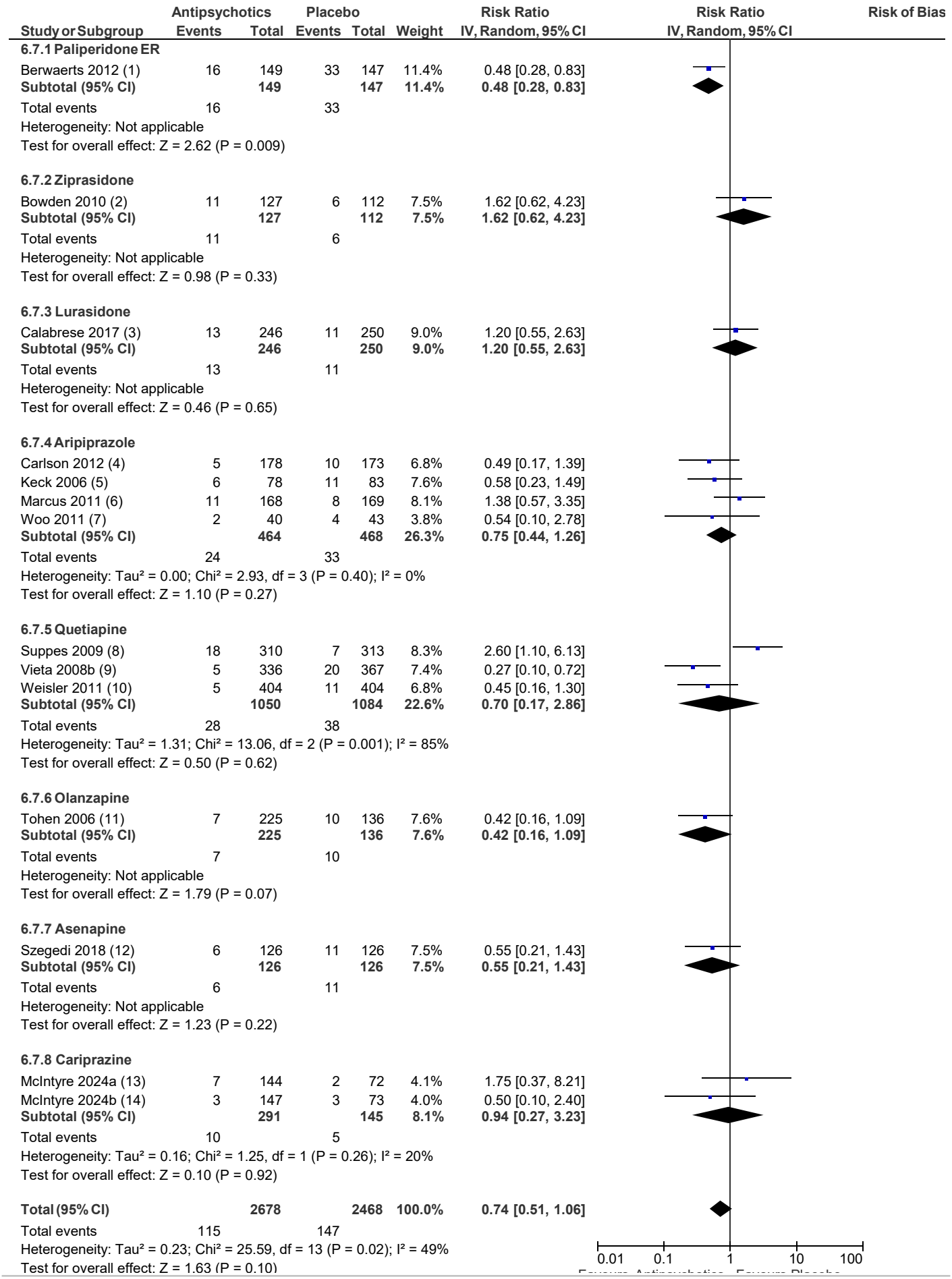


Risk of bias legend

Footnotes

(1) Paliperidon ER, index episode: mania/mixed
(2) Ziprasidone i tillæg til lithium/valproate, index episode:mania
(3) Lurasidon i tillæg til lithium/valproate, index episode:mania/depression
(4) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed
(5) Aripiprazole,index episode:mania/mixed
(6) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(7) Aripiprazole i tillæg til valproat, index episode:mania/mixed
(8) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(9) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression
(10) Quetiapin, index episode:mania/mixed/depression
(11) Olanzapin i tillæg til lithium/valproat, index episode:mania/mixed
(12) Olanzapin, index episode:mania/mixed
(13) Olanzapin, index episode:mania/mixed
(14) Asenapin, index episode:mania/mixed
(15) Perphenazine i tillæg til mood stabilizer (lithium/carbamazepine/ valproate), index...

6.7 Serious adverse events (SAE)



Favours Antipsychotics Favours Placebo

Test for subgroup differences: Chi² = 8.19, df = 7 (P = 0.32), I² = 14.5%

Footnotes

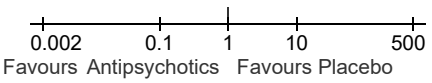
(1) Paliperidon ER, index episode: mania/mixed
(2) Ziprasidone i tillæg til lithium/valproate, index episode:mania
(3) Lurasidon i tillæg til lithium/valproate, index episode:mania/depression
(4) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed
(5) Aripiprazole,index episode:mania/mixed
(6) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(7) Aripiprazole i tillæg til valproat, index episode:mania/mixed
(8) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(9) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression
(10) Quetiapin, index episode:mania/mixed/depression
(11) Olanzapin, index episode:mania/mixed
(12) Asenapin, index episode:mania/mixed
(13) 1,5 mg/day
(14) 1,5 mg/day

Risk of bias legend

6.8 Weigt gain, over 7%

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
6.8.1 Paliperidone ER							
Berwaerts 2012 (1)	41	152	29	148	10.4%	1.38 [0.91, 2.09]	
Subtotal (95% CI)		**152**		**148**	**10.4%**	**1.38 [0.91, 2.09]**	
Total events	41		29				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.50 (P = 0.13)							
6.8.2 Ziprazidone							
Bowden 2010 (2)	7	127	6	112	4.7%	1.03 [0.36, 2.97]	
Subtotal (95% CI)		**127**		**112**	**4.7%**	**1.03 [0.36, 2.97]**	
Total events	7		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.05 (P = 0.96)							
6.8.3 Lurasidone							
Calabrese 2017 (3)	24	246	13	250	7.9%	1.88 [0.98, 3.60]	
Subtotal (95% CI)		**246**		**250**	**7.9%**	**1.88 [0.98, 3.60]**	
Total events	24		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.89 (P = 0.06)							
6.8.4 Aripiprazole							
Carlson 2012 (4)	21	178	6	173	5.9%	3.40 [1.41, 8.22]	
Keck 2006 (5)	7	56	0	60	0.9%	16.05 [0.94, 274.71]	
Marcus 2011 (6)	15	167	11	166	7.0%	1.36 [0.64, 2.86]	
Woo 2011 (7)	9	40	8	43	6.1%	1.21 [0.52, 2.83]	
Subtotal (95% CI)		**441**		**442**	**19.9%**	**1.97 [0.98, 3.95]**	
Total events	52		25				
Heterogeneity: Tau² = 0.22; Chi² = 5.67, df = 3 (P = 0.13); I² = 47%							
Test for overall effect: Z = 1.90 (P = 0.06)							
6.8.5 Quetiapine							
Suppes 2009 (8)	21	310	8	312	6.5%	2.64 [1.19, 5.87]	
Vieta 2008b (9)	25	336	7	367	6.3%	3.90 [1.71, 8.90]	
Weisler 2011 (10)	43	404	11	404	7.9%	3.91 [2.05, 7.47]	
Subtotal (95% CI)		**1050**		**1083**	**20.8%**	**3.49 [2.27, 5.36]**	
Total events	89		26				
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 2 (P = 0.72); I² = 0%							
Test for overall effect: Z = 5.70 (P < 0.00001)							
6.8.6 Olanzazepine							
Tohen 2004 (11)	14	51	3	48	4.0%	4.39 [1.35, 14.34]	
Tohen 2006 (12)	18	225	2	136	3.0%	5.44 [1.28, 23.08]	
Vieta 2012 (13)	35	131	12	135	8.3%	3.01 [1.63, 5.53]	
Subtotal (95% CI)		**407**		**319**	**15.3%**	**3.47 [2.09, 5.76]**	
Total events	67		17				
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%							
Test for overall effect: Z = 4.80 (P < 0.00001)							
6.8.7 Asenapine							
Szegedi 2018 (14)	6	126	1	126	1.6%	6.00 [0.73, 49.12]	
Subtotal (95% CI)		**126**		**126**	**1.6%**	**6.00 [0.73, 49.12]**	
Total events	6		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.67 (P = 0.09)							
6.8.8 Cariprazine							
McIntyre 2024a (15)	39	144	17	72	9.6%	1.15 [0.70, 1.88]	
McIntyre 2024b (16)	45	147	18	73	9.9%	1.24 [0.78, 1.98]	
Subtotal (95% CI)		**291**		**145**	**19.4%**	**1.20 [0.85, 1.68]**	
Total events	84		35				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%							
Test for overall effect: Z = 1.03 (P = 0.30)							
Total (95% CI)		**2840**		**2625**	**100.0%**	**2.09 [1.57, 2.78]**	
Total events	370		152				

Heterogeneity: Tau² = 0.16; Chi² = 32.00, df = 15 (P = 0.006); I² = 53%
Test for overall effect: Z = 5.09 (P < 0.00001)
Test for subgroup differences: Chi² = 24.89, df = 7 (P = 0.0008), I² = 71.9%

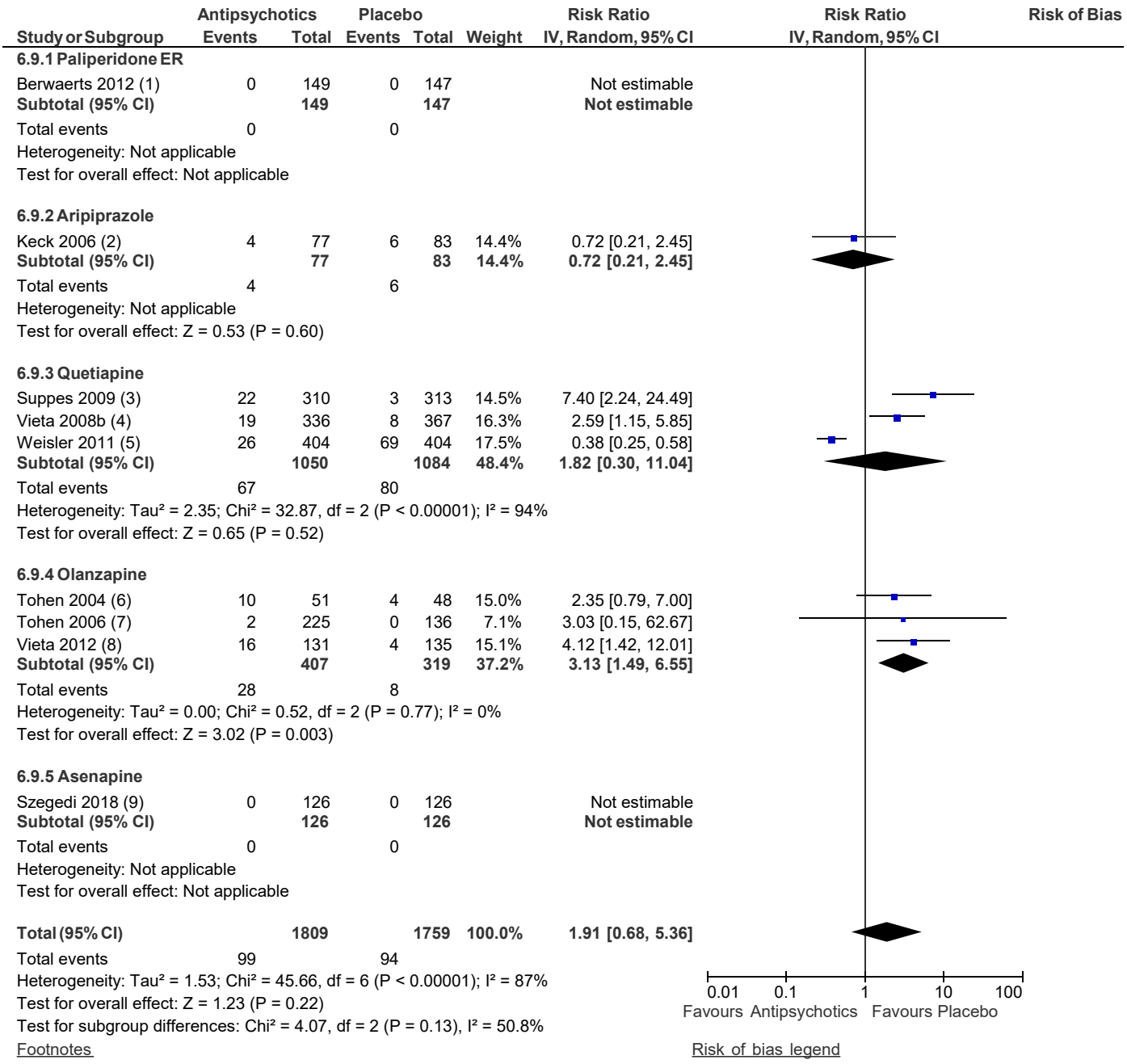


Footnotes

(1) Paliperidon ER, index episode: mania/mixed
(2) Ziprasidone i tillæg til lithium/valproate, index episode:mania
(3) Lurasidon i tillæg til lithium/valproate, index episode:mania/depression
(4) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed
(5) Aripiprazole,index episode:mania/mixed
(6) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(7) Aripiprazole i tillæg til valproat, index episode:mania/mixed
(8) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(9) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression
(10) Quetiapin, index episode:mania/mixed/depression
(11) Olanzapin i tillæg til lithium/valproat, index episode:mania/mixed
(12) Olanzapin, index episode:mania/mixed
(13) Olanzapin, index episode:mania/mixed
(14) Asenapin, index episode:mania/mixed
(15) 1,5 mg/day cariprazine
(16) 3 mg/day cariprazine

Risk of bias legend

6.9 Sedation

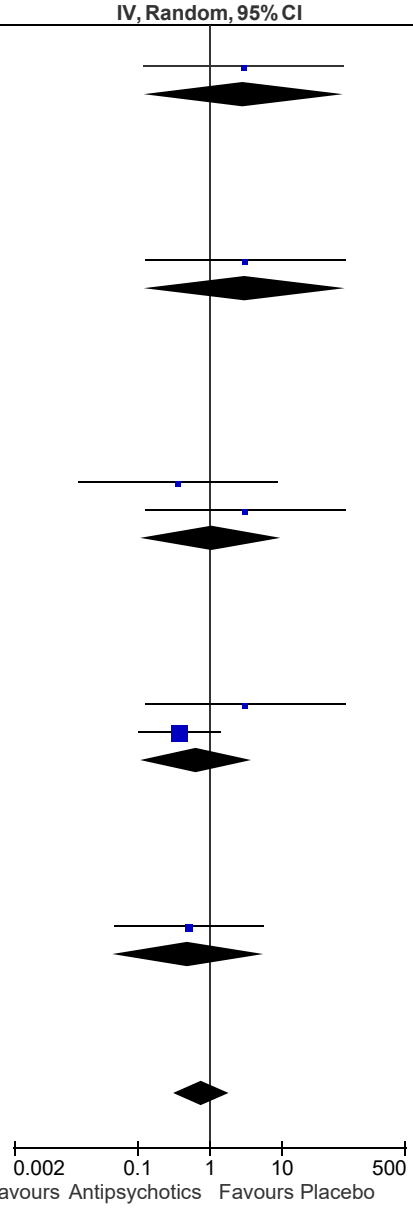


Footnotes

(1) Paliperidon ER, index episode: mania/mixed
(2) Aripiprazole,index episode:mania/mixed
(3) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(4) Quetiapin i tillæg til lithium/valproat, index episode:mania/mixed/depression
(5) Quetiapin, index episode:mania/mixed/depression
(6) Olanzapin i tillæg til lithium/valproat, index episode:mania/mixed
(7) Olanzapin, index episode:mania/mixed
(8) Olanzapin, index episode:mania/mixed
(9) Asenapin, index episode:mania/mixed

6.10 Suicidal behaviour

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
6.10.1 Paliperidone ER							
Berwaerts 2012 (1)	1	152	0	148	7.9%	2.92 [0.12, 71.15]	
Subtotal (95% CI)		**152**		**148**	**7.9%**	**2.92 [0.12, 71.15]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
6.10.2 Lurasidone							
Calabrese 2017 (2)	1	246	0	250	7.9%	3.05 [0.12, 74.47]	
Subtotal (95% CI)		**246**		**250**	**7.9%**	**3.05 [0.12, 74.47]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.49)							
6.10.3 Aripiprazole							
Carlson 2012 (3)	0	178	0	173		Not estimable	
Keck 2006 (4)	0	78	1	83	7.9%	0.35 [0.01, 8.57]	
Marcus 2011 (5)	1	168	0	169	7.9%	3.02 [0.12, 73.55]	
Subtotal (95% CI)		**424**		**425**	**15.9%**	**1.03 [0.11, 9.84]**	
Total events	1		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%							
Test for overall effect: Z = 0.03 (P = 0.98)							
6.10.4 Quetiapine							
Suppes 2009 (6)	1	310	0	313	7.9%	3.03 [0.12, 74.07]	
Weisler 2011 (7)	3	404	8	404	46.3%	0.38 [0.10, 1.40]	
Subtotal (95% CI)		**714**		**717**	**54.2%**	**0.63 [0.11, 3.68]**	
Total events	4		8				
Heterogeneity: Tau² = 0.63; Chi² = 1.40, df = 1 (P = 0.24); I² = 29%							
Test for overall effect: Z = 0.52 (P = 0.61)							
6.10.5 Asenapine							
Szegedi 2018 (8)	1	126	2	126	14.1%	0.50 [0.05, 5.44]	
Subtotal (95% CI)		**126**		**126**	**14.1%**	**0.50 [0.05, 5.44]**	
Total events	1		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							
Total (95% CI)		**1662**		**1666**	**100.0%**	**0.75 [0.31, 1.84]**	
Total events	8		11				
Heterogeneity: Tau² = 0.00; Chi² = 4.28, df = 6 (P = 0.64); I² = 0%							
Test for overall effect: Z = 0.63 (P = 0.53)							
Test for subgroup differences: Chi² = 1.48, df = 4 (P = 0.83), I² = 0%							



Footnotes

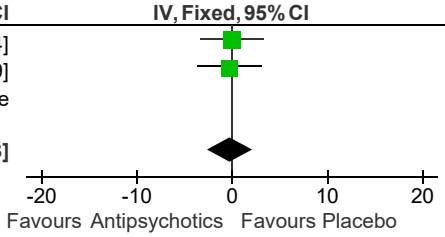
(1) Paliperidon ER, index episode: mania/mixed
(2) Lurasidon i tillæg til lithium/valproate, index episode:mania/depression
(3) Aripiprazole i tillæg til lamotrigine, index episode:mania/mixed
(4) Aripiprazole,index episode:mania/mixed
(5) Aripiprazole i tillæg til lithium/valproat, index episode:mania/mixed
(6) Qutiapin i tillæg til lithium/valproat, index episode: any episode regardless of polarity
(7) Quetiapin, index episode:mania/mixed/depression
(8) Asenapin, index episode:mania/mixed

Risk of bias legend

6.11 Global functioning

Study or Subgroup	Antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
McIntyre 2024a (1)	-1	10.4	140	-1	12.4	72	50.7%	0.00 [-3.34, 3.34]
McIntyre 2024b (2)	-1.3	11.1	140	-1	12.4	73	49.3%	-0.30 [-3.69, 3.09]
Weisler 2011 (3)	0	0	0	0	0	0		Not estimable
Total (95% CI)			**280**			**145**	**100.0%**	**-0.15 [-2.53, 2.23]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)

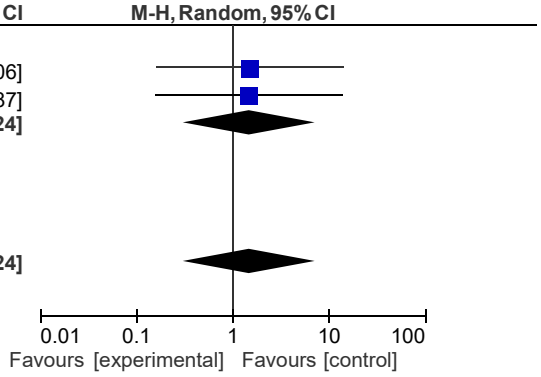


Footnotes
(1) 1,5 mg/day; Personal and Social Performance Scale (PSP) er højere score bedre....
(2) 3 mg/day; Personal and Social Performance Scale (PSP) er højere score bedre.
(3) data ikke indgå i metaanalyse

Risk of bias legend

6.12 Psychiatric hospitalization

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.12.1 Cariprazine						
McIntyre 2024a (1)	3	143	1	71	50.0%	1.49 [0.16, 14.06]
McIntyre 2024b (2)	3	145	1	71	50.0%	1.47 [0.16, 13.87]
Subtotal (95% CI)		**288**		**142**	**100.0%**	**1.48 [0.30, 7.24]**
Total events	6		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**288**		**142**	**100.0%**	**1.48 [0.30, 7.24]**
Total events	6		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Not applicable						

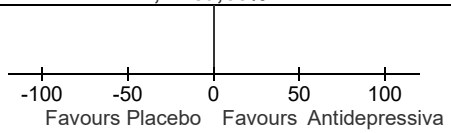


Footnotes
(1) 1.5 mg/day cariprazine
(2) 3 mg/day cariprazine

Risk of bias legend

6.13 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

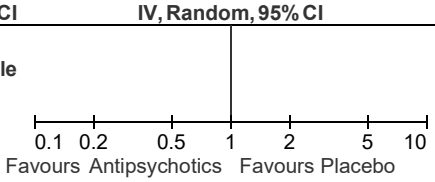


Risk of bias legend

7 Antipsychotics vs Placebo_Bipolar 2_Final

7.1 New episode, any type

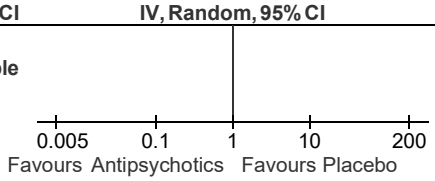
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

7.2 New episode, depression

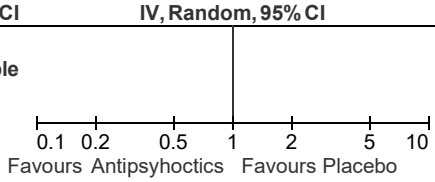
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

7.3 New episode, mania

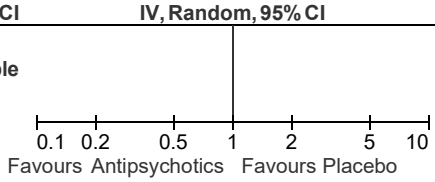
Study or Subgroup	Antipsyhoctics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

7.4 New episode, mixed

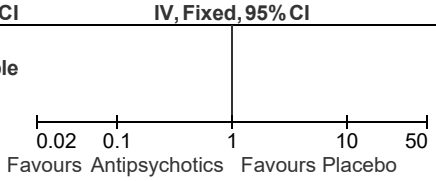
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

7.5 New episode, hypomania

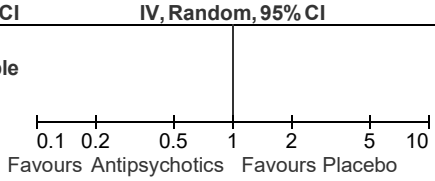
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

7.6 Withdrawal, any cause

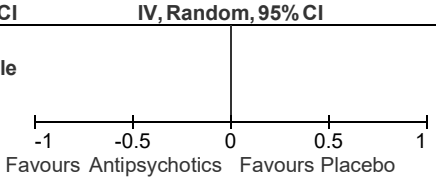
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

7.7 Serious adverse events (SAE)

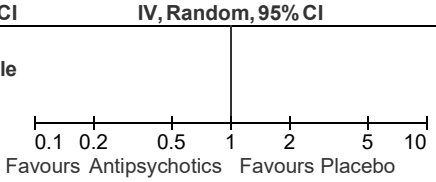
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

7.8 Weigt gain, over 7%

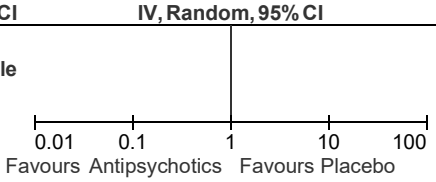
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

7.9 Sedation

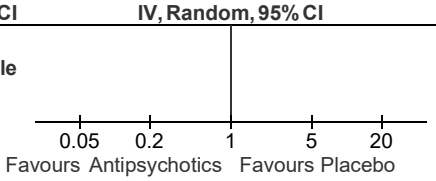
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

7.10 Suicidal behaviour

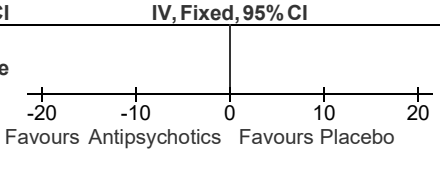
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

7.11 Global functioning

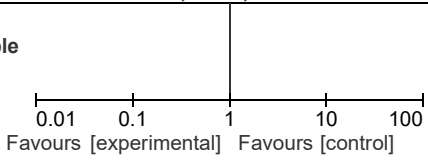
Study or Subgroup	Antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of B
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

7.13 Psychiatric hospitalization

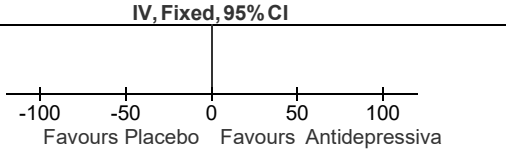
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

7.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

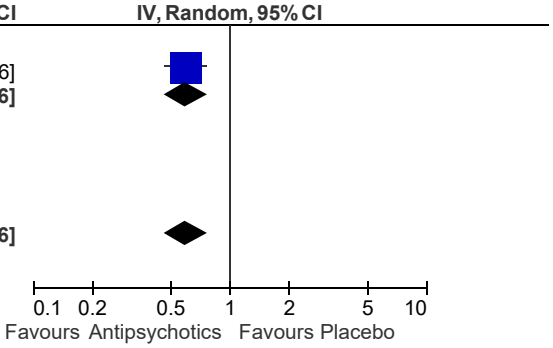


Risk of bias legend

8 Antipsychotics vs Placebo_Bipolar 1 og 2_Final

8.1 New episode, any type

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
8.1.5 Quetiapine						
Young 2014 (1)	69	291	117	294	100.0%	0.60 [0.46, 0.76]
Subtotal (95% CI)		**291**		**294**	**100.0%**	**0.60 [0.46, 0.76]**
Total events	69		117			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.07 (P < 0.0001)						
Total (95% CI)		**291**		**294**	**100.0%**	**0.60 [0.46, 0.76]**
Total events	69		117			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.07 (P < 0.0001)						
Test for subgroup differences: Not applicable						



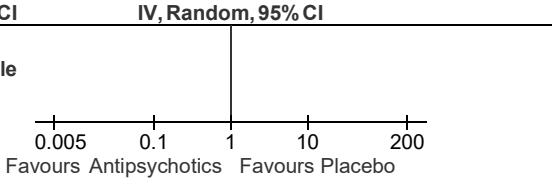
Footnotes

(1) Quetiapin (300+600mg), index episode: depression, bipolar type I+2; (60.4%) were...

Risk of bias legend

8.2 New episode, depression

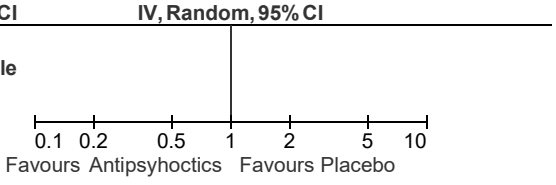
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

8.3 New episode, mania

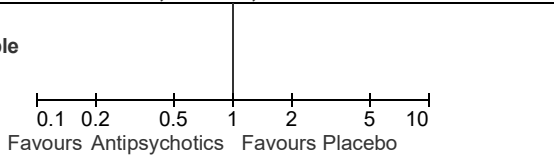
Study or Subgroup	Antipsyhoctics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

8.4 New episode, mixed

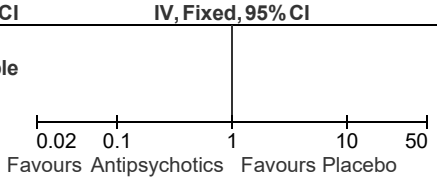
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

8.5 New episode, hypomania

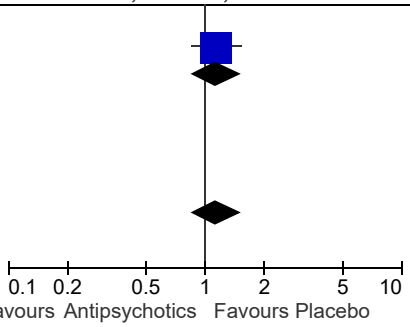
Study or Subgroup	Antipsychotics Events	Antipsychotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

8.6 Withdrawal, any cause

Study or Subgroup	Antipsychotics Events	Antipsychotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
8.6.5 Quetiapine								
Young 2014 (1)	71	291	63	294	100.0%	1.14 [0.85, 1.53]		
Subtotal (95% CI)		**291**		**294**	**100.0%**	**1.14 [0.85, 1.53]**		
Total events	71		63					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.85 (P = 0.39)								
Total (95% CI)		**291**		**294**	**100.0%**	**1.14 [0.85, 1.53]**		
Total events	71		63					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.85 (P = 0.39)								
Test for subgroup differences: Not applicable								



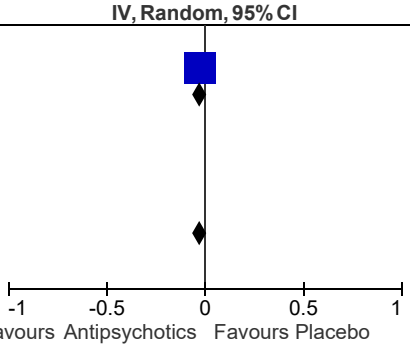
Footnotes

(1) Quetiapin, index episode: depression

Risk of bias legend

8.7 Serious adverse events (SAE)

Study or Subgroup	Antipsychotics Events	Antipsychotics Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
8.7.5 Quetiapine								
Young 2014 (1)	8	291	16	294	100.0%	-0.03 [-0.06, 0.01]		
Subtotal (95% CI)		**291**		**294**	**100.0%**	**-0.03 [-0.06, 0.01]**		
Total events	8		16					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
Total (95% CI)		**291**		**294**	**100.0%**	**-0.03 [-0.06, 0.01]**		
Total events	8		16					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
Test for subgroup differences: Not applicable								



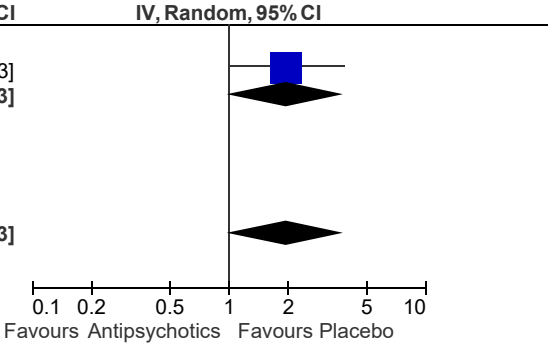
Footnotes

(1) Quetiapin, index episode: depression

Risk of bias legend

8.8 Weigt gain, over 7%

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
8.8.5 Quetiapine							
Young 2014 (1)	23	290	12	294	100.0%	1.94 [0.99, 3.83]	
Subtotal (95% CI)		**290**		**294**	**100.0%**	**1.94 [0.99, 3.83]**	
Total events	23		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.92 (P = 0.06)							
Total (95% CI)		**290**		**294**	**100.0%**	**1.94 [0.99, 3.83]**	
Total events	23		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.92 (P = 0.06)							
Test for subgroup differences: Not applicable							



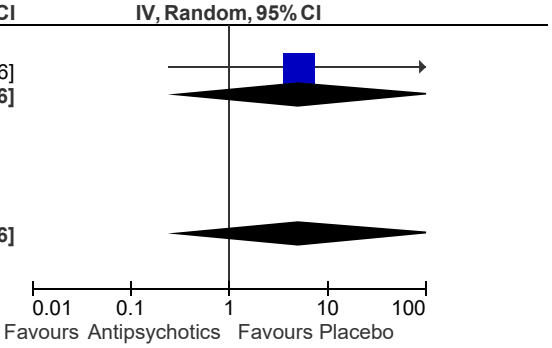
Footnotes

(1) Quetiapin, index episode: depression

Risk of bias legend

8.9 Sedation

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
8.9.3 Quetiapine							
Young 2014 (1)	2	291	0	294	100.0%	5.05 [0.24, 104.76]	
Subtotal (95% CI)		**291**		**294**	**100.0%**	**5.05 [0.24, 104.76]**	
Total events	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.05 (P = 0.30)							
Total (95% CI)		**291**		**294**	**100.0%**	**5.05 [0.24, 104.76]**	
Total events	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.05 (P = 0.30)							
Test for subgroup differences: Not applicable							



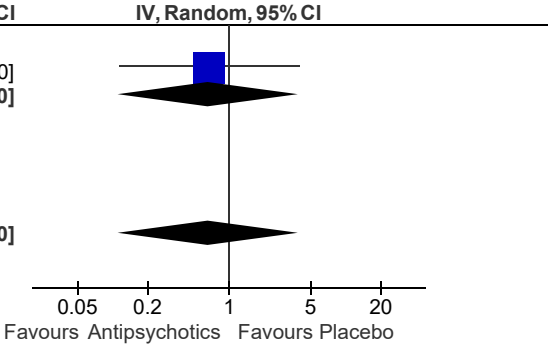
Footnotes

(1) Quetiapin, index episode: depression

Risk of bias legend

8.10 Suicidal behaviour

Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
8.10.4 Quetiapine							
Young 2014 (1)	2	291	3	294	100.0%	0.67 [0.11, 4.00]	
Subtotal (95% CI)		**291**		**294**	**100.0%**	**0.67 [0.11, 4.00]**	
Total events	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.43 (P = 0.66)							
Total (95% CI)		**291**		**294**	**100.0%**	**0.67 [0.11, 4.00]**	
Total events	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.43 (P = 0.66)							
Test for subgroup differences: Not applicable							



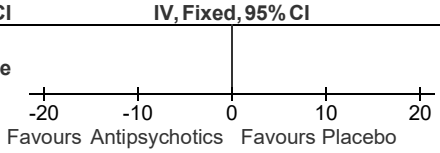
Footnotes

(1) Quetiapin, index episode: depression

Risk of bias legend

8.11 Global functioning

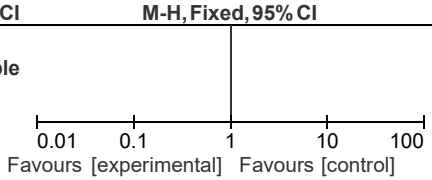
Study or Subgroup	Antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of B
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

8.13 Psychiatric hospitalization

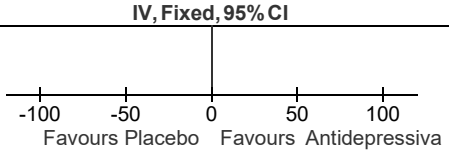
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

8.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of E
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										

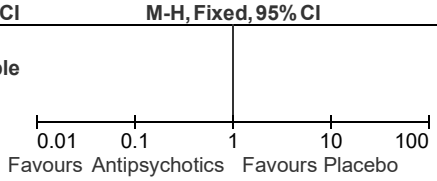


Risk of bias legend

9 Børn og unge_antipsychotics vs placebo_Bipolar 2

9.1 New episode, any type

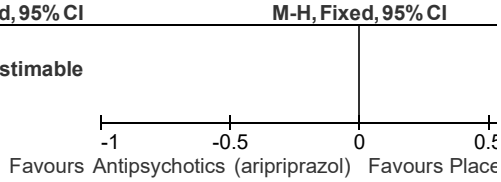
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

9.2 New episode, depression

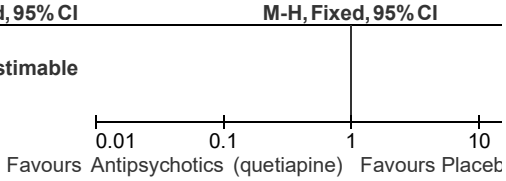
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

9.3 New epsiode, mania

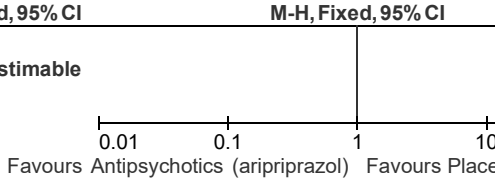
Study or Subgroup	Antipsychotics (quetiapine) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

9.4 New episode, mixed

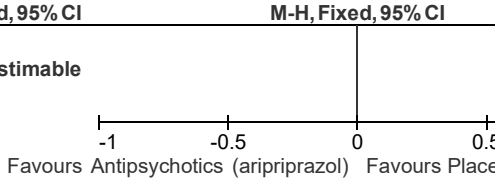
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

9.5 New episode, mixed, risk diff

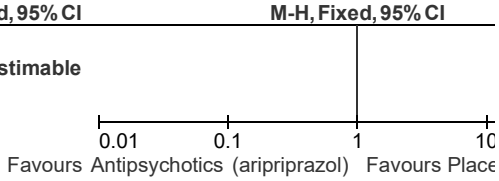
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

9.6 Withdrawal, any cause

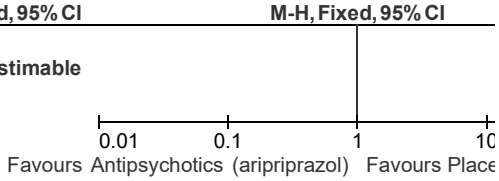
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

9.7 Sedation

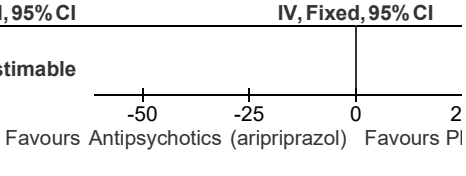
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

9.8 Weight gain in kilo

Study or Subgroup	Antipsychotics (aripriprazol) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

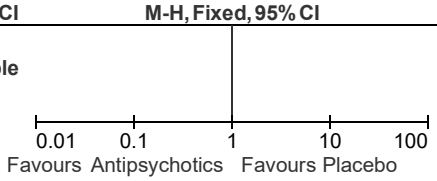


Risk of bias legend

10 Børn og unge_antipsychotics vs placebo_Bipolar 1

10.1 New episode, any type

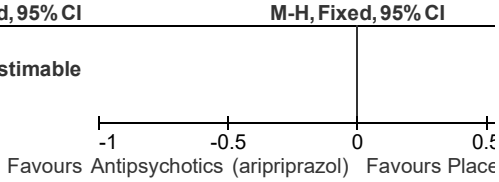
Study or Subgroup	Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

10.2 New episode, depression

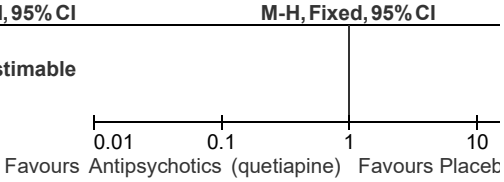
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

10.3 New epsiode, mania

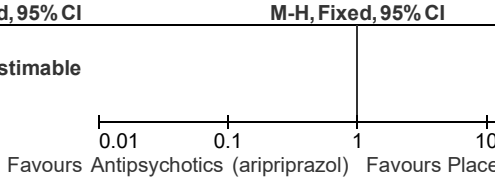
Study or Subgroup	Antipsychotics (quetiapine) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

10.4 New episode, mixed

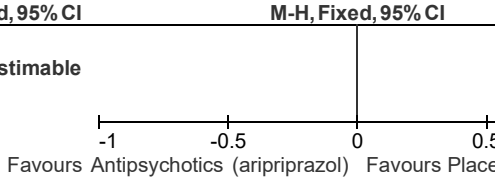
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

10.5 New episode, mixed, risk diff

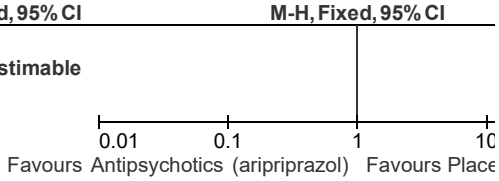
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

10.6 Withdrawal, any cause

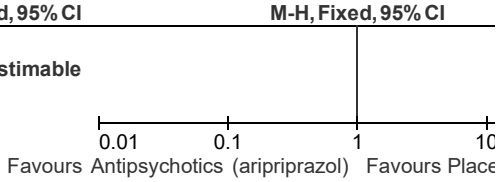
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

10.7 Sedation

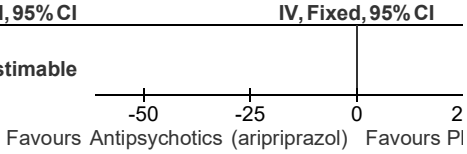
Study or Subgroup	Antipsychotics (aripriprazol) Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

10.8 Weight gain in kilo

Study or Subgroup	Antipsychotics (aripriprazol) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

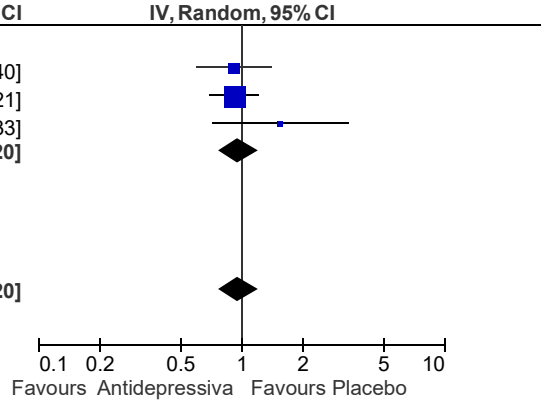


Risk of bias legend

11 Antidepressiva vs Placebo_Bipolar 1_Final

11.1 New episode, any type

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.1.1 Imipramin						
Prien 1984 (1)	18	36	23	42	27.5%	0.91 [0.60, 1.40]
Prien 1973b (2)	11	13	12	13	64.0%	0.92 [0.69, 1.21]
Kane/Quitkin 1981 (3)	12	37	8	38	8.4%	1.54 [0.71, 3.33]
Subtotal (95% CI)		**86**		**93**	**100.0%**	**0.96 [0.76, 1.20]**
Total events	41		43			
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**86**		**93**	**100.0%**	**0.96 [0.76, 1.20]**
Total events	41		43			
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						



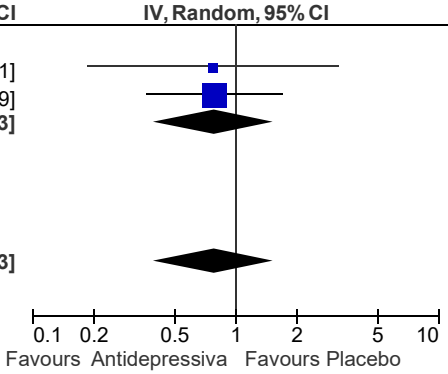
Footnotes

(1) Imipramine + lithium vs lithium, index episode: depression or mania, bipolar type not...
(2) Imipramine vs placebo, index episode: depression, bipolar type not specified
(3) lithium + imipramine vs lithium + placebo, index episode: ikke specificeret, bipolar type I

Risk of bias legend

11.2 New episode, depression

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.2.1 Imipramin						
Kane/Quitkin 1981 (1)	3	37	4	38	22.8%	0.77 [0.18, 3.21]
Prien 1984 (2)	8	36	12	42	77.2%	0.78 [0.36, 1.69]
Subtotal (95% CI)		**73**		**80**	**100.0%**	**0.78 [0.39, 1.53]**
Total events	11		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**73**		**80**	**100.0%**	**0.78 [0.39, 1.53]**
Total events	11		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Not applicable						



Risk of B

Footnotes

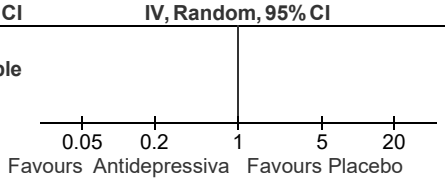
Risk of bias legend

(1) lithium + imipramine vs lithium + placebo, index episode: ikke specificeret, bipolar type I

(2) Imipramine + lithium vs lithium, index episode: depression or mania, bipolar type not...

11.3 New episode, hypomania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

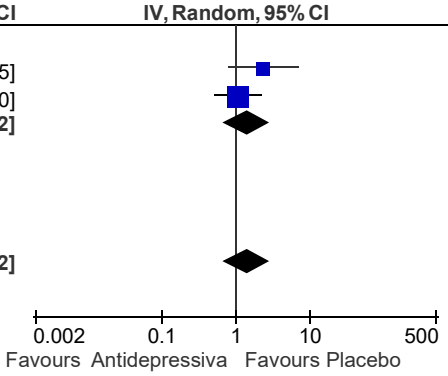


Risk of Bias

Risk of bias legend

11.4 New episode, mania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.4.1 Imipramin						
Kane/Quitkin 1981 (1)	9	37	4	38	36.1%	2.31 [0.78, 6.85]
Prien 1984 (2)	10	36	11	42	63.9%	1.06 [0.51, 2.20]
Subtotal (95% CI)		**73**		**80**	**100.0%**	**1.41 [0.67, 2.92]**
Total events	19		15			
Heterogeneity: Tau² = 0.08; Chi² = 1.36, df = 1 (P = 0.24); I² = 26%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Total (95% CI)		**73**		**80**	**100.0%**	**1.41 [0.67, 2.92]**
Total events	19		15			
Heterogeneity: Tau² = 0.08; Chi² = 1.36, df = 1 (P = 0.24); I² = 26%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Not applicable						



Risk of B

Footnotes

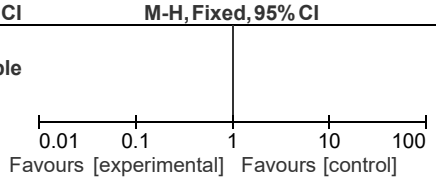
Risk of bias legend

(1) lithium + imipramine vs lithium + placebo, index episode: ikke specificeret, bipolar type I

(2) Imipramine + lithium vs lithium, index episode: depression or mania, bipolar type not...

11.5 New episode, mixed

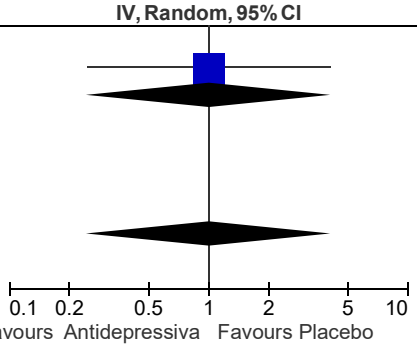
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

11.6 Withdrawal, any cause

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.6.1 Imipramin						
Prien 1973b (1)	3	13	3	13	100.0%	1.00 [0.25, 4.07]
Subtotal (95% CI)		**13**		**13**	**100.0%**	**1.00 [0.25, 4.07]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**13**		**13**	**100.0%**	**1.00 [0.25, 4.07]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



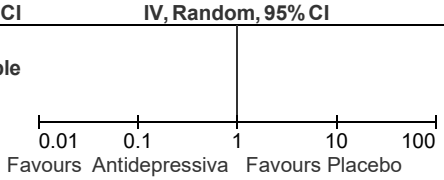
Footnotes

(1) Imipramine vs placebo, index episode: depression, bipolar type not specified

Risk of bias legend

11.7 Serious adverse events (SAE)

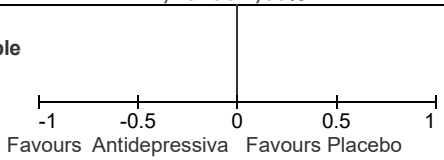
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

11.8 Serious adverse events (SAE), risk diff

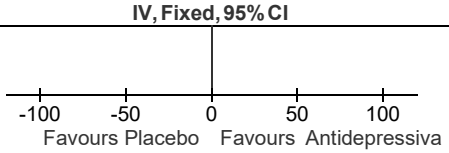
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

11.9 Quality of life

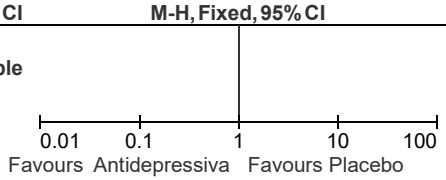
Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

11.10 Sedation

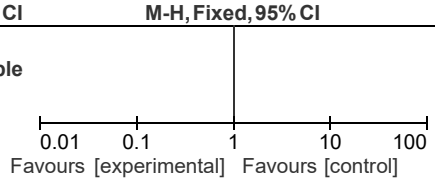
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

11.11 Suicidal behaviour

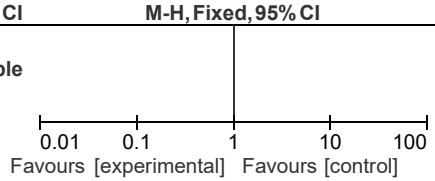
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

11.12 Psychiatric hospitalization

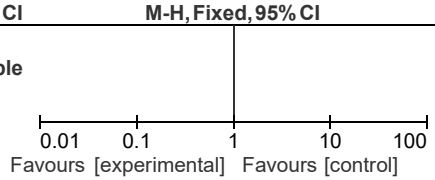
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

11.13 Global functioning

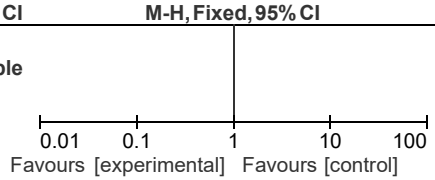
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

11.14 weight gain, over 7%

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

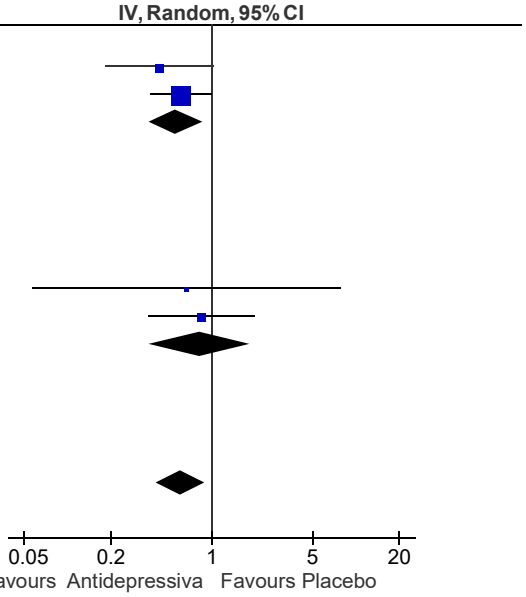


Risk of bias legend

12 Antidepressiva vs Placebo_Bipolar 2_Final

12.1 New episode, any type

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.1.1 Fluoxetin						
Amsterdam 2005 (1)	3	8	4	4	19.0%	0.43 [0.18, 1.03]
Amsterdam 2010 (2)	12	28	19	27	59.1%	0.61 [0.37, 1.00]
Subtotal (95% CI)		**36**		**31**	**78.0%**	**0.56 [0.36, 0.86]**
Total events	15		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.65 (P = 0.008)						
12.1.2 Imipramin						
Kane 1982 (3)	1	6	1	4	2.4%	0.67 [0.06, 7.85]
Kane 1982 (4)	3	5	5	7	19.6%	0.84 [0.36, 1.98]
Subtotal (95% CI)		**11**		**11**	**22.0%**	**0.82 [0.37, 1.84]**
Total events	4		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**47**		**42**	**100.0%**	**0.61 [0.42, 0.89]**
Total events	19		29			
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 3 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.57 (P = 0.01)						
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%						



Risk of bias legend

Footnotes

(1) Fluoxetine vs placebo, index episode: depression, bipolar type II

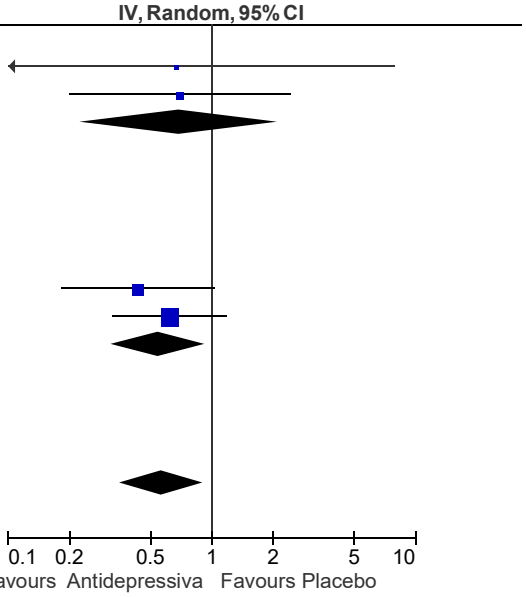
(2) Fluoxetine vs placebo, index episode: depression, bipolar type II

(3) Lithium + imipramine vs Lithium + placebo, index episode: not specified, bipolar type II

(4) Imipramine vs placebo, index episode: not specified, bipolar type II

12.2 New episode, depression

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.2.1 Imipramin						
Kane 1982 (1)	1	6	1	4	3.7%	0.67 [0.06, 7.85]
Kane 1982 (2)	2	5	4	7	14.2%	0.70 [0.20, 2.44]
Subtotal (95% CI)		**11**		**11**	**17.9%**	**0.69 [0.23, 2.11]**
Total events	3		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
12.2.2 Fluoxetin						
Amsterdam 2005 (3)	3	8	4	4	29.4%	0.43 [0.18, 1.03]
Amsterdam 2010 (4)	9	28	14	27	52.7%	0.62 [0.32, 1.19]
Subtotal (95% CI)		**36**		**31**	**82.1%**	**0.54 [0.32, 0.92]**
Total events	12		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Total (95% CI)		**47**		**42**	**100.0%**	**0.57 [0.35, 0.91]**
Total events	15		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 3 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



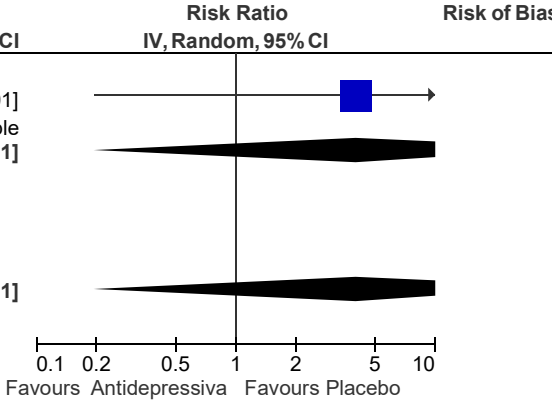
Footnotes

(1) Lithium + imipramine vs Lithium + placebo, index episode: ikke specificeret, bipolar...
(2) Imipramine vs placebo, index episode: ikke specificeret, bipolar type II
(3) Fluoxetine vs placebo, index episode: depression, bipolar type II
(4) Fluoxetine vs placebo, index episode: depression, bipolar type II

Risk of bias legend

12.3 New episode, mania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.3.2 Imipramin						
Kane 1982 (1)	1	5	0	7	100.0%	4.00 [0.20, 82.01]
Kane 1982 (2)	0	6	0	4		Not estimable
Subtotal (95% CI)		**11**		**11**	**100.0%**	**4.00 [0.20, 82.01]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**11**		**11**	**100.0%**	**4.00 [0.20, 82.01]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Not applicable						



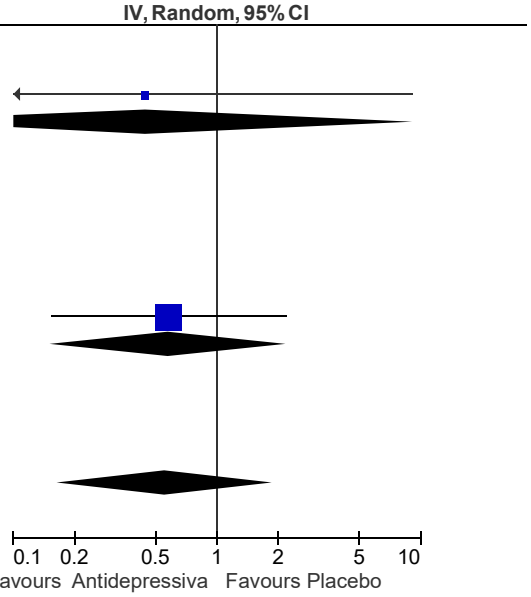
Footnotes

(1) Imipramine vs placebo, index episode: ikke specificeret, bipolar type II
(2) Lithium + imipramine vs Lithium + placebo, index episode: ikke specificeret, bipolar...

Risk of bias legend

12.4 New episode, hypomania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.4.1 Imipramin						
Kane 1982 (1)	0	6	0	4		Not estimable
Kane 1982 (2)	0	5	1	7	16.2%	0.44 [0.02, 9.11]
Subtotal (95% CI)		**11**		**11**	**16.2%**	**0.44 [0.02, 9.11]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
12.4.2 Fluoxetin						
Amsterdam 2005 (3)	0	8	0	4		Not estimable
Amsterdam 2010 (4)	3	28	5	27	83.8%	0.58 [0.15, 2.19]
Subtotal (95% CI)		**36**		**31**	**83.8%**	**0.58 [0.15, 2.19]**
Total events	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**47**		**42**	**100.0%**	**0.55 [0.16, 1.87]**
Total events	3		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



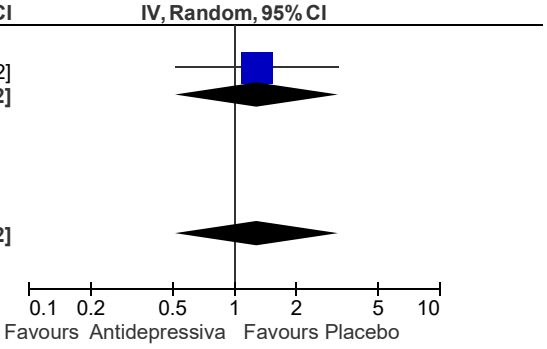
Footnotes

(1) Lithium + imipramine vs Lithium + placebo, index episode: ikke specificeret, bipolar...
(2) Imipramine vs placebo, index episode: ikke specificeret, bipolar type II
(3) Fluoxetine vs placebo, index episode: depression, bipolar type II
(4) Fluoxetine vs placebo, index episode: depression, bipolar type II

Risk of bias legend

12.5 Withdrawal, any cause

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.5.1 Fluoxetin						
Amsterdam 2010 (1)	8	28	6	27	100.0%	1.29 [0.51, 3.22]
Subtotal (95% CI)		**28**		**27**	**100.0%**	**1.29 [0.51, 3.22]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**28**		**27**	**100.0%**	**1.29 [0.51, 3.22]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Not applicable						



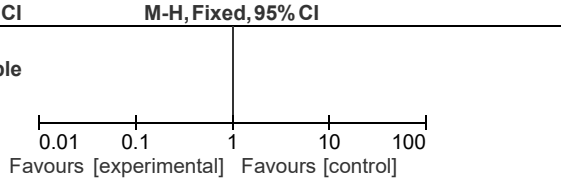
Footnotes

(1) Fluoxetine vs placebo, index episode: depression, bipolar type II

Risk of bias legend

12.6 New episode, mixed

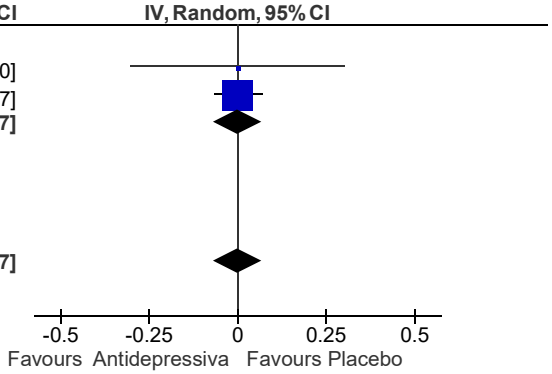
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Risk of bias legend

12.7 Serious adverse events (SAE), risk diff

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
12.7.1 Fluoxetin						
Amsterdam 2005 (1)	0	8	0	4	4.8%	0.00 [-0.30, 0.30]
Amsterdam 2010 (2)	0	28	0	27	95.2%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**36**		**31**	**100.0%**	**0.00 [-0.07, 0.07]**
Total events	0		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**36**		**31**	**100.0%**	**0.00 [-0.07, 0.07]**
Total events	0		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



Risk of Bia

Footnotes

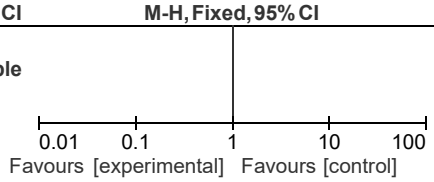
(1) Fluoxetine vs placebo, index episode: depression, bipolar type II

(2) Fluoxetine vs placebo, index episode: depression, bipolar type II

Risk of bias legend

12.8 Suicidal behaviour

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

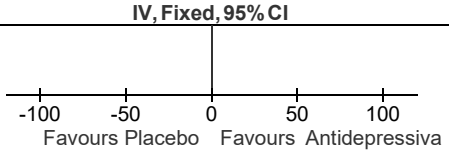


Risk of Bias

Risk of bias legend

12.9 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

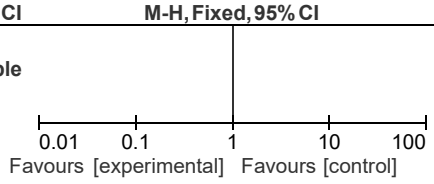


Risk of E

Risk of bias legend

12.10 Sedation

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

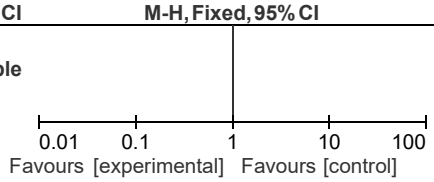


Risk of Bias

Risk of bias legend

12.11 Psychiatric hospitalization

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

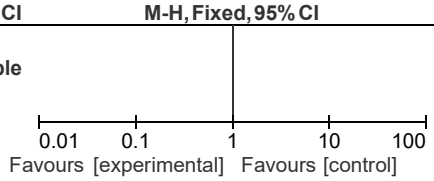


Risk of Bias

Risk of bias legend

12.12 Global functioning

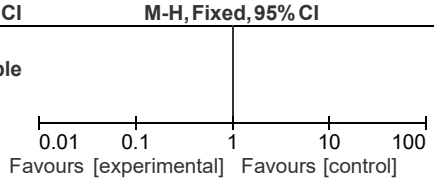
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

12.13 weight gain, over 7%

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

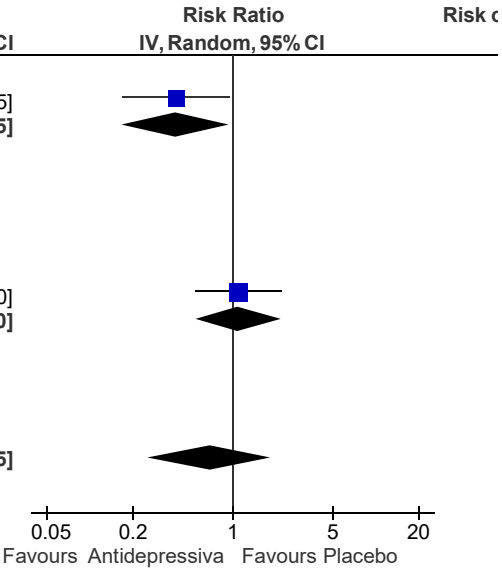


Risk of bias legend

13 Antidepressiva vs Placebo_Bipolar 1 og 2_Final

13.1 New episode, any type

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.1.1 Fluoxetin						
Tamayo 2009 (1)	6	55	15	55	46.5%	0.40 [0.17, 0.95]
Subtotal (95% CI)		**55**		**55**	**46.5%**	**0.40 [0.17, 0.95]**
Total events	6		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						
13.1.2 Tianeptine						
Kauer SantAnna 2019 (2)	12	36	10	33	53.5%	1.10 [0.55, 2.20]
Subtotal (95% CI)		**36**		**33**	**53.5%**	**1.10 [0.55, 2.20]**
Total events	12		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**91**		**88**	**100.0%**	**0.69 [0.26, 1.85]**
Total events	18		25			
Heterogeneity: Tau² = 0.35; Chi² = 3.18, df = 1 (P = 0.07); I² = 69%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Chi² = 3.18, df = 1 (P = 0.07), I² = 68.5%						



Footnotes

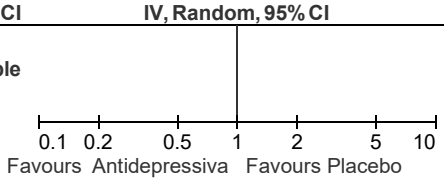
(1) Fluoxetin + olanzapin vs olanzapine, index episode: depression, bipolar type I and II

(2) Tianeptin vs placebo,i tillæg til lithium/valproate, index episode: depression, bipolar type I...

Risk of bias legend

13.2 New episode, depression

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

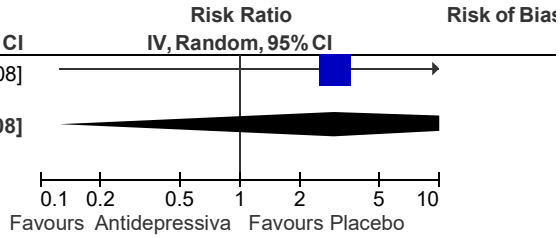


Risk of bias legend

13.3 New episode, mania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Tamayo 2009 (1)	1	55	0	55	100.0%	3.00 [0.12, 72.08]	
Total (95% CI)		**55**		**55**	**100.0%**	**3.00 [0.12, 72.08]**	
Total events	1		0				

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



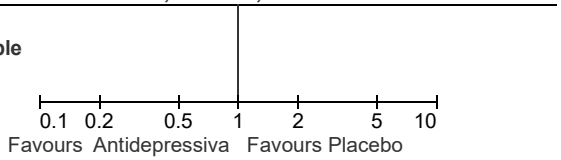
Footnotes
(1) Fluoxetin + olanzapin vs olanzapine, index episode: depression, bipolar type I and II

Risk of bias legend

13.4 New episode, hypomania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

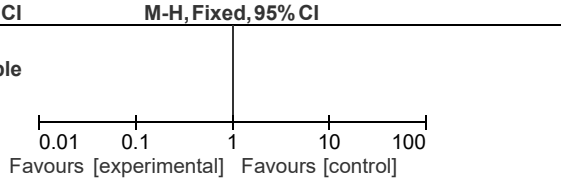


Risk of bias legend

13.5 New episode, mixed

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

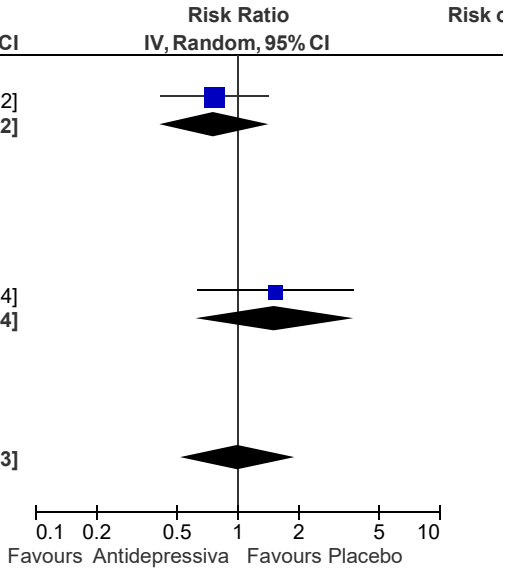
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Risk of bias legend

13.6 Withdrawal, any cause

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.6.1 Fluxetin						
Tamayo 2009 (1)	13	55	17	55	61.4%	0.76 [0.41, 1.42]
Subtotal (95% CI)		**55**		**55**	**61.4%**	**0.76 [0.41, 1.42]**
Total events	13		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
13.6.2 Tianeptine						
Kauer SantAnna 2019 (2)	10	36	6	33	38.6%	1.53 [0.62, 3.74]
Subtotal (95% CI)		**36**		**33**	**38.6%**	**1.53 [0.62, 3.74]**
Total events	10		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**91**		**88**	**100.0%**	**1.00 [0.52, 1.93]**
Total events	23		23			
Heterogeneity: Tau² = 0.09; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 1.56, df = 1 (P = 0.21), I² = 35.7%						



Footnotes

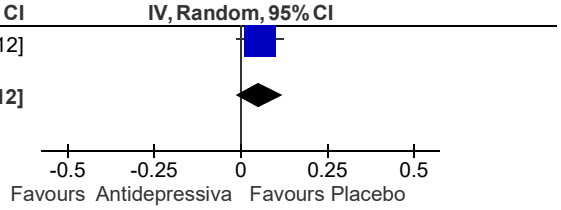
(1) Fluoxetin + olanzapin vs olanzapine, index episode: depression, bipolar type I and II

(2) Tianeptin vs placebo,i tillæg til lithium/valproate, index episode: depression, bipolar type I...

Risk of bias legend

13.7 Serious adverse events (SAE), risk diff

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
Tamayo 2009 (1)	3	55	0	55	100.0%	0.05 [-0.01, 0.12]
Total (95% CI)		**55**		**55**	**100.0%**	**0.05 [-0.01, 0.12]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						



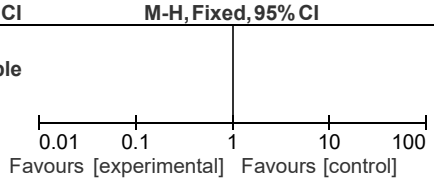
Footnotes

(1) Fluoxetin + olanzapin vs olanzapine, index episode: depression, bipolar type I and II

Risk of bias legend

13.8 Suicidal behaviour

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

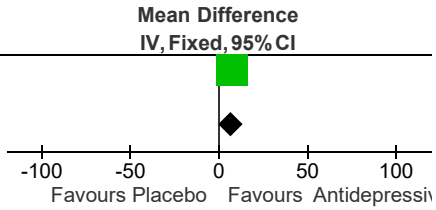


Risk of bias legend

13.9 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tamayo 2009 (1)	-1.5	15.9797	41	-8.7	15.9797	43	100.0%	7.20 [0.36, 14.04]
Total (95% CI)			**41**			**43**	**100.0%**	**7.20 [0.36, 14.04]**

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



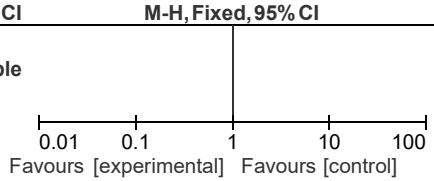
Footnotes
(1) Fluoxetin + olanzapin vs olanzapine, index episode: depression, bipolar type I and II

Risk of bias legend

13.10 Sedation

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

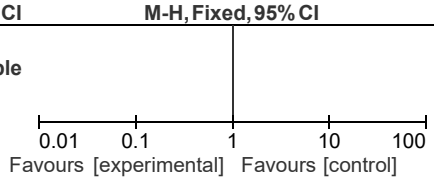


Risk of bias legend

13.11 Psychiatric hospitalization

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

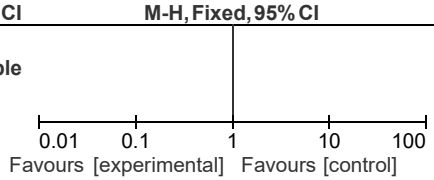


Risk of bias legend

13.12 Global functioning

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

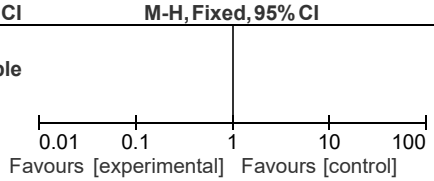


Risk of bias legend

13.13 weight gain, over 7%

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

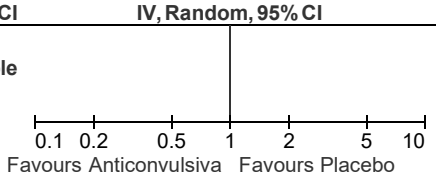


Risk of bias legend

14 Børn og unge_Antidepressiva vs Placebo_Bipolar 1

14.1 New episode, any type

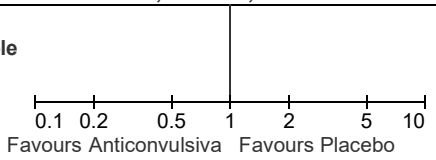
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.2 New episode, depression

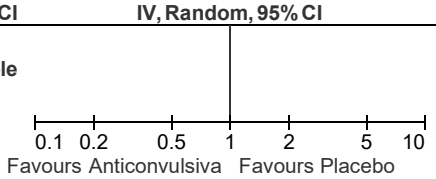
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.3 New episode, mania

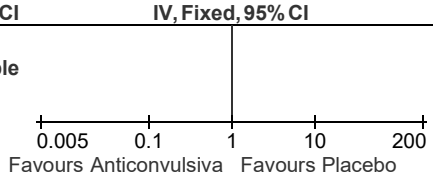
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.4 New episode, mixed

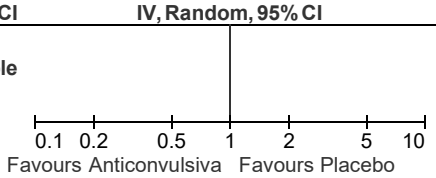
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.5 Withdrawal, any cause

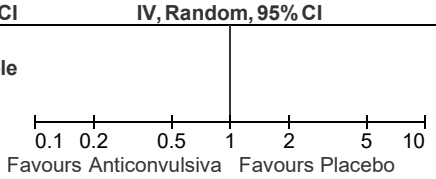
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.6 Serious adverse events (SAE)

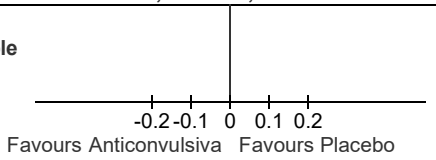
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.7 Serious adverse events (SAE), risk diff

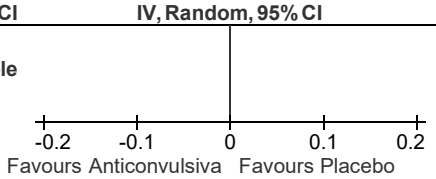
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.8 Suicidal behaviour

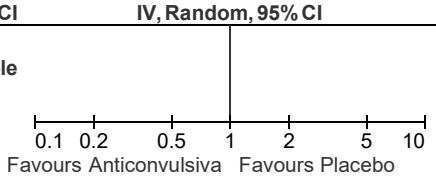
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.9 Sedation

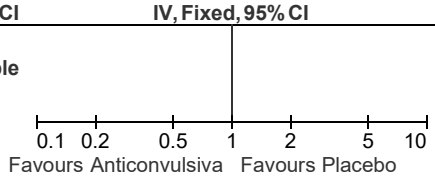
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.10 Psychiatric hospitalization

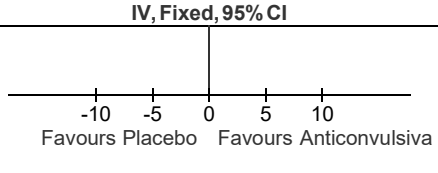
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.11 Global functioning

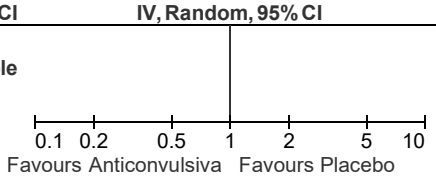
Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bi
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

14.12 Weigt gain, over 7%

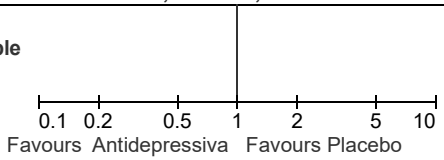
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.13 New episode, hypomania

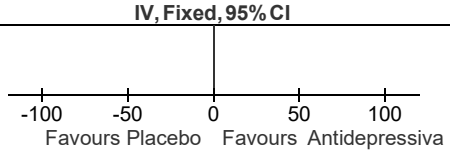
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

14.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of E
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										

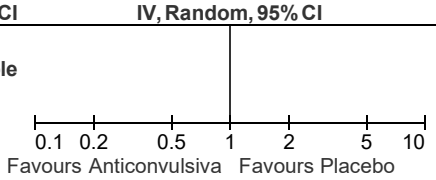


Risk of bias legend

15 Børn og unge_Antidepressiva vs Placebo_Bipolar 2

15.1 New episode, any type

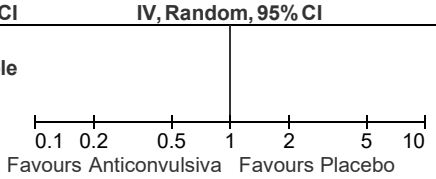
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.2 New episode, depression

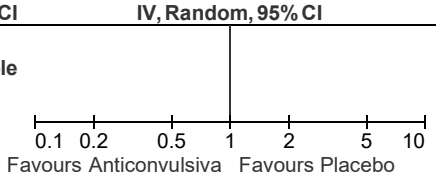
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.3 New episode, mania

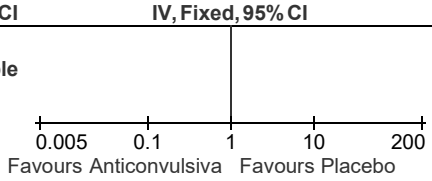
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.4 New episode, mixed

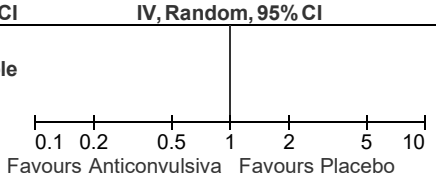
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.5 Withdrawal, any cause

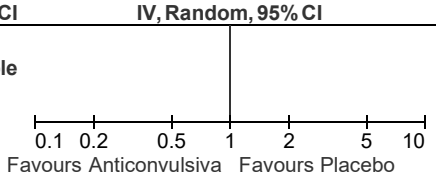
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.6 Serious adverse events (SAE)

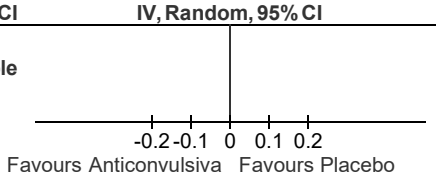
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.7 Serious adverse events (SAE), risk diff

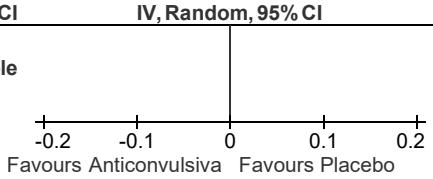
Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.8 Suicidal behaviour

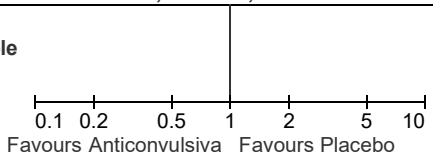
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.9 Sedation

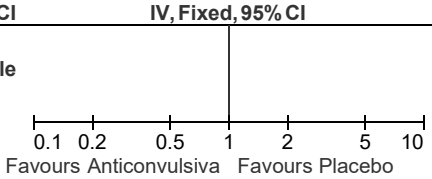
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.10 Psychiatric hospitalization

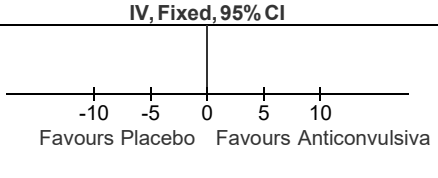
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.11 Global functioning

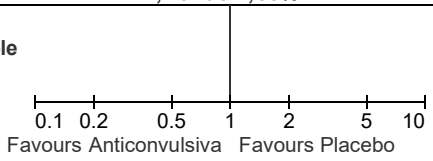
Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bi
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

15.12 Weigt gain, over 7%

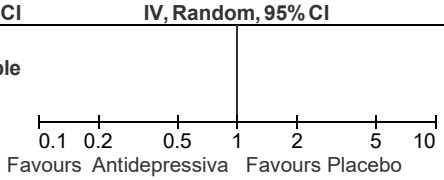
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

15.13 New episode, hypomania

Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

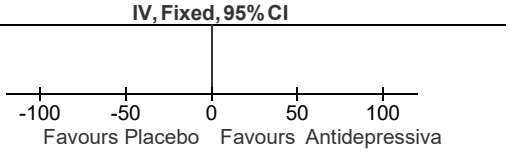


Risk of bias legend

15.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

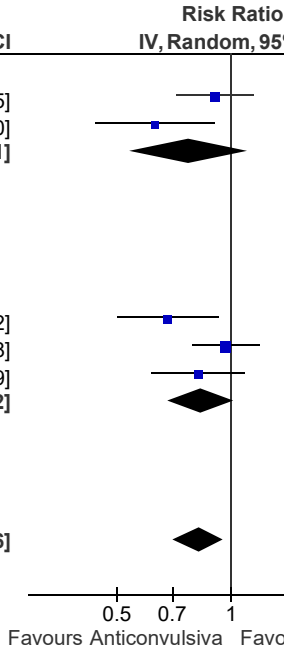


Risk of bias legend

16 Anticonvulsiva vs Placebo_Bipolar 1_Final

16.1 New episode, any type

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
16.1.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	59	110	65	110	23.7%	0.91 [0.72, 1.15]
Bowden 2000 (2)	45	187	36	94	13.4%	0.63 [0.44, 0.90]
Subtotal (95% CI)		**297**		**204**	**37.1%**	**0.78 [0.54, 1.11]**
Total events	104		101			
Heterogeneity: Tau² = 0.04; Chi² = 2.81, df = 1 (P = 0.09); I² = 64%						
Test for overall effect: Z = 1.39 (P = 0.16)						
16.1.2 Lamotrigine						
Bowden 2003 (3)	28	58	49	69	17.0%	0.68 [0.50, 0.92]
Calabrese 2003 (4)	115	215	66	119	27.2%	0.96 [0.79, 1.18]
Zhang 2022 (5)	50	131	62	133	18.7%	0.82 [0.62, 1.09]
Subtotal (95% CI)		**404**		**321**	**62.9%**	**0.83 [0.68, 1.02]**
Total events	193		177			
Heterogeneity: Tau² = 0.01; Chi² = 3.59, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Total (95% CI)		**701**		**525**	**100.0%**	**0.82 [0.70, 0.96]**
Total events	297		278			
Heterogeneity: Tau² = 0.01; Chi² = 6.54, df = 4 (P = 0.16); I² = 39%						
Test for overall effect: Z = 2.53 (P = 0.01)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%						



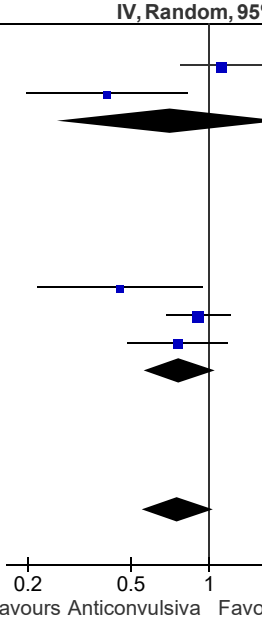
Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I
(2) Valproate vs placebo, index episode: mania, bipolar I
(3) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I
(4) Lamotrigine vs placebo, index episode: depression, bipolar I
(5) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.2 New episode, depression

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
16.2.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	39	110	35	110	24.6%	1.11 [0.77, 1.62]
Bowden 2000 (2)	12	187	15	94	12.9%	0.40 [0.20, 0.82]
Subtotal (95% CI)		**297**		**204**	**37.5%**	**0.70 [0.26, 1.90]**
Total events	51		50			
Heterogeneity: Tau² = 0.43; Chi² = 6.11, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.70 (P = 0.49)						
16.2.2 Lamotrigine						
Bowden 2003 (3)	8	58	21	69	12.5%	0.45 [0.22, 0.95]
Calabrese 2003 (4)	77	215	47	119	28.6%	0.91 [0.68, 1.21]
Zhang 2022 (5)	26	131	35	133	21.5%	0.75 [0.48, 1.18]
Subtotal (95% CI)		**404**		**321**	**62.5%**	**0.77 [0.56, 1.05]**
Total events	111		103			
Heterogeneity: Tau² = 0.03; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Total (95% CI)		**701**		**525**	**100.0%**	**0.76 [0.55, 1.04]**
Total events	162		153			
Heterogeneity: Tau² = 0.07; Chi² = 9.46, df = 4 (P = 0.05); I² = 58%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



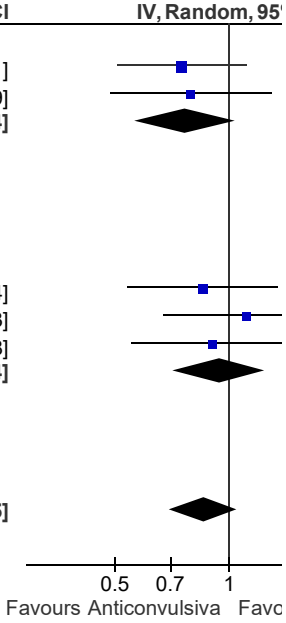
Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I
(2) Valproate vs placebo, index episode: mania, bipolar I
(3) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I
(4) Lamotrigine vs placebo, index episode: depression, bipolar I
(5) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.3 New episode, mania

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
16.3.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	30	110	40	110	27.5%	0.75 [0.51, 1.11]
Bowden 2000 (2)	33	187	21	94	17.8%	0.79 [0.49, 1.29]
Subtotal (95% CI)		**297**		**204**	**45.4%**	**0.77 [0.56, 1.04]**
Total events	63		61			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
16.3.2 Lamotrigine						
Bowden 2003 (3)	20	58	28	69	20.5%	0.85 [0.54, 1.34]
Calabrese 2003 (4)	38	215	19	119	16.8%	1.11 [0.67, 1.83]
Zhang 2022 (5)	24	131	27	133	17.4%	0.90 [0.55, 1.48]
Subtotal (95% CI)		**404**		**321**	**54.6%**	**0.94 [0.71, 1.24]**
Total events	82		74			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**701**		**525**	**100.0%**	**0.86 [0.70, 1.05]**
Total events	145		135			
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 4 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 0.94, df = 1 (P = 0.33), I² = 0%						



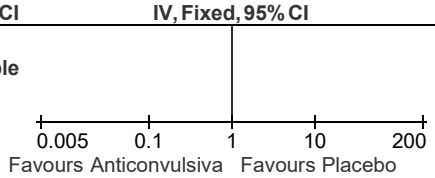
Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I
(2) Valproate vs placebo, index episode: mania, bipolar I
(3) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I
(4) Lamotrigine vs placebo, index episode: depression, bipolar I
(5) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.4 New episode, mixed

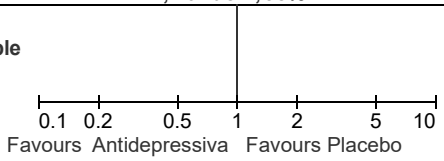
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

16.5 New episode, hypomania

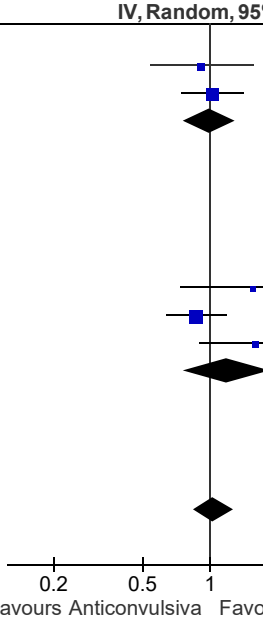
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

16.6 Withdrawal, any cause

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
16.6.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	21	110	23	110	14.0%	0.91 [0.54, 1.55]
Bowden 2000 (2)	71	187	35	94	32.6%	1.02 [0.74, 1.40]
Subtotal (95% CI)		**297**		**204**	**46.6%**	**0.99 [0.75, 1.30]**
Total events	92		58			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
16.6.2 Lamotrigine						
Bowden 2003 (3)	13	59	10	70	7.4%	1.54 [0.73, 3.26]
Calabrese 2003 (4)	68	221	43	121	34.1%	0.87 [0.63, 1.18]
Zhang 2022 (5)	25	131	16	133	11.9%	1.59 [0.89, 2.83]
Subtotal (95% CI)		**411**		**324**	**53.4%**	**1.19 [0.76, 1.86]**
Total events	106		69			
Heterogeneity: Tau² = 0.09; Chi² = 4.44, df = 2 (P = 0.11); I² = 55%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**708**		**528**	**100.0%**	**1.03 [0.84, 1.27]**
Total events	198		127			
Heterogeneity: Tau² = 0.01; Chi² = 4.64, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%						



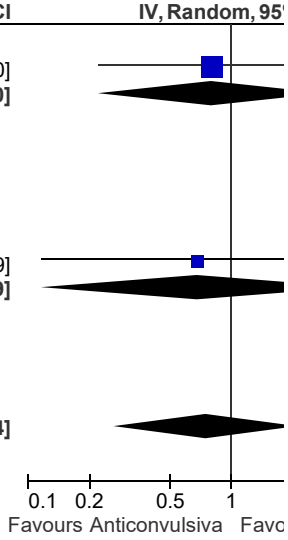
Risk of bias legend

Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I
(2) Valproate vs placebo, index episode: mania, bipolar I
(3) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I
(4) Lamotrigine vs placebo, index episode: depression, bipolar I
(5) Lamotrigine vs placebo, index episode: not specified, bipolar I

16.7 Serious adverse events (SAE)

Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
16.7.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	4	110	5	110	65.5%	0.80 [0.22, 2.90]
Subtotal (95% CI)		**110**		**110**	**65.5%**	**0.80 [0.22, 2.90]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
16.7.2 Lamotrigine						
Zhang 2022 (2)	2	131	3	133	34.5%	0.68 [0.11, 3.99]
Subtotal (95% CI)		**131**		**133**	**34.5%**	**0.68 [0.11, 3.99]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**241**		**243**	**100.0%**	**0.76 [0.27, 2.14]**
Total events	6		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



Footnotes

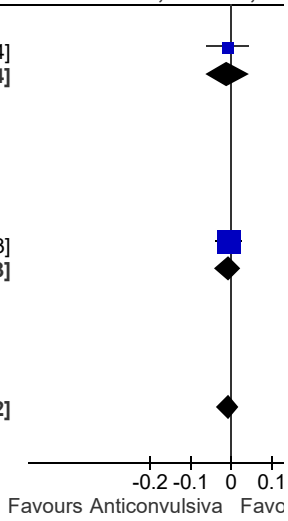
(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I

(2) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.8 Serious adverse events (SAE), risk diff

Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
16.8.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	4	110	5	110	28.2%	-0.01 [-0.06, 0.04]
Subtotal (95% CI)		**110**		**110**	**28.2%**	**-0.01 [-0.06, 0.04]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
16.8.2 Lamotrigine						
Zhang 2022 (2)	2	131	3	133	71.8%	-0.01 [-0.04, 0.03]
Subtotal (95% CI)		**131**		**133**	**71.8%**	**-0.01 [-0.04, 0.03]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**241**		**243**	**100.0%**	**-0.01 [-0.04, 0.02]**
Total events	6		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



Footnotes

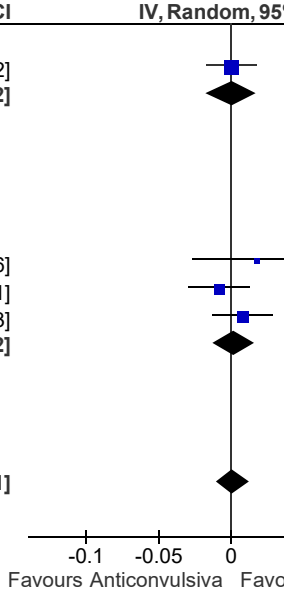
(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I

(2) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.9 Suicidal behaviour

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
16.9.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	0	110	0	110	39.0%	0.00 [-0.02, 0.02]
Subtotal (95% CI)		**110**		**110**	**39.0%**	**0.00 [-0.02, 0.02]**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
16.9.2 Lamotrigine						
Bowden 2003 (2)	1	58	0	69	6.0%	0.02 [-0.03, 0.06]
Calabrese 2003 (3)	0	169	1	121	27.0%	-0.01 [-0.03, 0.01]
Zhang 2022 (4)	1	131	0	133	27.9%	0.01 [-0.01, 0.03]
Subtotal (95% CI)		**358**		**323**	**61.0%**	**0.00 [-0.01, 0.02]**
Total events	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Total (95% CI)		**468**		**433**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						



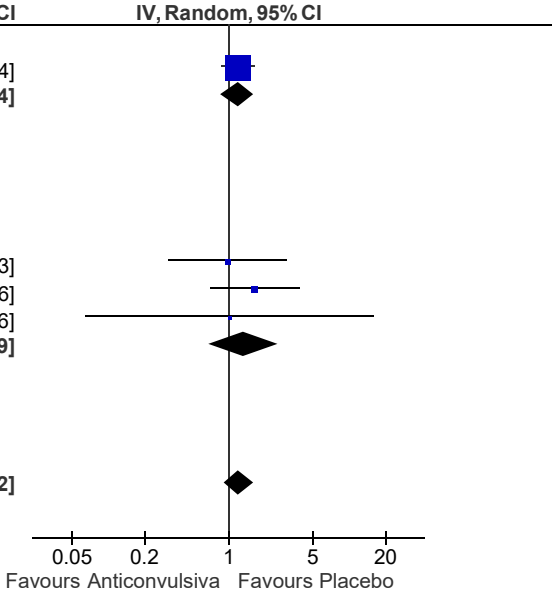
Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I
(2) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I
(3) Lamotrigine vs placebo, index episode: depression, bipolar I
(4) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.10 Sedation

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
16.10.1 Valproate							
Bowden 2000 (1)	78	187	33	94	80.9%	1.19 [0.86, 1.64]	
Subtotal (95% CI)		**187**		**94**	**80.9%**	**1.19 [0.86, 1.64]**	
Total events	78		33				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.05 (P = 0.30)							
16.10.2 Lamotrigine							
Bowden 2003 (2)	5	59	6	69	6.5%	0.97 [0.31, 3.03]	
Calabrese 2003 (3)	16	169	7	121	11.5%	1.64 [0.69, 3.86]	
Zhang 2022 (4)	1	131	1	133	1.1%	1.02 [0.06, 16.06]	
Subtotal (95% CI)		**359**		**323**	**19.1%**	**1.33 [0.69, 2.59]**	
Total events	22		14				
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 2 (P = 0.76); I² = 0%							
Test for overall effect: Z = 0.85 (P = 0.40)							
Total (95% CI)		**546**		**417**	**100.0%**	**1.21 [0.91, 1.62]**	
Total events	100		47				
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 3 (P = 0.89); I² = 0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%							



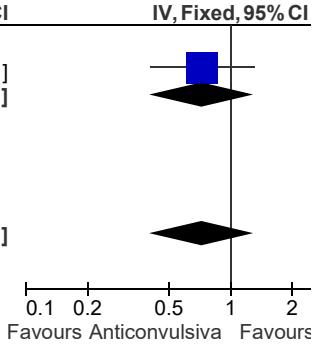
Footnotes

(1) Valproate vs placebo, index episode: mania, bipolar I
(2) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I
(3) Lamotrigine vs placebo, index episode: depression, bipolar I
(4) Lamotrigine vs placebo, index episode: not specified, bipolar I

Risk of bias legend

16.11 Psychiatric hospitalization

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
16.11.1 Valproate						
BALANCEinvestigatorsandcollaborators 2010 (1)	16	110	22	110	100.0%	0.73 [0.40, 1.31]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**0.73 [0.40, 1.31]**
Total events	16		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**110**		**110**	**100.0%**	**0.73 [0.40, 1.31]**
Total events	16		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						



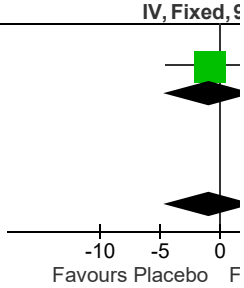
Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar II

Risk of bias legend

16.12 Global functioning

Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
16.12.1 Valproate								
BALANCEinvestigatorsandcollaborators 2010 (1)	79.3	15.3	110	80.2	13	110	100.0%	-0.90 [-4.65, 2.85]
Subtotal (95% CI)			**110**			**110**	**100.0%**	**-0.90 [-4.65, 2.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**110**			**110**	**100.0%**	**-0.90 [-4.65, 2.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
Test for subgroup differences: Not applicable								



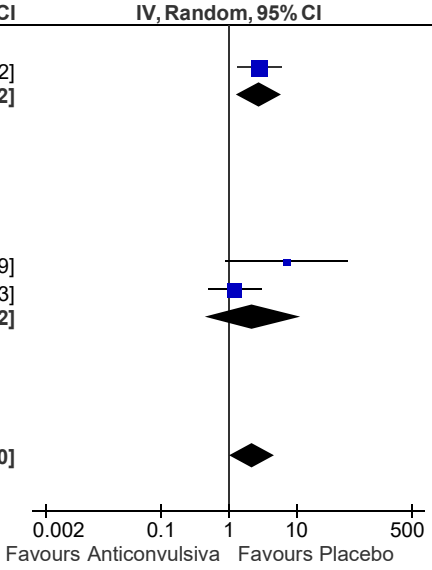
Footnotes

(1) Valproate + lithuim vs lithium, index episode: mania, bipolar I

Risk of bias legend

16.13 Weigt gain, over 7%

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
16.13.1 Valproate						
Bowden 2000 (1)	39	187	7	94	47.6%	2.80 [1.30, 6.02]
Subtotal (95% CI)		**187**		**94**	**47.6%**	**2.80 [1.30, 6.02]**
Total events	39		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.64 (P = 0.008)						
16.13.2 Lamotrigine						
Bowden 2003 (2)	6	58	1	69	12.0%	7.14 [0.88, 57.59]
Calabrese 2003 (3)	12	169	7	121	40.4%	1.23 [0.50, 3.03]
Subtotal (95% CI)		**227**		**190**	**52.4%**	**2.28 [0.44, 11.82]**
Total events	18		8			
Heterogeneity: Tau² = 0.88; Chi² = 2.30, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Total (95% CI)		**414**		**284**	**100.0%**	**2.25 [1.03, 4.90]**
Total events	57		15			
Heterogeneity: Tau² = 0.18; Chi² = 3.21, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						



Footnotes

(1) Valproate vs placebo, index episode: mania, bipolar I

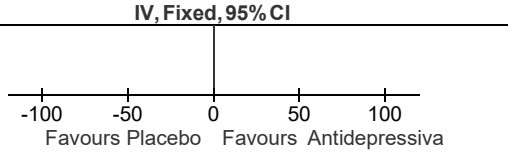
(2) Lamotrigine vs placebo, index episode: mania/hypo mania, bipolar I

(3) Lamotrigine vs placebo, index episode: depression, bipolar I

Risk of bias legend

16.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

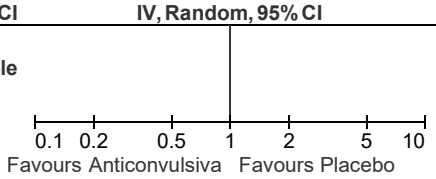


Risk of bias legend

17 Anticonvulsiva vs Placebo_Bipolar 2_Final

17.1 New episode, any type

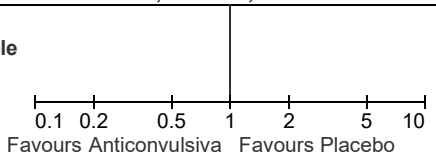
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.2 New episode, depression

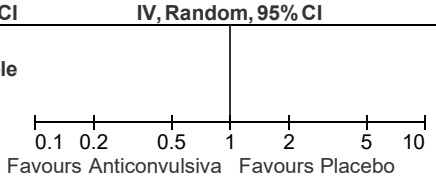
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.3 New episode, mania

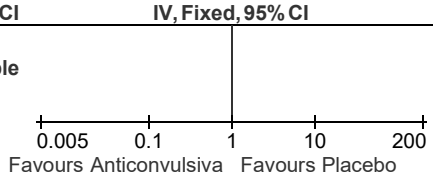
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.4 New episode, mixed

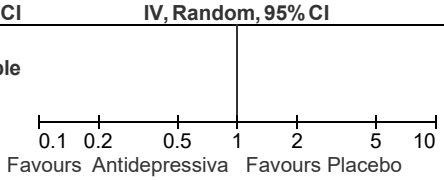
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.5 New episode, hypomania

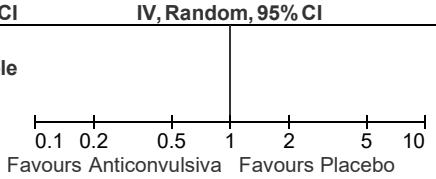
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.6 Withdrawal, any cause

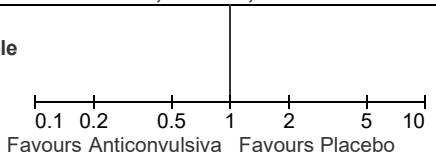
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.8 Serious adverse events (SAE)

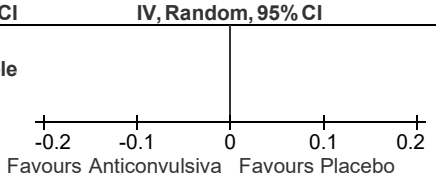
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.9 Suicidal behaviour

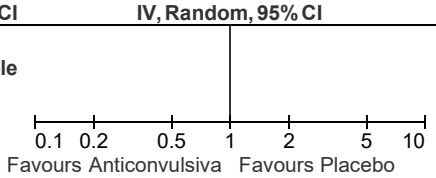
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.10 Sedation

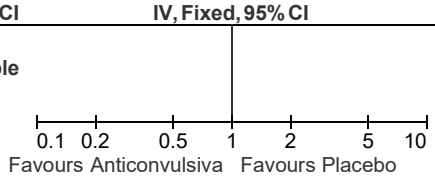
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.11 Psychiatric hospitalization

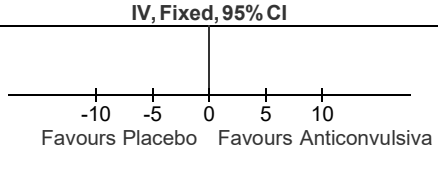
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.12 Global functioning

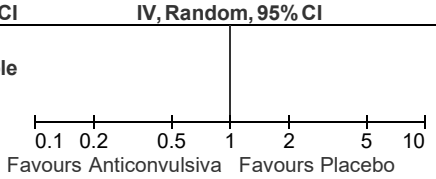
Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bi
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

17.13 Weigt gain, over 7%

Study or Subgroup	Anticonvulsiva Events	Anticonvulsiva Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

17.14 Quality of life

Study or Subgroup	Antidepressiva Mean	Antidepressiva SD	Antidepressiva Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of E
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										

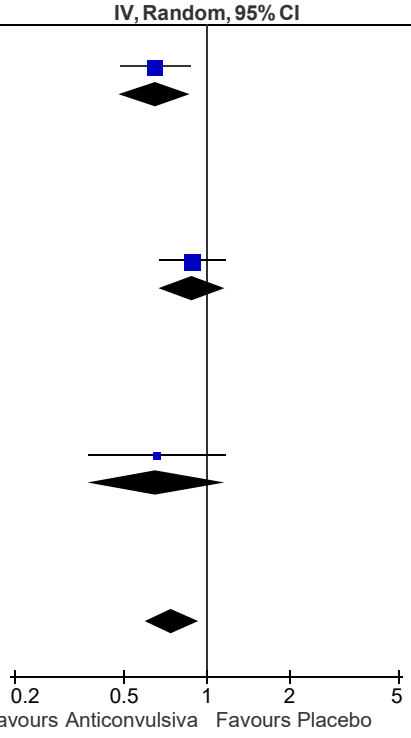


Risk of bias legend

18 Anticonvulsiva vs Placebo_Bipolar 1 og 2_Final

18.1 New episode, any type

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
18.1.1 Valproate							
Bowden 2012 (1)	23	41	39	45	41.3%	0.65 [0.48, 0.87]	
Subtotal (95% CI)		**41**		**45**	**41.3%**	**0.65 [0.48, 0.87]**	
Total events	23		39				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.90 (P = 0.004)							
18.1.2 Lamotrigine							
Calabrese 2000 (2)	45	90	49	87	44.8%	0.89 [0.67, 1.17]	
Subtotal (95% CI)		**90**		**87**	**44.8%**	**0.89 [0.67, 1.17]**	
Total events	45		49				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.84 (P = 0.40)							
18.1.3 Oxcarbazepine							
Vieta 2008a (3)	10	26	17	29	13.9%	0.66 [0.37, 1.17]	
Subtotal (95% CI)		**26**		**29**	**13.9%**	**0.66 [0.37, 1.17]**	
Total events	10		17				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
Total (95% CI)		**157**		**161**	**100.0%**	**0.75 [0.60, 0.94]**	
Total events	78		105				
Heterogeneity: Tau² = 0.01; Chi² = 2.59, df = 2 (P = 0.27); I² = 23%							
Test for overall effect: Z = 2.54 (P = 0.01)							
Test for subgroup differences: Chi² = 2.59, df = 2 (P = 0.27), I² = 22.8%							



Footnotes

(1) Lamotrigine + valproate vs lamotrigine + placebo, Index episode: depression, bipolar...

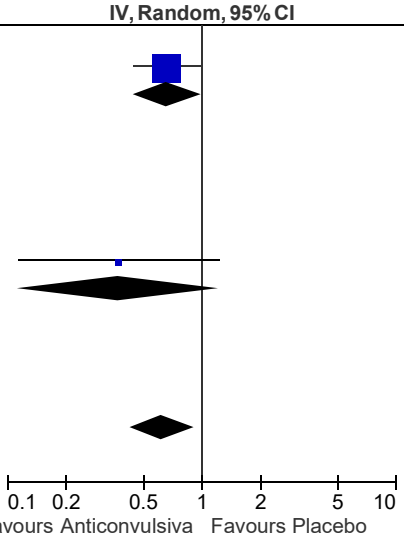
(2) Lamotrigine vs placebo, index episode: any episode or euthymic, bipolar I + II

(3) Oxcarbazepin + lithium vs lithium + placebo,index episode:not specified, not in acute...

Risk of bias legend

18.2 New episode, depression

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
18.2.1 Valproate						
Bowden 2012 (1)	18	41	30	45	89.8%	0.66 [0.44, 0.99]
Subtotal (95% CI)		**41**		**45**	**89.8%**	**0.66 [0.44, 0.99]**
Total events	18		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.03 (P = 0.04)						
18.2.3 Oxcarbazepine						
Vieta 2008a (2)	3	26	9	29	10.2%	0.37 [0.11, 1.23]
Subtotal (95% CI)		**26**		**29**	**10.2%**	**0.37 [0.11, 1.23]**
Total events	3		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Total (95% CI)		**67**		**74**	**100.0%**	**0.62 [0.42, 0.91]**
Total events	21		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 2.44 (P = 0.01)						
Test for subgroup differences: Chi² = 0.79, df = 1 (P = 0.37), I² = 0%						



Footnotes

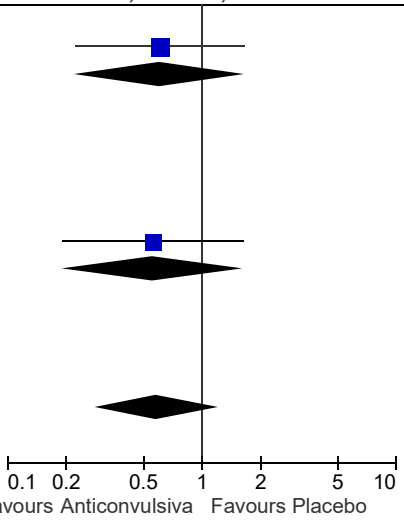
Risk of bias legend

(1) Lamotrigine + valproate vs lamotrigine + placebo, Index episode: depression, bipolar...

(2) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in acute...

18.3 New episode, mania

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
18.3.1 Valproate						
Bowden 2012 (1)	5	41	9	45	53.3%	0.61 [0.22, 1.67]
Subtotal (95% CI)		**41**		**45**	**53.3%**	**0.61 [0.22, 1.67]**
Total events	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
18.3.3 Oxcarbazepine						
Vieta 2008a (2)	4	26	8	29	46.7%	0.56 [0.19, 1.64]
Subtotal (95% CI)		**26**		**29**	**46.7%**	**0.56 [0.19, 1.64]**
Total events	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**67**		**74**	**100.0%**	**0.58 [0.28, 1.22]**
Total events	9		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						



Footnotes

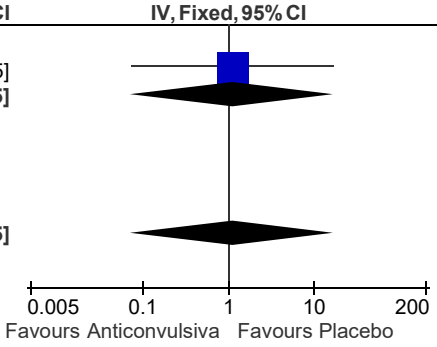
Risk of bias legend

(1) Lamotrigine + valproate vs lamotrigine + placebo, Index episode: depression, bipolar...

(2) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in acute...

18.4 New episode, mixed

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
18.4.1 Oxcarbazepine								
Vieta 2008a (1)	1	26	1	29	100.0%	1.12 [0.07, 16.95]		
Subtotal (95% CI)		**26**		**29**	**100.0%**	**1.12 [0.07, 16.95]**		
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.94)								
Total (95% CI)		**26**		**29**	**100.0%**	**1.12 [0.07, 16.95]**		
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.94)								
Test for subgroup differences: Not applicable								



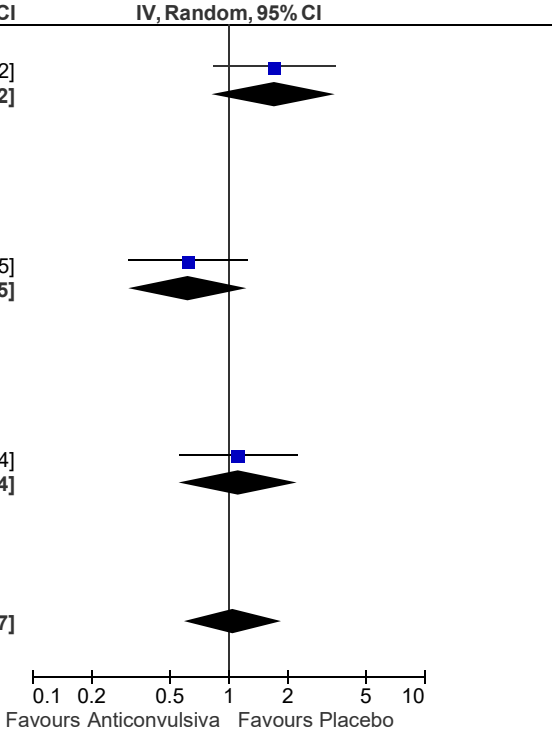
Footnotes

(1) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in...

Risk of bias legend

18.5 Withdrawal, any cause

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
18.5.1 Valproate							
Bowden 2012 (1)	14	41	9	45	32.6%	1.71 [0.83, 3.52]	
Subtotal (95% CI)		**41**		**45**	**32.6%**	**1.71 [0.83, 3.52]**	
Total events	14		9				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							
18.5.2 Lamotrigine							
Calabrese 2000 (2)	11	93	17	89	33.7%	0.62 [0.31, 1.25]	
Subtotal (95% CI)		**93**		**89**	**33.7%**	**0.62 [0.31, 1.25]**	
Total events	11		17				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.34 (P = 0.18)							
18.5.3 Oxcarbazepine							
Vieta 2008a (3)	10	26	10	29	33.7%	1.12 [0.55, 2.24]	
Subtotal (95% CI)		**26**		**29**	**33.7%**	**1.12 [0.55, 2.24]**	
Total events	10		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
Total (95% CI)		**160**		**163**	**100.0%**	**1.05 [0.59, 1.87]**	
Total events	35		36				
Heterogeneity: Tau² = 0.13; Chi² = 3.95, df = 2 (P = 0.14); I² = 49%							
Test for overall effect: Z = 0.17 (P = 0.86)							
Test for subgroup differences: Chi² = 3.95, df = 2 (P = 0.14), I² = 49.4%							



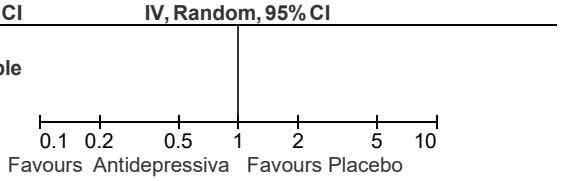
Footnotes

(1) Lamotrigine + valproate vs lamotrigine + placebo, Index episode: depression, bipolar...
(2) Lamotrigine vs placebo, index episode: any episode or euthymic, bipolar I + II
(3) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in acute...

Risk of bias legend

18.6 New episode, hypomania

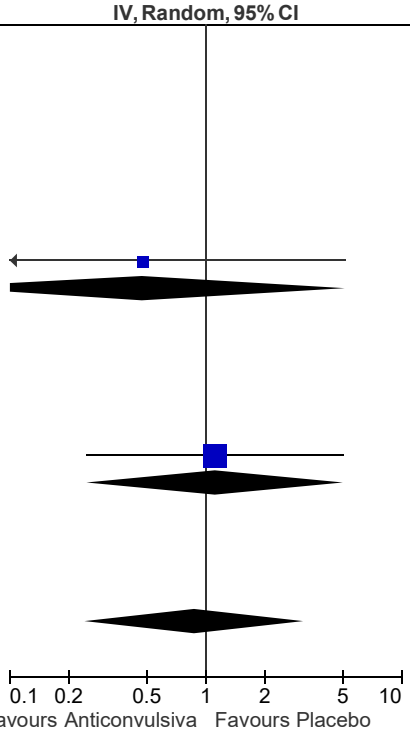
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Risk of bias legend

18.7 Serious adverse events (SAE)

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
18.7.1 Valproate							
Bowden 2012 (1)	0	41	0	45		Not estimable	
Subtotal (95% CI)		**41**		**45**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
18.7.2 Lamotrigine							
Calabrese 2000 (2)	1	92	2	88	28.7%	0.48 [0.04, 5.18]	
Subtotal (95% CI)		**92**		**88**	**28.7%**	**0.48 [0.04, 5.18]**	
Total events	1		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
18.7.3 Oxcarbazepine							
Vieta 2008a (3)	3	26	3	29	71.3%	1.12 [0.25, 5.05]	
Subtotal (95% CI)		**26**		**29**	**71.3%**	**1.12 [0.25, 5.05]**	
Total events	3		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.14 (P = 0.89)							
Total (95% CI)		**159**		**162**	**100.0%**	**0.88 [0.24, 3.13]**	
Total events	4		5				
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%							
Test for overall effect: Z = 0.21 (P = 0.84)							
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%							



Footnotes

(1) Lamotrigine + valproate vs lamotrigine + placebo, Index episode: depression, bipolar...

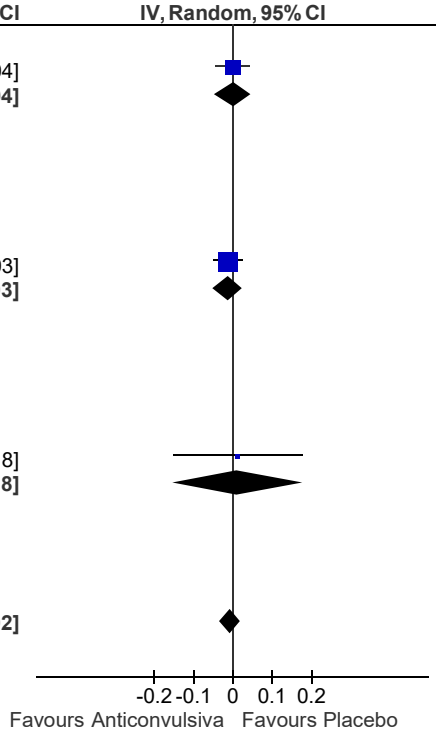
(2) Lamotrigine vs placebo, index episode: any episode or euthymic, bipolar I + II

(3) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in acute...

Risk of bias legend

18.8 Serious adverse events (SAE), risk diff

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
18.8.1 Valproate						
Bowden 2012 (1)	0	41	0	45	40.6%	0.00 [-0.04, 0.04]
Subtotal (95% CI)		**41**		**45**	**40.6%**	**0.00 [-0.04, 0.04]**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
18.8.2 Lamotrigine						
Calabrese 2000 (2)	1	92	2	88	56.5%	-0.01 [-0.05, 0.03]
Subtotal (95% CI)		**92**		**88**	**56.5%**	**-0.01 [-0.05, 0.03]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
18.8.3 Oxcarbazepine						
Vieta 2008a (3)	3	26	3	29	2.9%	0.01 [-0.15, 0.18]
Subtotal (95% CI)		**26**		**29**	**2.9%**	**0.01 [-0.15, 0.18]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**159**		**162**	**100.0%**	**-0.01 [-0.03, 0.02]**
Total events	4		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%						



Risk of Bias

Risk of bias legend

Footnotes

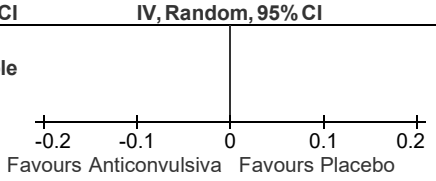
(1) Lamotrigine + valproate vs lamotrigine + placebo, Index episode: depression, bipolar...

(2) Lamotrigine vs placebo, index episode: any episode or euthymic, bipolar I + II

(3) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in acute...

18.9 Suicidal behaviour

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

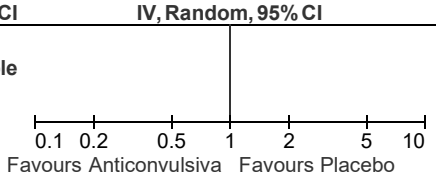


Risk of Bias

Risk of bias legend

18.10 Sedation

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

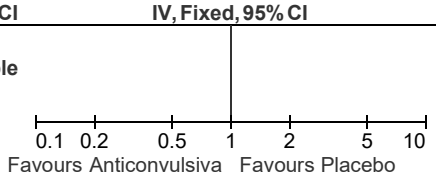


Risk of Bias

Risk of bias legend

18.11 Psychiatric hospitalization

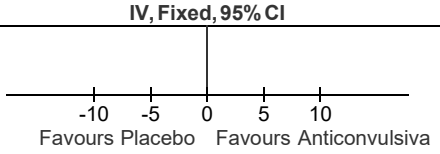
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

18.12 Global functioning

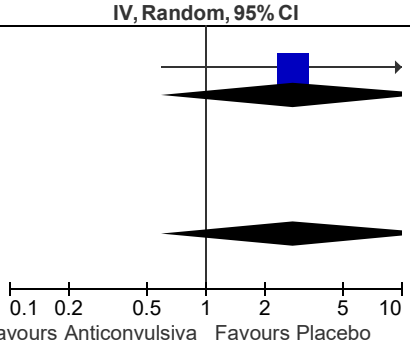
Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bi
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

18.13 Weigt gain, over 7%

Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
18.13.3 Oxcarbazepine								
Vieta 2008a (1)	5	26	2	29	100.0%	2.79 [0.59, 13.16]		
Subtotal (95% CI)		**26**		**29**	**100.0%**	**2.79 [0.59, 13.16]**		
Total events	5		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.20)								
Total (95% CI)		**26**		**29**	**100.0%**	**2.79 [0.59, 13.16]**		
Total events	5		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.20)								
Test for subgroup differences: Not applicable								



Footnotes

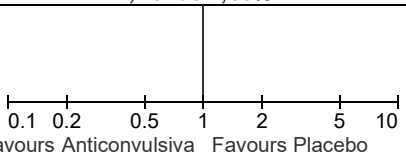
(1) Oxcarbazepe + lithium vs lithium + placebo,index episode:not specified, not in acute...

Risk of bias legend

19 Børn og unge_Anticonvulsiva vs Placebo_Bipolar 1

19.1 New episode, any type

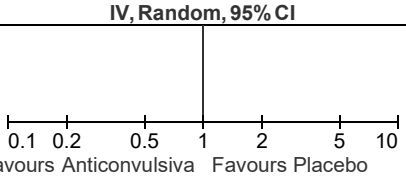
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.2 New episode, depression

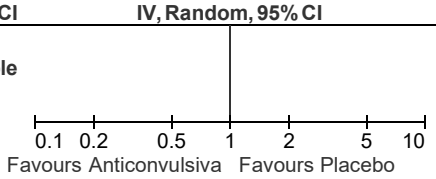
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.3 New episode, mania

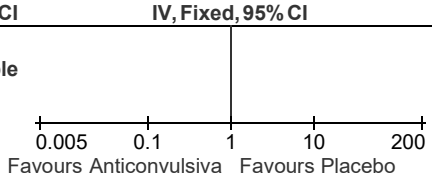
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.4 New episode, mixed

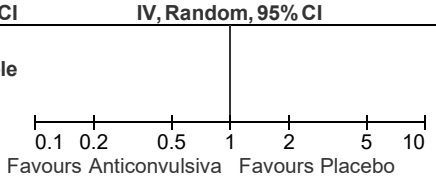
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.5 Withdrawal, any cause

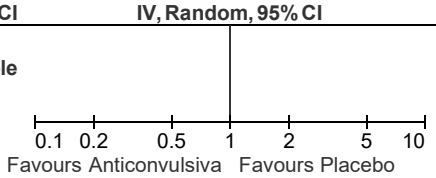
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.6 Serious adverse events (SAE)

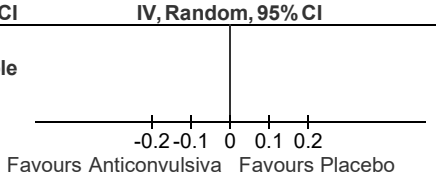
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.7 Serious adverse events (SAE), risk diff

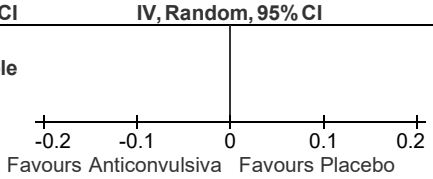
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.8 Suicidal behaviour

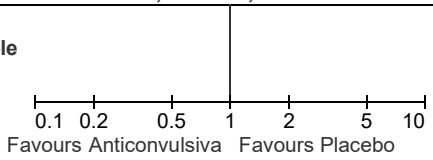
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.9 Sedation

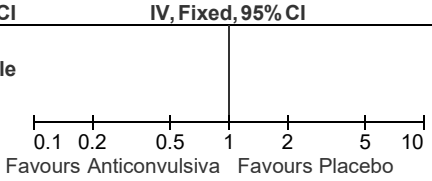
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.10 Psychiatric hospitalization

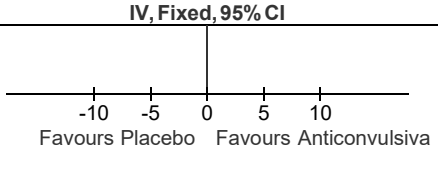
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.11 Global functioning

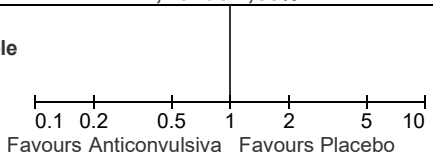
Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bi
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

19.12 Weigt gain, over 7%

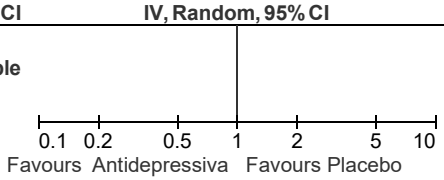
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.13 New episode, hypomania

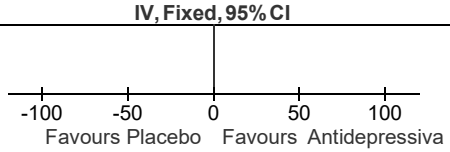
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

19.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of E
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										

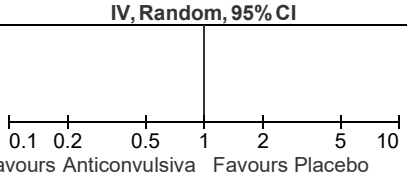


Risk of bias legend

20 Børn og unge_Anticonvulsiva vs Placebo_Bipolar 2

20.1 New episode, any type

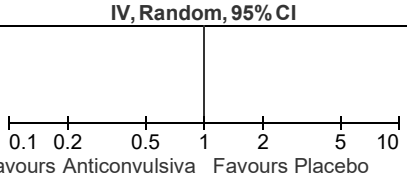
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.2 New episode, depression

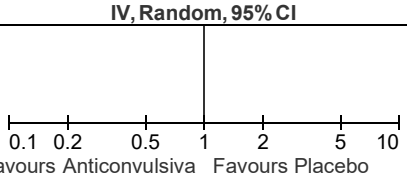
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.3 New episode, mania

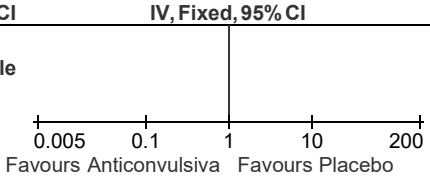
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.4 New episode, mixed

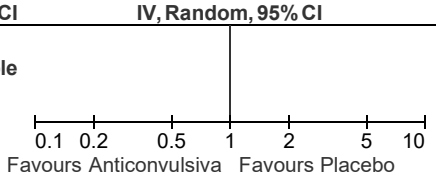
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.5 Withdrawal, any cause

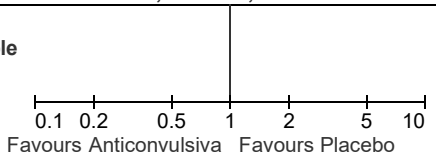
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.6 Serious adverse events (SAE)

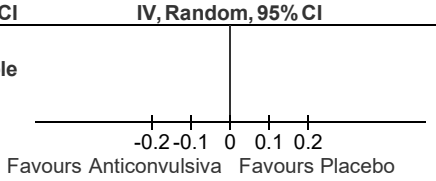
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.7 Serious adverse events (SAE), risk diff

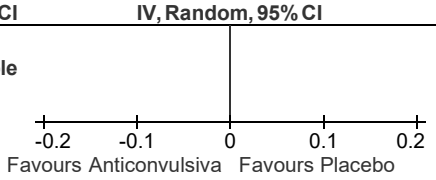
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.8 Suicidal behaviour

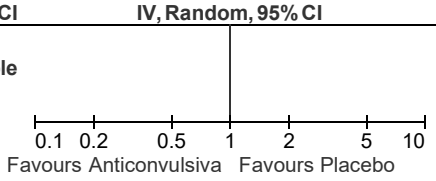
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.9 Sedation

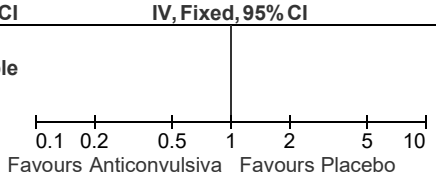
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.10 Psychiatric hospitalization

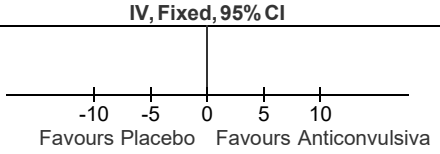
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.11 Global functioning

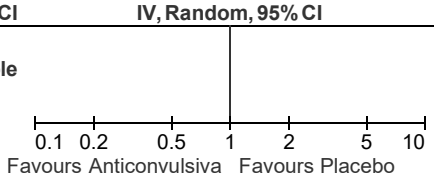
Study or Subgroup	Anticonvulsiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bi
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										



Risk of bias legend

20.12 Weigt gain, over 7%

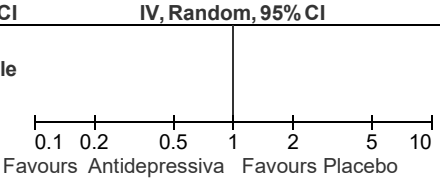
Study or Subgroup	Anticonvulsiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.13 New episode, hypomania

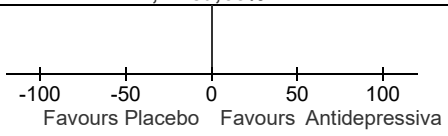
Study or Subgroup	Antidepressiva Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Risk of bias legend

20.14 Quality of life

Study or Subgroup	Antidepressiva Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of E
Total (95% CI)			**0**			**0**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										

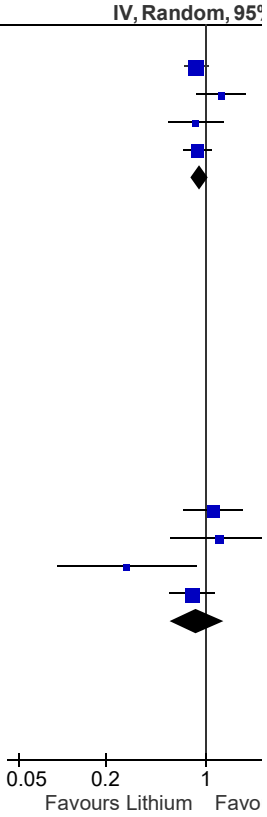


Risk of bias legend

22 Lithium vs Anticonvulsiva_subgroup bipolar type

22.1 New episode, any type

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
22.1.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	65	110	76	110	42.9%	0.86 [0.70, 1.04]
Bowden 2000 (2)	28	91	45	187	12.5%	1.28 [0.86, 1.91]
Bowden 2003 (3)	18	44	28	58	10.3%	0.85 [0.54, 1.32]
Calabrese 2003 (4)	56	120	115	215	34.3%	0.87 [0.69, 1.10]
Subtotal (95% CI)		**365**		**570**	**100.0%**	**0.90 [0.78, 1.05]**
Total events	167		264			
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 1.35 (P = 0.18)						
22.1.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.1.3 Bipolar 1 og 2						
Calabrese 2005 (5)	18	32	14	28	31.7%	1.13 [0.70, 1.82]
Coxhead 1992 (6)	8	16	6	15	18.8%	1.25 [0.57, 2.75]
Hartong 2003 (7)	3	23	14	30	11.4%	0.28 [0.09, 0.86]
Kleindienst 2000 (8)	31	86	38	85	38.1%	0.81 [0.56, 1.16]
Subtotal (95% CI)		**157**		**158**	**100.0%**	**0.86 [0.56, 1.32]**
Total events	60		72			
Heterogeneity: Tau² = 0.09; Chi² = 5.99, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 0.68 (P = 0.50)						



Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%

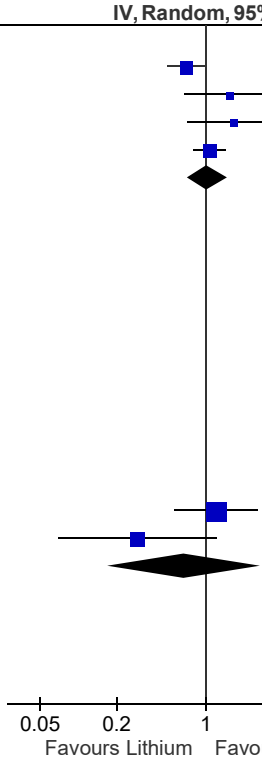
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs valproate, index episode: mania, bipolar I
(3) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(4) Lithium vs lamotrigine, index episode: depression, bipolar I
(5) Lithium vs valproate, index episode: mania/ hypo mania/mixed, bipolar type I or II
(6) Lithium vs carbamazepine, index episode: not specified, bipolar type not specified
(7) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II
(8) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.2 New episode, depression

Study or Subgroup	Lithium Events	Lithium Total	Anticonvulsiva Events	Anticonvulsiva Total	Weight	Risk Ratio IV, Random, 95% CI
22.2.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	35	110	50	110	34.7%	0.70 [0.50, 0.99]
Bowden 2000 (2)	9	91	12	187	13.9%	1.54 [0.67, 3.52]
Bowden 2003 (3)	10	44	8	58	13.5%	1.65 [0.71, 3.83]
Calabrese 2003 (4)	46	120	77	215	38.0%	1.07 [0.80, 1.43]
Subtotal (95% CI)		**365**		**570**	**100.0%**	**1.03 [0.72, 1.48]**
Total events	100		147			
Heterogeneity: Tau² = 0.07; Chi² = 6.66, df = 3 (P = 0.08); I² = 55%						
Test for overall effect: Z = 0.16 (P = 0.87)						
22.2.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.2.3 Bipolar 1 og 2						
Calabrese 2005 (5)	11	32	8	28	59.5%	1.20 [0.56, 2.56]
Hartong 2003 (6)	2	23	9	30	40.5%	0.29 [0.07, 1.21]
Subtotal (95% CI)		**55**		**58**	**100.0%**	**0.68 [0.17, 2.66]**
Total events	13		17			
Heterogeneity: Tau² = 0.67; Chi² = 2.96, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 0.56 (P = 0.58)						



Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%

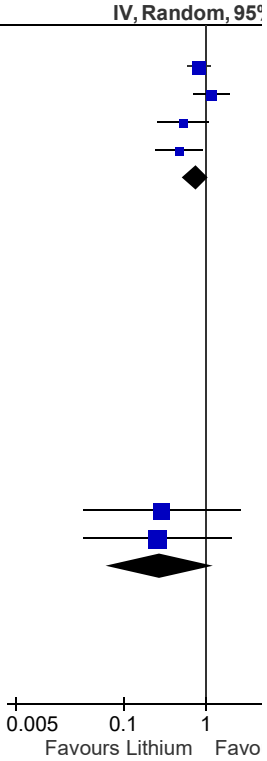
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs valproate, Index episode: mania, bipolar I
(3) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(4) Lithium vs lamotrigine, index episode: depression, bipolar I
(5) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II
(6) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.3 New episode, mania

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
22.3.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	40	110	49	110	36.7%	0.82 [0.59, 1.13]
Bowden 2000 (2)	19	91	33	187	26.2%	1.18 [0.71, 1.96]
Bowden 2003 (3)	8	44	20	58	17.5%	0.53 [0.26, 1.08]
Calabrese 2003 (4)	10	120	38	215	19.6%	0.47 [0.24, 0.91]
Subtotal (95% CI)		**365**		**570**	**100.0%**	**0.75 [0.52, 1.09]**
Total events	77		140			
Heterogeneity: Tau² = 0.07; Chi² = 6.05, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 1.52 (P = 0.13)						
22.3.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.3.3 Bipolar 1 og 2						
Calabrese 2005 (5)	1	32	3	28	47.0%	0.29 [0.03, 2.65]
Hartong 2003 (6)	1	23	5	30	53.0%	0.26 [0.03, 2.08]
Subtotal (95% CI)		**55**		**58**	**100.0%**	**0.27 [0.06, 1.25]**
Total events	2		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.09)						



Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.1%

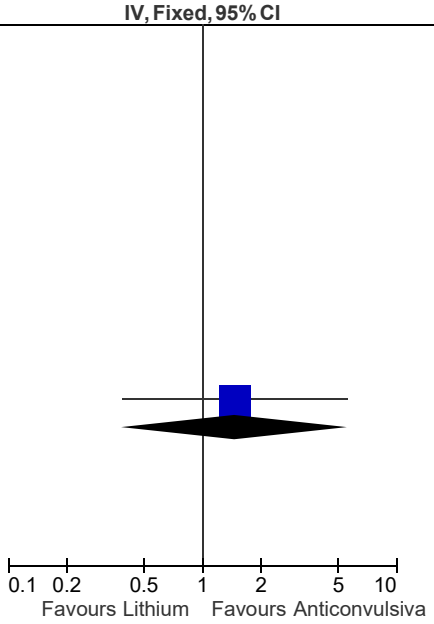
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs valproate, Index episode: mania, bipolar I
(3) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(4) Lithium vs lamotrigine, index episode: depression, bipolar I
(5) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II
(6) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.4 New episode, hypomania

Study or Subgroup	Lithium Events	Lithium Total	Anticonvulsiva Events	Anticonvulsiva Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
22.4.1 Bipolar 1								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
22.4.2 Bipolar 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
22.4.3 Bipolar 1 og 2								
Calabrese 2005 (1)	5	32	3	28	100.0%	1.46 [0.38, 5.56]		
Subtotal (95% CI)		**32**		**28**	**100.0%**	**1.46 [0.38, 5.56]**		
Total events	5		3					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								



Test for subgroup differences: Not applicable

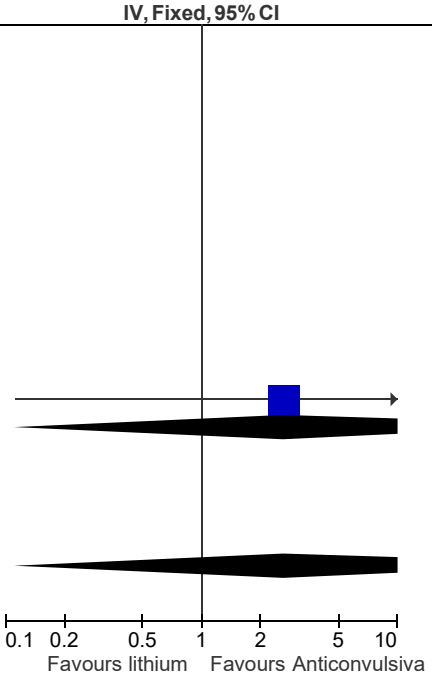
Footnotes

(1) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II

Risk of bias legend

22.5 New episode, mixed

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
22.5.1 Bipolar 1							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
22.5.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
22.5.3 Bipolar 1 og 2							
Calabrese 2005 (1)	1	32	0	28	100.0%	2.64 [0.11, 62.23]	
Subtotal (95% CI)		**32**		**28**	**100.0%**	**2.64 [0.11, 62.23]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
Total (95% CI)		**32**		**28**	**100.0%**	**2.64 [0.11, 62.23]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
Test for subgroup differences: Not applicable							



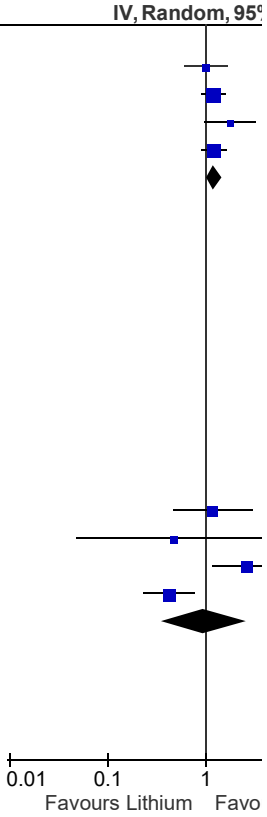
Footnotes

(1) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II

Risk of bias legend

22.6 Withdrawal, any cause

Study or Subgroup	Lithium Events	Lithium Total	Anticonvulsiva Events	Anticonvulsiva Total	Weight	Risk Ratio IV, Random, 95% CI
22.6.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	23	110	23	110	13.0%	1.00 [0.60, 1.67]
Bowden 2000 (2)	41	91	71	187	40.4%	1.19 [0.89, 1.59]
Bowden 2003 (3)	18	46	13	59	9.5%	1.78 [0.97, 3.24]
Calabrese 2003 (4)	45	121	68	221	37.1%	1.21 [0.89, 1.64]
Subtotal (95% CI)		**368**		**577**	**100.0%**	**1.21 [1.01, 1.46]**
Total events	127		175			
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 3 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
22.6.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.6.3 Bipolar 1 og 2						
Calabrese 2005 (5)	8	32	6	28	27.3%	1.17 [0.46, 2.95]
Coxhead 1992 (6)	1	16	2	15	12.4%	0.47 [0.05, 4.65]
Hartong 2003 (7)	12	23	6	30	28.8%	2.61 [1.15, 5.90]
Kleindienst 2000 (8)	12	86	28	85	31.5%	0.42 [0.23, 0.78]
Subtotal (95% CI)		**157**		**158**	**100.0%**	**0.95 [0.35, 2.59]**
Total events	33		42			
Heterogeneity: Tau² = 0.73; Chi² = 13.04, df = 3 (P = 0.005); I² = 77%						
Test for overall effect: Z = 0.09 (P = 0.93)						



Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%

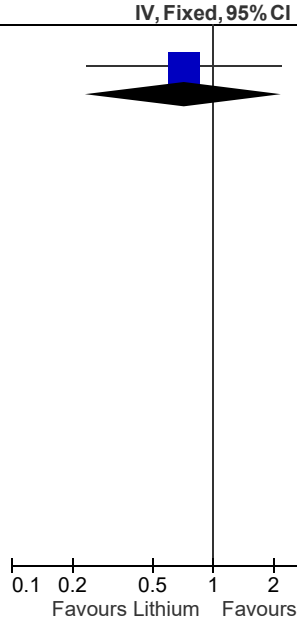
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs valproate, Index episode: mania, bipolar I
(3) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(4) Lithium vs lamotrigine, index episode: depression, bipolar type 1
(5) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II
(6) Lithium vs carbamazepine, index episode: not specified, bipolar type not specified
(7) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II
(8) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.7 Serious adverse events (SAE)

Study or Subgroup	Lithium Events	Lithium Total	Anticonvulsiva Events	Anticonvulsiva Total	Weight	Risk Ratio IV, Fixed, 95% CI
22.7.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	5	110	7	110	100.0%	0.71 [0.23, 2.18]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**0.71 [0.23, 2.18]**
Total events	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
22.7.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.7.3 Bipolar 1 og 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

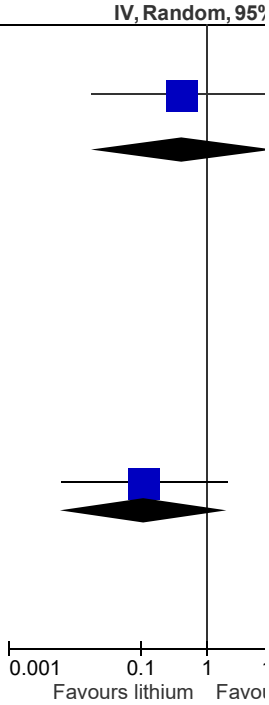
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I

Risk of bias legend

22.8 Suicidal behaviour

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
22.8.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	0	110	0	110		Not estimable
Bowden 2003 (2)	0	46	1	58	100.0%	0.42 [0.02, 10.04]
Calabrese 2003 (3)	0	120	0	169		Not estimable
Subtotal (95% CI)		**276**		**337**	**100.0%**	**0.42 [0.02, 10.04]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
22.8.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.8.3 Bipolar 1 og 2						
Kleindienst 2000 (4)	0	86	4	85	100.0%	0.11 [0.01, 2.01]
Subtotal (95% CI)		**86**		**85**	**100.0%**	**0.11 [0.01, 2.01]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						



Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%

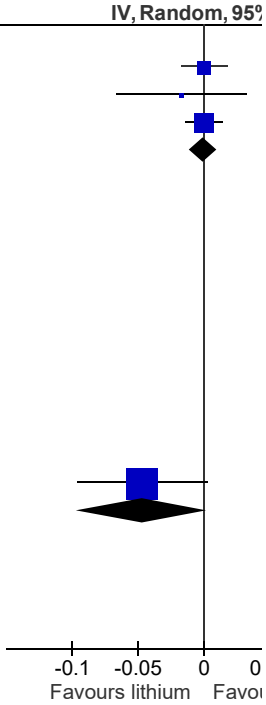
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(3) Lithium vs lamotrigine, index episode: depression, bipolar I
(4) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.9 Suicidal behaviour, risk diff

Study or Subgroup	Lithium Events	Lithium Total	Anticonvulsiva Events	Anticonvulsiva Total	Weight	Risk Difference IV, Random, 95% CI
22.9.1 Bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	0	110	0	110	37.0%	0.00 [-0.02, 0.02]
Bowden 2003 (2)	0	46	1	58	4.6%	-0.02 [-0.07, 0.03]
Calabrese 2003 (3)	0	120	0	169	58.3%	0.00 [-0.01, 0.01]
Subtotal (95% CI)		**276**		**337**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	0		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
22.9.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.9.3 Bipolar 1 og 2						
Kleindienst 2000 (4)	0	86	4	85	100.0%	-0.05 [-0.10, 0.00]
Subtotal (95% CI)		**86**		**85**	**100.0%**	**-0.05 [-0.10, 0.00]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						



Test for subgroup differences: Chi² = 3.18, df = 1 (P = 0.07), I² = 68.6%

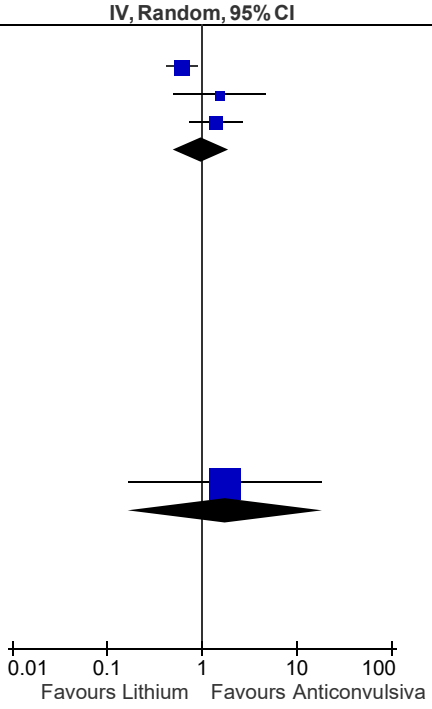
Footnotes

(1) Lithuim vs valproate, index episode: mania, bipolar I
(2) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(3) Lithium vs lamotrigine, index episode: depression, bipolar I
(4) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.10 Sedation

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
22.10.1 Bipolar 1							
Bowden 2000 (1)	24	94	78	187	44.2%	0.61 [0.42, 0.90]	
Bowden 2003 (2)	6	46	5	59	21.1%	1.54 [0.50, 4.73]	
Calabrese 2003 (3)	16	120	16	169	34.7%	1.41 [0.73, 2.70]	
Subtotal (95% CI)		**260**		**415**	**100.0%**	**0.99 [0.51, 1.94]**	
Total events	46		99				
Heterogeneity: Tau² = 0.23; Chi² = 6.05, df = 2 (P = 0.05); I² = 67%							
Test for overall effect: Z = 0.02 (P = 0.98)							
22.10.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
22.10.3 Bipolar 1 og 2							
Calabrese 2005 (4)	2	32	1	28	100.0%	1.75 [0.17, 18.28]	
Subtotal (95% CI)		**32**		**28**	**100.0%**	**1.75 [0.17, 18.28]**	
Total events	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							



Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%

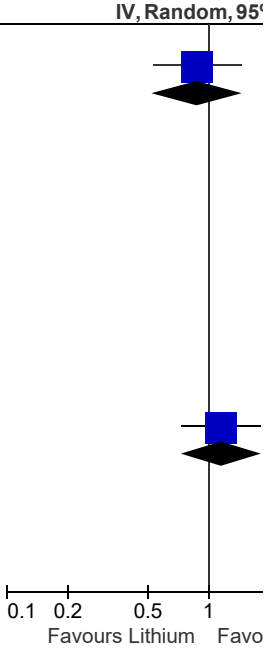
Footnotes

(1) Lithium vs valproate, Index episode: mania, bipolar I
(2) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(3) Lithium vs lamotrigine, index episode: depression, bipolar I
(4) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II

Risk of bias legend

22.11 Psychiatric hospitalization

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
22.11.1 bipolar 1						
BALANCEinvestigatorsandcollaborators 2010 (1)	22	110	25	110	100.0%	0.88 [0.53, 1.46]
Subtotal (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)						
22.11.2 Bipolar 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.11.3 Bipolar 1 og 2						
Kleindienst 2000 (2)	28	86	24	85	100.0%	1.15 [0.73, 1.82]
Subtotal (95% CI)		**86**		**85**	**100.0%**	**1.15 [0.73, 1.82]**
Total events	28		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						



Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%

Footnotes

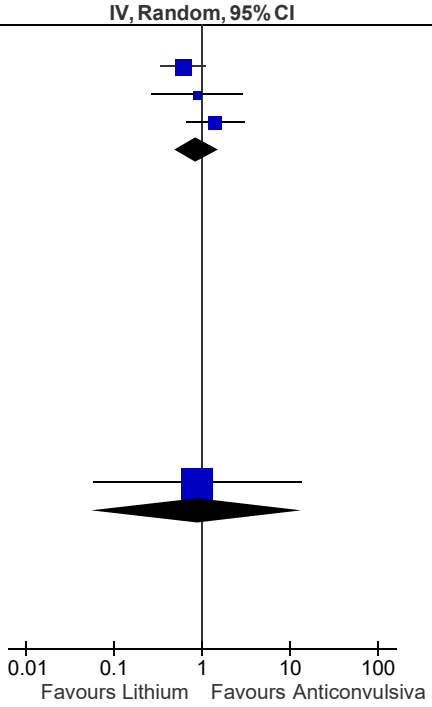
(1) Lithuim vs valproate, index episode: mania, bipolar I

(2) Lithium vs carbamazepine, index episode: not specified, bipolar type I + II

Risk of bias legend

22.12 Weigt gain, over 7%

Study or Subgroup	Lithium Events	Total	Anticonvulsiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias
22.12.1 Bipolar 1								
Bowden 2000 (1)	12	94	39	187	47.6%	0.61 [0.34, 1.11]		
Bowden 2003 (2)	4	44	6	58	17.5%	0.88 [0.26, 2.93]		
Calabrese 2003 (3)	12	120	12	169	35.0%	1.41 [0.66, 3.03]		
Subtotal (95% CI)		**258**		**414**	**100.0%**	**0.87 [0.50, 1.51]**		
Total events	28		57					
Heterogeneity: Tau² = 0.07; Chi² = 2.83, df = 2 (P = 0.24); I² = 29%								
Test for overall effect: Z = 0.49 (P = 0.63)								
22.12.2 Bipolar 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
22.12.3 Bipolar 1 og 2								
Calabrese 2005 (4)	1	32	1	28	100.0%	0.88 [0.06, 13.35]		
Subtotal (95% CI)		**32**		**28**	**100.0%**	**0.88 [0.06, 13.35]**		
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								



Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%

Footnotes

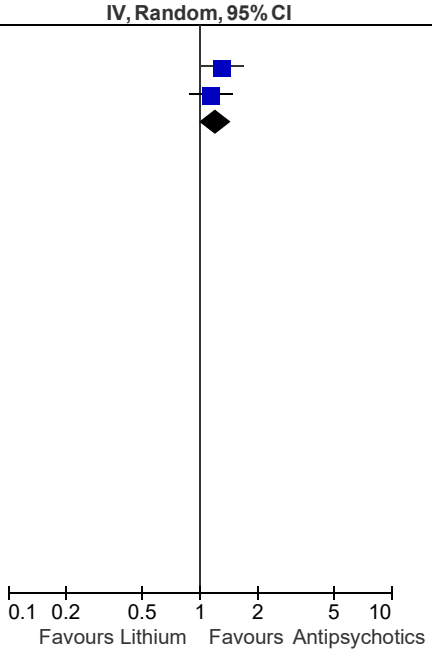
(1) Lithium vs valproate, index episode: mania, bipolar I
(2) Lithium vs lamotrigine, index episode: mania/ hypo mania, bipolar I
(3) Lithium vs lamotrigine, index episode: depression, bipolar I
(4) Lithium vs valproate, index episode: mania/ hypo mania, mixed, bipolar type I or II

Risk of bias legend

25 Lithium vs Antipsychotics_subgroup bipolar type

25.1 New episode, any type

Study or Subgroup	Lithium Events	Total	Antipsychotics Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
25.1.1 Bipolar 1							
Tohen 2005 (1)	83	214	65	217	49.1%	1.29 [0.99, 1.69]	
Weisler 2011 (2)	89	364	87	404	50.9%	1.14 [0.88, 1.47]	
Subtotal (95% CI)		**578**		**621**	**100.0%**	**1.21 [1.01, 1.46]**	
Total events	172		152				
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%							
Test for overall effect: Z = 2.03 (P = 0.04)							
25.1.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
25.1.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Not applicable

Footnotes

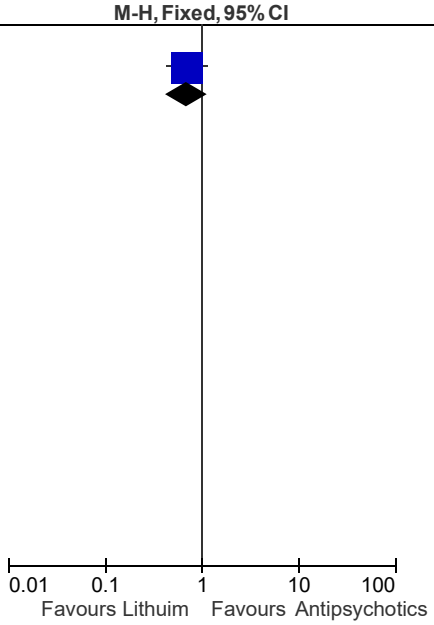
(1) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

(2) Lithium vs quetiapine, index episode: mania, depression or mixed, bipolar type I

Risk of bias legend

25.2 New episode, depression

Study or Subgroup	Lithium Events	Total	Antipsychotics Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
25.2.1 Bipolar 1								
Tohen 2005 (1)	23	214	34	217	100.0%	0.69 [0.42, 1.12]		
Subtotal (95% CI)		**214**		**217**	**100.0%**	**0.69 [0.42, 1.12]**		
Total events	23		34					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
25.2.2 Bipolar 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
25.2.3 Bipolar 1 og 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

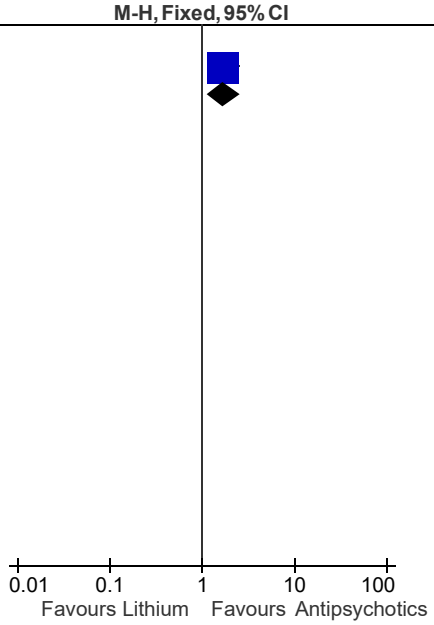
Footnotes

(1) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

Risk of bias legend

25.3 New episode, mania

Study or Subgroup	Lithium Events	Lithium Total	Antipsychotics Events	Antipsychotics Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias
25.3.1 Bipolar 1							
Tohen 2005 (1)	50	214	30	217	100.0%	1.69 [1.12, 2.55]	
Subtotal (95% CI)		**214**		**217**	**100.0%**	**1.69 [1.12, 2.55]**	
Total events	50		30				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.50 (P = 0.01)							
25.3.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
25.3.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Not applicable

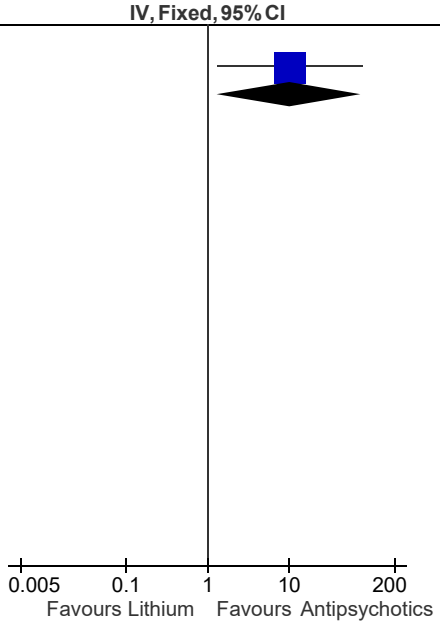
Footnotes

(1) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

Risk of bias legend

25.4 New episode, mixed

Study or Subgroup	Lithium Events	Lithium Total	Antipsychotics Events	Antipsychotics Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
25.4.1 Bipolar 1								
Tohen 2005 (1)	10	214	1	217	100.0%	10.14 [1.31, 78.53]		
Subtotal (95% CI)		**214**		**217**	**100.0%**	**10.14 [1.31, 78.53]**		
Total events	10		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.22 (P = 0.03)								
25.4.2 Bipolar 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
25.4.3 Bipolar 1 og 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

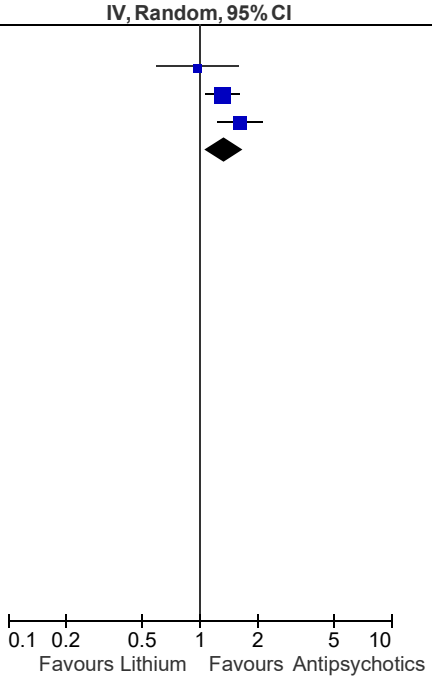
Footnotes

(1) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

Risk of bias legend

25.5 Withdrawal, any cause

Study or Subgroup	Lithium Events	Lithium Total	Antipsychotics Events	Antipsychotics Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
25.5.1 Bipolar 1							
Berk 2017 (1)	15	30	16	31	16.5%	0.97 [0.59, 1.59]	
Tohen 2005 (2)	110	214	85	217	46.9%	1.31 [1.06, 1.62]	
Weisler 2011 (3)	99	364	68	404	36.6%	1.62 [1.23, 2.13]	
Subtotal (95% CI)		**608**		**652**	**100.0%**	**1.35 [1.07, 1.69]**	
Total events	224		169				
Heterogeneity: Tau² = 0.02; Chi² = 3.44, df = 2 (P = 0.18); I² = 42%							
Test for overall effect: Z = 2.58 (P = 0.010)							
25.5.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
25.5.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Not applicable

Footnotes

(1) Lithium vs quetiapine, Index episode: mania, bipolar I

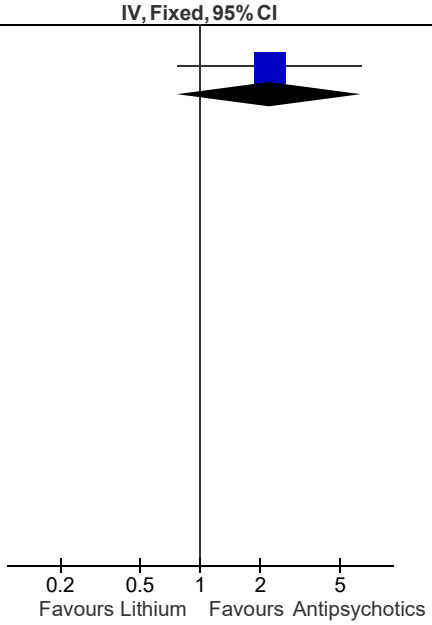
(2) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

(3) Lithium vs quetiapine, index episode: mania, depression or mixed, bipolar type I

Risk of bias legend

25.6 Serious adverse events (SAE)

Study or Subgroup	Lithium Events	Lithium Total	Antipsychotics Events	Antipsychotics Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
25.6.1 Bipolar 1							
Weisler 2011 (1)	10	364	5	404	100.0%	2.22 [0.77, 6.43]	
Subtotal (95% CI)		**364**		**404**	**100.0%**	**2.22 [0.77, 6.43]**	
Total events	10		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							
25.6.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
25.6.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Not applicable

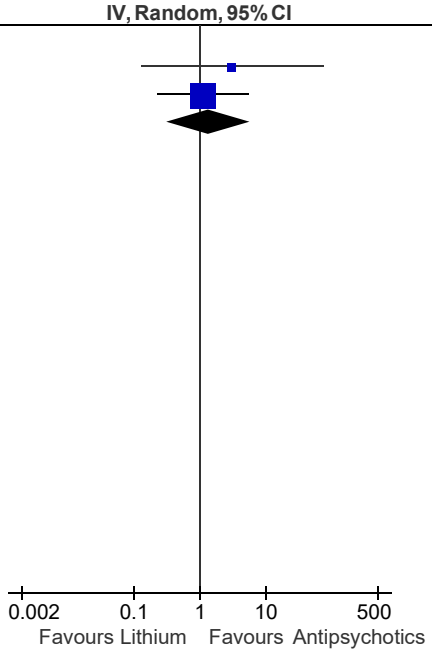
Footnotes

(1) Lithium vs quetiapine, index episode: mania, depression or mixed, bipolar type I

Risk of bias legend

25.7 Suicidal behaviour

Study or Subgroup	Lithium Events	Total	Antipsychotics Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
25.7.1 Bipolar 1							
Tohen 2005 (1)	1	214	0	217	19.9%	3.04 [0.12, 74.26]	
Weisler 2011 (2)	3	364	3	404	80.1%	1.11 [0.23, 5.46]	
Subtotal (95% CI)		**578**		**621**	**100.0%**	**1.36 [0.33, 5.65]**	
Total events	4		3				
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%							
Test for overall effect: Z = 0.42 (P = 0.67)							
25.7.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
25.7.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Not applicable

Footnotes

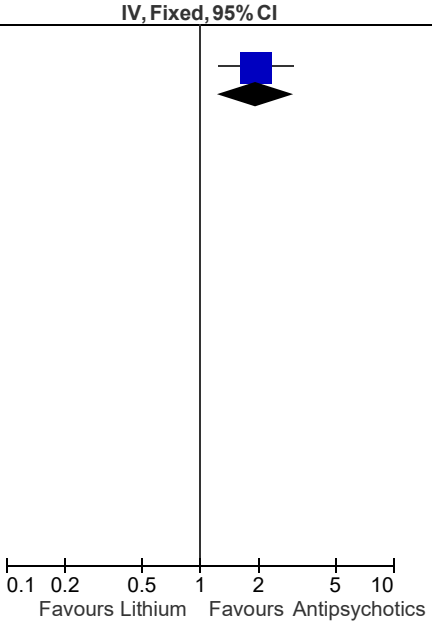
(1) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

(2) Lithium vs quetiapine, index episode: mania, depression or mixed, bipolar type I

Risk of bias legend

25.8 Sedation

Study or Subgroup	Lithium Events	Total	Antipsychotics Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias
25.8.1 Bipolar 1								
Weisler 2011 (1)	52	418	26	404	100.0%	1.93 [1.23, 3.03]		
Subtotal (95% CI)		**418**		**404**	**100.0%**	**1.93 [1.23, 3.03]**		
Total events	52		26					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.87 (P = 0.004)								
25.8.2 Bipolar 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
25.8.3 Bipolar 1 og 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

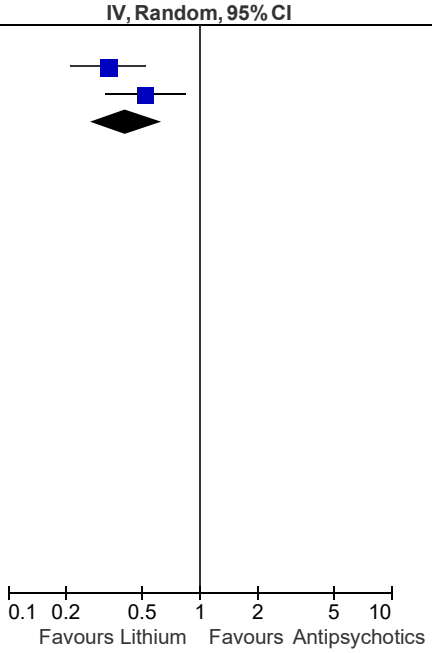
Footnotes

(1) Lithium vs quetiapine, index episode: mania, depression or mixed, bipolar type I

Risk of bias legend

25.9 Weigt gain, over 7%

Study or Subgroup	Lithium Events	Lithium Total	Antipsychotics Events	Antipsychotics Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
25.9.1 Bipolar 1							
Tohen 2005 (1)	21	214	64	217	52.0%	0.33 [0.21, 0.52]	
Weisler 2011	23	418	43	404	48.0%	0.52 [0.32, 0.84]	
Subtotal (95% CI)		**632**		**621**	**100.0%**	**0.41 [0.27, 0.63]**	
Total events	44		107				
Heterogeneity: Tau² = 0.04; Chi² = 1.68, df = 1 (P = 0.20); I² = 40%							
Test for overall effect: Z = 4.04 (P < 0.0001)							
25.9.2 Bipolar 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
25.9.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Not applicable

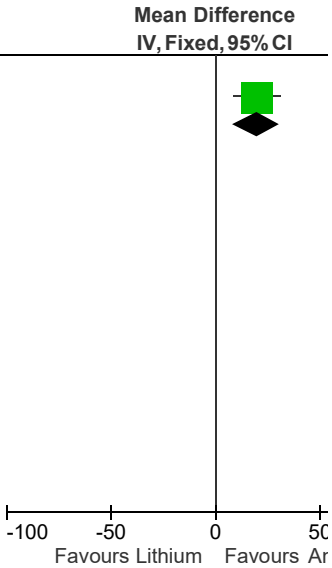
Footnotes

(1) Lithium vs olanzapine, Index episode: mania/mixed, bipolar I

Risk of bias legend

25.12 Global functioning

Study or Subgroup	Lithium Mean	SD	Total	Antipsychotics Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
25.12.1 Bipolar 1								
Berk 2017 (1)	7.9	18.33030278	21	-11.7	18.30737556	19	100.0%	19.60 [8.23, 30.97]
Subtotal (95% CI)			**21**			**19**	**100.0%**	**19.60 [8.23, 30.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.38 (P = 0.0007)								
25.12.2 Bipolar 2								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
25.12.3 Bipolar 1 og 2								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

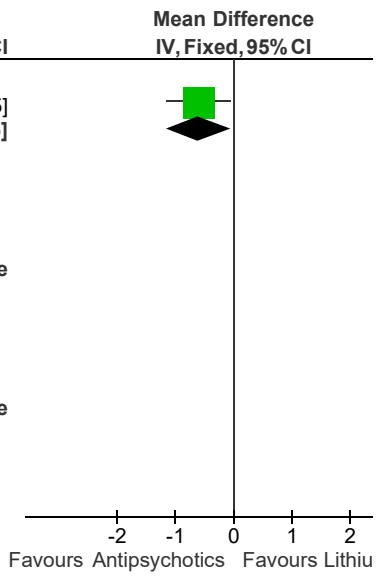
Footnotes

(1) Lithium vs quetiapine, Index episode: maina, bipolar I

Risk of bias legend

25.13 Quality of life

Study or Subgroup	Lithium Mean	SD	Total	Antipsychotics Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
25.13.1 Bipolar 1								
Berk 2017 (1)	-0.3	0.91651514	21	0.3	0.87177979	19	100.0%	-0.60 [-1.15, -0.05]
Subtotal (95% CI)			**21**			**19**	**100.0%**	**-0.60 [-1.15, -0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.12 (P = 0.03)								
25.13.2 Bipolar 2								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
25.13.3 Bipolar 1 og 2								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

Footnotes

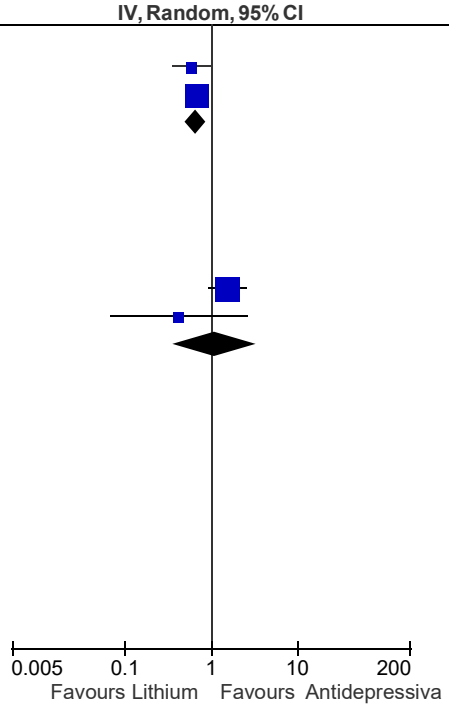
(1) Lithium vs quetiapine, Index episode: mania, bipolar I

Risk of bias legend

26 Lithium vs Antidepressiva_subgroup bipolar type

26.1 New episode, any type

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
26.1.1 Bipolar 1						
Prien 1973b (1)	9	18	11	13	27.5%	0.59 [0.35, 0.99]
Prien 1984 (2)	23	42	29	36	72.5%	0.68 [0.49, 0.93]
Subtotal (95% CI)		**60**		**49**	**100.0%**	**0.65 [0.50, 0.86]**
Total events	32		40			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 3.07 (P = 0.002)						
26.1.2 Bipolar 2						
Amsterdam 2010 (3)	17	26	12	28	74.2%	1.53 [0.92, 2.54]
Kane 1982 (4)	1	4	3	5	25.8%	0.42 [0.07, 2.63]
Subtotal (95% CI)		**30**		**33**	**100.0%**	**1.09 [0.36, 3.32]**
Total events	18		15			
Heterogeneity: Tau² = 0.37; Chi² = 1.77, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 0.15 (P = 0.88)						
26.1.3 Bipolar 1 og 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Chi² = 0.77, df = 1 (P = 0.38), I² = 0%

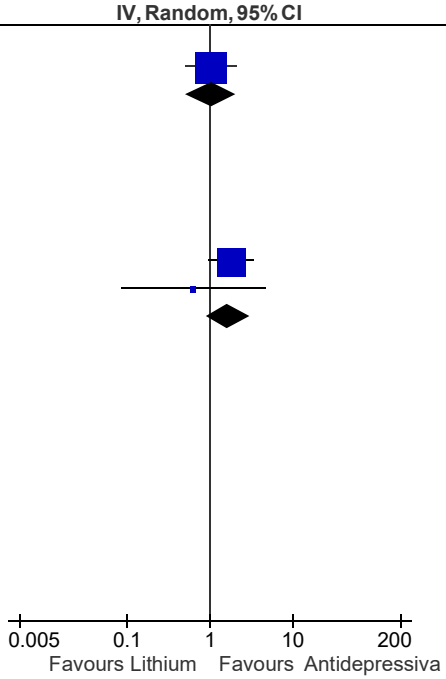
Footnotes

(1) Lithium vs TCA (imipramine),index episode: depression, bipolar type 1
(2) Lithium vs TCA (imipramine),index episode: mania or depression, bipolar type 1
(3) Lithium vs fluoxetine, Index episode: depression, bipolar type II
(4) Lithium vs TCA (imipramine), index episode: not specified, bipolar type II

Risk of bias legend

26.2 New episode, depression

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
26.2.1 Bipolar 1						
Prien 1984 (1)	12	42	10	36	100.0%	1.03 [0.50, 2.10]
Subtotal (95% CI)		**42**		**36**	**100.0%**	**1.03 [0.50, 2.10]**
Total events	12		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
26.2.2 Bipolar 2						
Amsterdam 2010 (2)	15	26	9	28	91.0%	1.79 [0.96, 3.37]
Kane 1982 (3)	1	4	2	5	9.0%	0.63 [0.08, 4.66]
Subtotal (95% CI)		**30**		**33**	**100.0%**	**1.63 [0.89, 2.98]**
Total events	16		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
26.2.3 Bipolar 1 og 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Chi² = 0.94, df = 1 (P = 0.33), I² = 0%

Footnotes

(1) Lithium vs TCA (imipramine),index episode: mania or depression, bipolar type 1

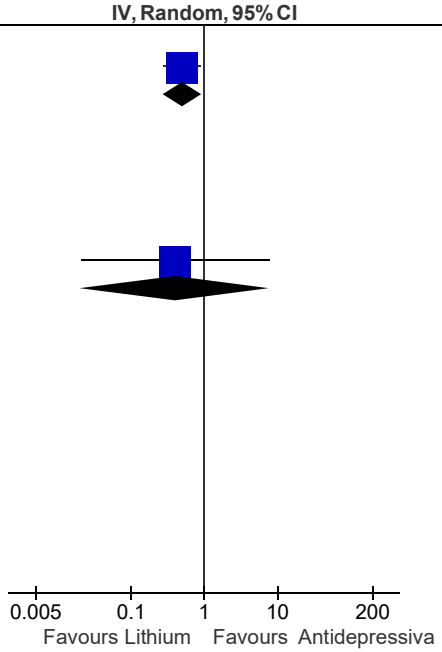
(2) Lithium vs fluoxetine, Index episode: depression, bipolar type II

(3) Lithium vs TCA (imipramine), index episode: not specified, bipolar type II

Risk of bias legend

26.3 New episode, mania

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias
26.3.1 Bipolar 1							
Prien 1984 (1)	11	42	19	36	100.0%	0.50 [0.27, 0.90]	
Subtotal (95% CI)		**42**		**36**	**100.0%**	**0.50 [0.27, 0.90]**	
Total events	11		19				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.31 (P = 0.02)							
26.3.2 Bipolar 2							
Kane 1982 (2)	0	4	1	5	100.0%	0.40 [0.02, 7.82]	
Subtotal (95% CI)		**4**		**5**	**100.0%**	**0.40 [0.02, 7.82]**	
Total events	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
26.3.3 Bipolar 1 og 2							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%

Footnotes

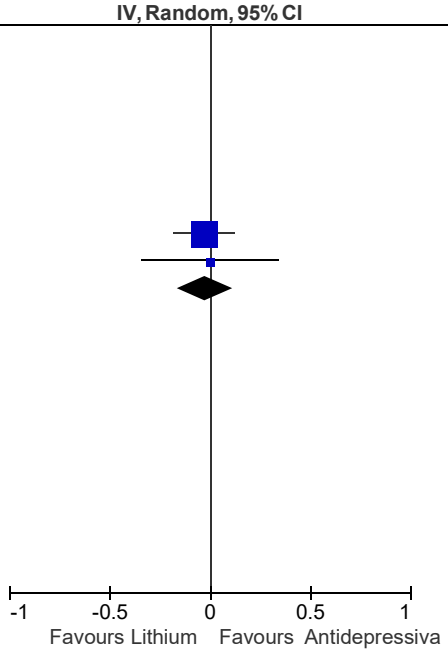
(1) Lithium vs TCA (imipramine),index episode: mania or depression, bipolar type 1

(2) Lithium vs TCA (imipramine), index episode: not specified, bipolar type II

Risk of bias legend

26.4 New episode, hypomania

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Difference IV, Random, 95% CI
26.4.1 Bipolar 1						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
26.4.2 Bipolar 2						
Amsterdam 2010 (1)	2	26	3	28	83.3%	-0.03 [-0.18, 0.12]
Kane 1982 (2)	0	4	0	5	16.7%	0.00 [-0.34, 0.34]
Subtotal (95% CI)		**30**		**33**	**100.0%**	**-0.03 [-0.17, 0.12]**
Total events	2		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
26.4.3 Bipolar 1 og 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

Footnotes

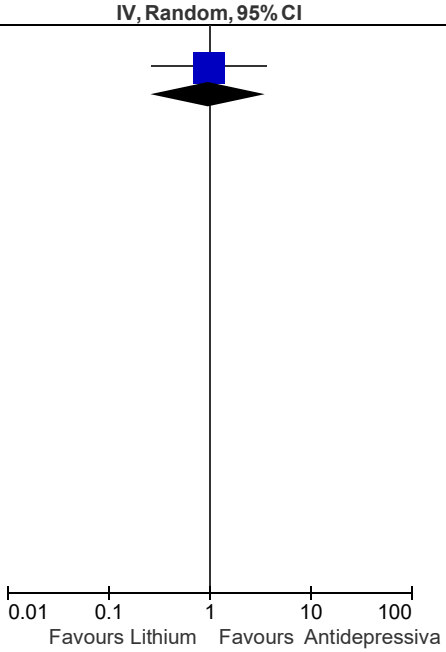
(1) Lithium vs fluoxetine, Index episode: depression, bipolar type II

(2) Lithium vs TCA (imipramine), index episode: not specified, bipolar type II

Risk of bias legend

26.5 Withdrawal, any cause

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Ratio IV, Random, 95% CI
26.5.1 Bipolar 1						
Prien 1973b (1)	4	18	3	13	100.0%	0.96 [0.26, 3.59]
Subtotal (95% CI)		**18**		**13**	**100.0%**	**0.96 [0.26, 3.59]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.96)						
26.5.2 Bipolar 2						
Amsterdam 2010 (2)	0	26	0	28		Not estimable
Subtotal (95% CI)		**26**		**28**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
26.5.3 Bipolar 1 og 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

Footnotes

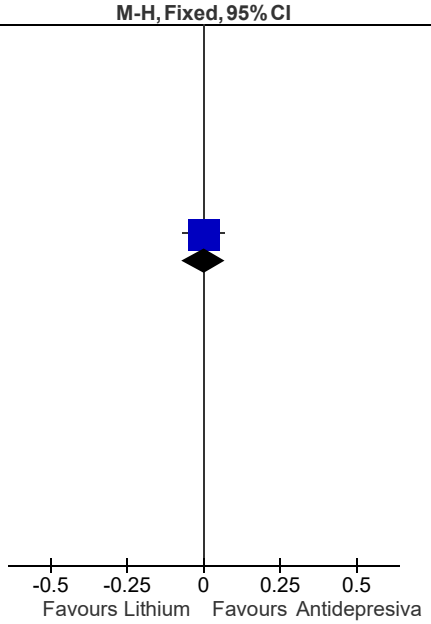
(1) Lithium vs TCA (imipramine),index episode: depression, bipolar type:1

(2) Lithium vs fluoxetine, Index episode: depression, bipolar type II

Risk of bias legend

26.6 Serious adverse events (SAE), risk difference

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI	Risk of Bias
26.6.1 Bipolar 1								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
26.6.2 Bipolar 2								
Amsterdam 2010 (1)	0	26	0	28	100.0%	0.00 [-0.07, 0.07]		
Subtotal (95% CI)		**26**		**28**	**100.0%**	**0.00 [-0.07, 0.07]**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
26.6.3 Bipolar 1 og 2								
Subtotal (95% CI)		**0**		**0**		**Not estimable**		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

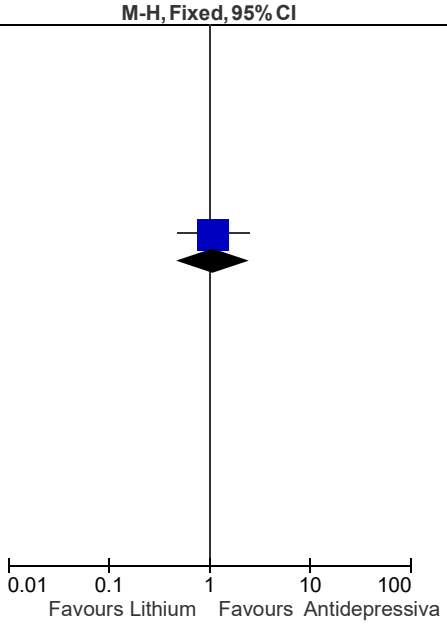
Footnotes

(1) Lithium vs fluoxetine, Index episode: depression, bipolar type II

Risk of bias legend

26.7 Sedation

Study or Subgroup	Lithium Events	Total	Antidepressiva Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
26.7.1 Bipolar 1						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
26.7.2 Bipolar 2						
Amsterdam 2010 (1)	8	26	8	28	100.0%	1.08 [0.47, 2.45]
Subtotal (95% CI)		**26**		**28**	**100.0%**	**1.08 [0.47, 2.45]**
Total events	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
26.7.3 Bipolar 1 og 2						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

Footnotes

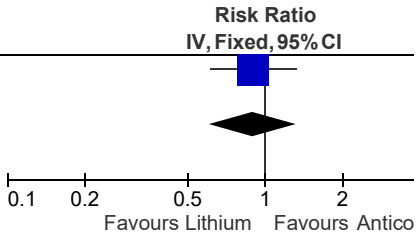
(1) Lithium vs fluoxetine, Index episode: depression, bipolar type II

Risk of bias legend

27 Børn og unge_Lithium vs Anticonvulsants (Valproate)

27.1 New episode, any type

Study or Subgroup	Lithium Events	Total	Anticonvulsants (Divalproex) Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Findling 2005 (1)	18	30	20	30	100.0%	0.90 [0.61, 1.32]
Total (95% CI)		**30**		**30**	**100.0%**	**0.90 [0.61, 1.32]**
Total events	18		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						



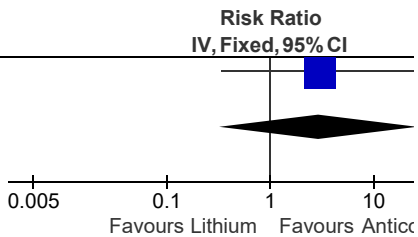
Footnotes

(1) Lithium vs valproate, Index episode: not specified, bipolar type I or II

Risk of bias legend

27.2 New episode, depression

Study or Subgroup	Lithium Events	Total	Anticonvulsants (Divalproex) Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Findling 2005 (1)	3	30	1	30	100.0%	3.00 [0.33, 27.23]
Total (95% CI)		**30**		**30**	**100.0%**	**3.00 [0.33, 27.23]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						



Footnotes

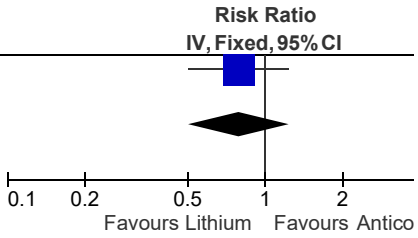
(1) Lithium vs valproate, Index episode: not specified, bipolar type I or II

Risk of bias legend

27.3 New episode, mania

Study or Subgroup	Lithium) Events	Total	Anticonvulsants (Divalproex) Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Findling 2005 (1)	15	30	19	30	100.0%	0.79 [0.50, 1.24]
Total (95% CI)		**30**		**30**	**100.0%**	**0.79 [0.50, 1.24]**
Total events	15		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)



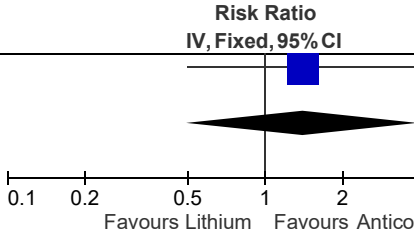
Footnotes
(1) Lithium vs valproate, Index episode: not specified, bipolar type I or II

Risk of bias legend

27.4 Withdrawal, any cause

Study or Subgroup	Lithium Events	Total	Anticonvulsants (Divalproex) Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Findling 2005 (1)	7	30	5	30	100.0%	1.40 [0.50, 3.92]
Total (95% CI)		**30**		**30**	**100.0%**	**1.40 [0.50, 3.92]**
Total events	7		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



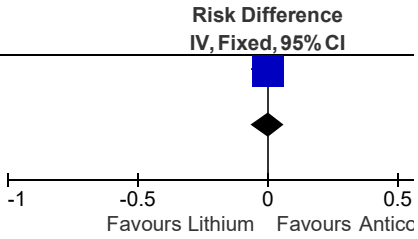
Footnotes
(1) Lithium vs valproate, Index episode: not specified, bipolar type I or II

Risk of bias legend

27.5 Suicidal behaviour

Study or Subgroup	Lithium Events	Total	Anticonvulsants (Divalproex) Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Findling 2005 (1)	0	30	0	30	100.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**30**		**30**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



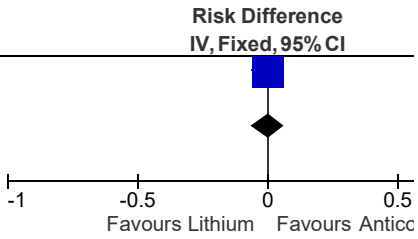
Footnotes
(1) Lithium vs valproate, Index episode: not specified, bipolar type I or II

Risk of bias legend

27.6 Psychiatric hospitalization

Study or Subgroup	Lithium Events	Total	Anticonvulsants (Divalproex) Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Findling 2005 (1)	0	30	0	30	100.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**30**		**30**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



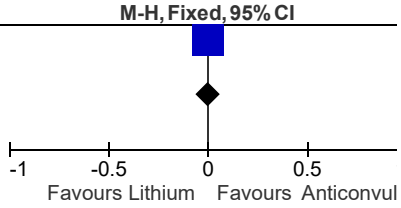
Footnotes
(1) Lithium vs valproate, Index episode: not specified, bipolar type I or II

Risk of bias legend

27.7 Sariuos adverse events

Study or Subgroup	Lithium Events	Lithium Total	Anticonvulsants (Divalproex) Events	Anticonvulsants (Divalproex) Total	Weight	Risk Difference M-H, Fixed, 95% CI
Findling 2005	0	30	0	30	100.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**30**		**30**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



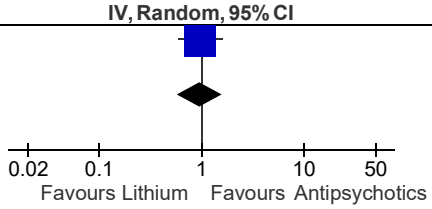
Risk of bias legend

28 Børn og unge_Lithium vs Antipsychotics (quetiapin)

28.1 Withdrawal, any cause

Study or Subgroup	Lithium Events	Lithium Total	Antipsychotics Events	Antipsychotics Total	Weight	Risk Ratio IV, Random, 95% CI
Berk 2017 (1)	15	30	16	31	100.0%	0.97 [0.59, 1.59]
Total (95% CI)		**30**		**31**	**100.0%**	**0.97 [0.59, 1.59]**
Total events	15		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)



Risk of Bias

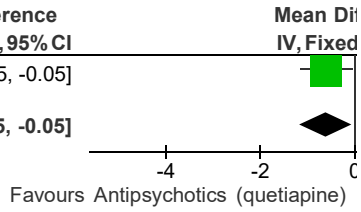
Footnotes
(1) Lithium vs quetiapine, Index episode: maina, bipolar I

Risk of bias legend

28.2 Quality of life

Study or Subgroup	Lithium Mean	Lithium SD	Lithium Total	Antipsychotics (quetiapine) Mean	Antipsychotics (quetiapine) SD	Antipsychotics (quetiapine) Total	Weight	Mean Difference IV, Fixed, 95% CI
Berk 2017 (1)	-0.3	0.91651514	21	0.3	0.87177979	19	100.0%	-0.60 [-1.15, -0.05]
Total (95% CI)			**21**			**19**	**100.0%**	**-0.60 [-1.15, -0.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)



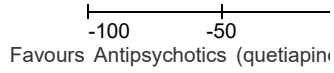
Footnotes
(1) Lithium vs quetiapine, Index episode: maina, bipolar I

Risk of bias legend

28.3 Global functioning

Study or Subgroup	Lithium Mean	Lithium SD	Lithium Total	Antipsychotics (quetiapine) Mean	Antipsychotics (quetiapine) SD	Antipsychotics (quetiapine) Total	Weight	Mean Difference IV, Fixed, 95% CI
Berk 2017 (1)	7.9	18.33030278	21	-11.7	18.30737556	19	100.0%	19.60 [8.23, 30.97]
Total (95% CI)			**21**			**19**	**100.0%**	**19.60 [8.23, 30.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.38 (P = 0.0007)



Footnotes
(1) Lithium vs quetiapine, Index episode: maina, bipolar I

Risk of bias legend